# An Overview about Bipolar Disorder Endophenotypes

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**Conflict of interest:** None declared
**Funding:** No funding sources

## Abstract
Despite considerable evidence that risk for bipolar disorder is inherited, the molecular genetic basis for this illness remains elusive. A recent genome wide association analysis with over 5,000 cases and 6,000 controls implicated two risk genes for the illness, ANK3 and CACNA1C. Endophenotype could help in reducing heterogeneity by defining biological traits that are more direct expressions of gene effects. The aim of this review is to examine the recent literature on clinical, epidemiological, neurobiological, and genetic findings and to select and evaluate candidate endophenotypes for bipolar disorder. research on endophenotypes could be useful to improve psychopathological diagnostics in the long run by dissecting psychiatric macro phenotypes into biologically valid components.

**Keywords:** Bipolar Disorder, endophenotypes

**Tob Regul Sci. ™ 2022;8(1): 2238-2250**
**DOI: doi.org/10.18001/TRS.8.1.169**

## Introduction:

Bipolar spectrum disorders are a major public health problem, with estimates of lifetime prevalence in the general population of the United States at 3.9 percent, with a range from 1.5 to 6.0 percent. Bipolar disorder is also associated with significant mortality risk, with approximately 25 percent of patients attempting suicide and 11 percent of patients completing. Furthermore, inadequate treatment and service structure causes high rates of jailing for bipolar patients. Bipolar depression is still undertreated, too, with patients suffering such symptoms 31.9 percent of the time over nearly 13 years **(1).**

Bipolar I disorder starts on average at 18 years and bipolar II disorder at 22 years. A community study using the Mood Disorder Questionnaire (MDQ) revealed a prevalence of 3.7 percent. The National Comorbidity Study showed onset typically between 18 and 44, with higher rates between 18 and 34 than 35 and 54. In a survey of members of the DBSA, more than half of the patients did not seek care for five years and the correct diagnosis was not made until an average of eight years after they first sought treatment. **(1).**

For reminding, the term "endophenotype" was described as an internal, intermediate phenotype (i.e., not obvious to the unaided eye) that fills the gap in the causal chain between genes and distal diseases and therefore might help to resolve questions about etiology. The endophenotype concept assumes that the number of genes involved in the variations of endophenotypes representing more elementary phenomena (as opposed to the behavioral macros found in the DSM) and is less than the num- ber involved in producing the full disease. Endophenotypes provide means for identifying the "upstream" traits underlying clinical phenotypes, as well as the "downstream" biological consequences of genes **(1).**

**Frequency of bipolar disorder in obsessive–compulsive disorder patients**

Abouhendy et al. found that 51 (85%) patients (23 male and 28 female) were diagnosed with OCD without BD, and about 15% (six male and three female) of OCD patients were found to have additional lifetime diagnosis of BD **(2).**

The evaluation of a candidate endophenotype is generally based on the endophenotype criteria concept developed by **Gottesman and Gould (3).** However, taking into account the increasing recognition of the importance of epigenetic transformations and developmental factors in the expression of psychiatric phenotypes **(1)**, the criterion "state independence" might be particularly difficult to achieve for candidate endophenotypes. Therefore, it was proposed to slightly modify this criterion, emphasizing the role of time and age. Below are the modified criteria:

1. An endophenotype is associated with illness, in the general population.
2. An endophenotype is heritable.
3. An endophenotype is state independent (i.e. manifests in an individual whether or not illness is active) but age-normed and might need to be elicited by a challenge.
4. Within families, endophenotype and illness co-segregate (i.e. the endophenotype is more prevalent among the ill relatives of ill probands compared with the healthy relatives of the ill probands).
5. An endophenotype identified in probands is found in their unaffected relatives at a higher rate than in the general population.

Apart from the above criteria, disease specificity and clinical and biological plausibility have also been discussed as evaluation criteria for endophenotypes **(4),** to relate phenotypic definitions to clinically relevant outcomes, to enhance the elucidation of clinically relevant pathophysiological mechanisms, and to increase prior probability of utility in genetic studies **(5).**

It is important to emphasize that endophenotypes are heritable quantitative measurable biological traits that reflect genetically relevant aspects of the heterogeneous pathophysiology of the disease. As such, endophenotypes are clearly different from diagnostic biomarkers that are evaluated by measures of sensitivity and specificity. This is because it cannot be assumed that the current definitions of psychiatric diseases are biologically valid. Further, a biomarker is not necessarily embedded in the genotype and behavior/psychopathology pathway of a disease as it is the case of an endophenotype.

## Molecular endophenotypes

### Altered neuroimmune state

A large body of evidence supports the association between an altered neuroimmune state and BD, although it remains unclear if this reflects a trait or state marker of illness activity or both. The rationale stems from the so-called "sickness behavior," an interplay between inflammatory states and social and behavioural changes, which includes mood changes, social withdrawal and heightened sensitivity to both positive and negative social stimuli to help an individual to determine which persons might be supportive and which individuals will not and should be avoided, in order to better recruit help and care to facilitate recovery from sickness. Moreover, patients with mood disorders show comorbidities with autoimmune pathologies and subjects suffering of autoimmune diseases present an increased risk of developing BD **(6).** There is also preliminary pre-clinical evidence suggesting that traditional mood stabilizers modulate neuroinflammation and contrasting clinical results about the action of mood stabilizers on inflammation as well as some evidence exists about the adjunctive use of drugs with anti-inflammatory properties (i.e. acetylsalicylic, celecoxib and omega-3 fatty acids) for managing BD, in particular bipolar depression **(7).**

Variance in the inflammatory response seems to be associated with genetic variance in healthy subjects given a strong impact of genetic heritability on inflammatory molecules. A comprehensive study of cytokine production in healthy subjects showed that host genetics plays a significant role in inter-individual variability of cytokine production in response to different types of stimuli with particularly high genetic influence on monocyte derived cytokines, including the IL-1β/IL-6 pathway. In addition, the authors identified 17 new genome-wide significant loci (QTLs) that influence cytokine production, finding biological pathways that contain cytokine QTLs map to pattern recognition receptors (TLR1-6-10 cluster), cytokine and complement inhibitors, and the kallikrein system **(8).**

### Neuro-immune-developmental hypothesis

In comparison to healthy controls, BD offspring showed increased proinflammatory state during adolescence, an anti-inflammatory state during young adulthood and a virtually normalized immune state in adulthood. A background of reduced numbers of circulating CD3+ and CD3+CD4+ T cells is continuously presents, suggesting a partial T cell defect leading to a deregulated immune system. In particular, BD offspring showed increased inflammatory gene expression in monocytes, high serum PTX3 levels, but normal CCL2 levels during adolescence. In young adulthood, monocyte activation remained in a lesser degree with serum PTX3 levels remained high, and signs of monocyte migration became apparent through increased CCL2 levels. Finally at adulthood, circulating monocytes lost their activation state, but CCL2 levels remained increased suggesting a stronger migrating activity of these monocytes to the tissues. These results were replicated in another study that showed a high inflammatory state in adolescent BD offspring found reduced numbers of Tregs with high expression of pro-inflammatory genes in monocytes. The same studies demonstrated a reduced numbers of T cells capable of producing the proinflammatory cytokines IFN-γ and IL-17 during young adulthood. Finally, a stabilisation of these states at adulthood was reported with a reduced expression of pro-inflammatory genes in

monocytes. Of note, these temporal dynamic changes of the immune state seem to differentiate BD from major depressive disorder (MDD) as some studies suggested that MDD patients share with BD patients an early partial T cell defect but as opposed to BD this immunogical signature becomes more prominent with increasing age, also including an increased immune activation **(9).**

Altered neuroimmune state could be a candidate endophenotype for BD and in particular it speaks about a neuro-immune-developmental pathogenesis of BD. In particular, an early proinflammatory state either during pregnancy or adolescence **(10)** may perturb the fetal and young brain development shaping brain structures and in particular WM, followed by a virtually normalized immune state at adulthood with a background of continuously low-grade inflammation responsible of shortening telomere length and accelerated aging, leading to the characteristics symptoms of BD.

**Circadian rhythm instability**

Clinical features of BD, such as diurnal variation in mood, early morning awakening, and cyclicity and seasonality of recurrences, have led to speculation that dysregulation of circadian rhythm might be a central mechanism in the pathophysiology of BD. Disturbance of the sleep–wake cycle was found to be the most common prodrome of mania; experimentally induced sleep deprivation is associated with the onset of hypomania or mania in a considerable portion of patients; and antimanic drugs were shown to stabilize circadian rhythms **(11).**

Findings are conflicting with regard to whereas abnormalities in the circadian rhythm are state independent. Some evidence indicates that the circadian rhythm in euthymic BD patients is persistently unstable and can be aggravated with environmental influences, such as weather conditions and seasonal changes **(12).** Indeed, euthymic BD patients, compared with healthy controls, display trait-like alterations in several circadian features such as sleep time and time in bed, sleep onset latency, melatonin secretion and periods of being awake after sleep onset. In addition, in a systematic analysis of circadian rhythm activity in pedigrees segregating severe BD (BP-I), **Pagani et al. (13)** showed that euthymic BD patients slept longer and woke up later compared to their URs. The authors also provided evidence for a genome-wide significant linkage for inter-daily stability, a measure of day-to-day variability of the waveform of activity, near chromosome 12pter. Interestingly, in this genomic region some genes could influence circadian rhythm, including the histone lysine demethylase JARID1a (*KMD5A*) and calcium channel subunit 1C (*CACNA1C*). In contrast, a subsequent study that extended this pedigree and included independent control subjects found no sleep disturbance difference between BD patients, URs and controls, after adjustments for current mood symptoms. This could suggest that state characteristics play a role in circadian abnormalities in BD **(14).**

**Imaging endophenotypes**

White matter abnormalities (WMA) are abnormalities in the brain that are seen as bright foci on T2-weighted MRI scans. Most recent techniques include diffusion tensor imaging (DTI) and voxel-based morphometry (VBM). DTI draws maps of the diffusion pattern of water molecules, allowing the detection of microstructural details of normal or altered anatomy of a given region. One of the most used measures of WM DTI studies is fractional anisotropy (FA) which

describes the directional selectivity of the random diffusion of water molecules with higher FA values (maximum value is 1.0) are observed along heavily myelinated WM tracts. Voxel-based morphometry (VBM), is an automated MRI technique typically uses T1-weighted volumetric MRI scans and essentially performs statistical tests across all voxels (volumetric picture elements) in the image to identify volume differences between groups **(14).** Several studies showed widespread WM disruption in adults BD patients as well as in at-risk subjects.

Evidence of early WMA comes from studies on patients with a first episode BD. A meta-analytic study on this matter found reduced intracranial and WM total volumes in first-episode mania in particular in regions subserving emotional regulation, reward processing and cognitive function. Several studies have continuously reported decreased fractional anisotropy (FA) in WM tracts connecting circuits implicated in the impaired emotion regulation and reward processing in BD such as prefrontal cortex (PFC) regions with the ventral striatum and amygdala. These findings were confirmed by a more recent meta-analysis that found significant total WM volume reduction in first episode BD patients compared to controls. The authors also found some common brain abnormalities present in first-episode schizophrenia or BD with a significant overlap but whole grey matter volume deficits and lateral ventricular enlargement appear to be more prominent in first-episode schizophrenia whereas WM volume reduction seems more prominent in BD **(14).**

Fawzy et al. concluded that cognitive dysfunction is present in psychotic bipolar disorder patients and it is strongly inter-related with sociodemographic and clinical characteristics **(15).**

WMA as a putative BD endophenotype may have clinical implications. WMA were found to be predictive of lithium and antidepressant response in BD patients. On the other hand, lithium intake has been associated with neuroprotective effects on WM. In particular, higher FA associated with lithium use could reflect a direct influence of lithium on water diffusion or a beneficial effect on myelination as an increase in axial diffusivity has been linked to the duration of lithium treatment, and influenced by gene variants affecting *GSK-3* via the Wnt/β-catenin and the Akt/CREB pathways. Thus, it has been suggested that lithium treatment could counteract the WMA associated with BD **(16).**

Findings from twin, family, and association studies have revealed that much of the variability in WM tracts across multiple DTI measures is influenced by genetic factors and heritability estimates were high in bilateral WM tracts and the corpus callosum. In contrast to genetic influences, shared environmental influences were non-significant for either global or tract-specific influences **(17).**

**Anterior cingulate cortex and glutamatergic abnormalities**

The anterior cingulate cortex (ACC) is the frontal part of the cingulate cortex, with connections to both the limbic system and the prefrontal cortex. The ACC can be divided into two sub regions. The perigenual ACC (pACC) is responsible for processing emotions and regulating the endocrine and autonomic responses to emotions. The dorsal ACC (dACC), also known as the midcingulate cortex, is responsible for cognitive processing, specifically reward-based decision making **(18).**

Volume reductions in the ACC located ventral (subgenual) and anterior (pregenual) to the genu of the corpus callosum have been implicated by numerous studies of mood disorders.

Specifically, a volume reduction in the left subgenual ACC has been associated with familial MDD and BD by magnetic resonance imaging (MRI) morphometric measures and by post-mortem neuropathological studies, which have shown glial reduction in the corresponding grey matter. These findings of volume reduction of ACC are supported by other magnetic resonance imaging studies of the ACC in BD patients which have found reduced cortical thickness in the left anterior cingulate region independent of acute symptoms, suggesting state-independence **(19).**

This reduction in volume exists early in the illness across MDD and BD but seems to become more pronounced during illness progression, according to preliminary evidence in twins discordant for MDD. A volumetric MRI study found reduced subgenual PFC volume in subjects at high familial risk for BD. Consistently, another volumetric MRI study comparing URs of patients with BD or schizophrenia showed that anterior ACC abnormalities were specifically associated with genetic risk of BD. However, most recent studies on ACC volume and ACC cortical thickness failed to show any significant abnormalities in ACC in URs of BD compared to HC with the exception of one study **(20).** This discrepancy is likely due to small sample size and the presence of lifetime MDD diagnosis in the first-degree relatives of BD of the latter study.

The mechanisms underlying these structural ACC changes remain unclear. However, glutamate may be relevant in BD. In particular, the ACC contains abundant concentrations of glucocorticoid receptors that play a major role in attenuating the glucocorticoid response to stress. In addition, psychosocial stress enhancement glutamate release and may lead to glutamatergic toxicity **(21).**

There is considerable evidence for a high heritability of cortical thickness stress response and cerebral glutamate levels. Both stress response and glutamate levels have a neurotoxic effect through increases neuronal intracellular calcium levels leading to neuronal cell death or damage. Moreover, animal studies found an important role of the Metabotropic glutamate receptor 7 (*GRM7*) in early cortical development. For example, *Grm7* knockdown increases neural progenitor cell (NPC) proliferation, decreases terminal mitosis and neuronal differentiation, leading to abnormal neuronal morphology by interacting with CREB and Yes-associated protein (YAP). Overexpression of *Grm7* along with *Creb* knockdown, or *Yap* knockdown have shown to ameliorate these defects in neurogenesis. These findings may be relevant for BD since *GRM7* polymorphisms have been associated with the disorder **(22).**

Reduced cortical thickness along with glutamatergic abnormalities found in BD and URs bring together the endophenotype criteria of state independent and heritability. This putative endophenotype is not specific for BD; similar abnormalities were also found in MDD and schizophrenia. However, magnetic resonance spectroscopy studies have found disorder-specific changes of the central glutamate system. In BD, Glutamate–Glutamine (Glx) has found to be increased in all mood states. In contrast, reduced prefrontal and subcortical GLx has appeared as a consistent finding in MDD. Given the limited reliability and validity of symptom-based diagnostic methods to differentiate between unipolar and bipolar depression, glutamate-related imaging measures have the potential to significantly improve precision and neurobiological validity of mood disorder subtyping.

Taken together, a possible explanation for reduced cortical thickness in BD is a dynamic interplay between the genetic factors influencing brain morphology (i.e. glutamatergic and glucocorticoid system) and environmental factors (i.e. stress) starting from fetal development.

Cognitive, emotional and reward processing endophenotypes

**Attention and executive functions**

Comparative neuropsychological studies in severe psychiatric disorders showed that cognitive impairments in BD patients were similar to those of patients with schizophrenia or MDD with the differences being predominantly quantitative rather than qualitative. In particular executive dysfunction is a key contributor to psychosocial disability, poor occupational functioning and lower quality of life in BD. Executive functions is an umbrella term covering several functions involved in general-purpose control mechanisms, such as planning, inhibition and mental flexibility. Nevertheless, numerous studies and meta-analysis have shown deficits of executive functions across all phase of illness, including euthymia. Specifically, a recent meta-analysis found deficits across set-shifting, inhibition, planning, verbal fluency, working memory, and sustained attention in euthymic BD patients compared to controls **(23).**

Individual differences in executive functions are almost entirely genetic in origin as reported by a multivariate twin study of three executive functions (inhibiting dominant responses, updating working memory representations, and shifting attention between task sets) which found that executive functions are influenced by a highly heritable (99%) common factor that goes beyond general intelligence or perceptual speed. A highly heritable aspect of executive functions is executive attention, a process that involves dopamine-rich frontal areas including the anterior cingulate. In keeping with this, recent results suggest that the dopamine transporter gene (*SLC6A3*) polymorphism influences attentional processes. Specifically, individuals with the *9R allele* of the Dopamine transporter gene (*SLC6A3*), when compared to those *10R*, were characterized by less efficient orienting processes and poorer attentional switching. Of note, *SLC6A3* polymorphisms have been associated with BD by several studies. It has been suggested that prefrontal DA and dopaminergic system-related genes play a dominant role in modulating top-down but not bottom-up attention. Consistent with this, deficient top-down regulatory mechanisms during anticipation of reward and excessive emotion regulation during anticipation of losses is an important feature of BD patients as shown by fronto-limbic disconnection during reward anticipation in BD **(24).**

Regarding co-segregation of this putative endophenotype, there is compelling evidence that URs of BD patients show reduced executive functions including, executive control, sustained attention, abstract problem-solving, working memory, interference control, set-shifting and response inhibition, compared to healthy controls. Consistent with this, meta-analytic evidence indicated worse performance in URs in all cognitive domains studied, including executive functions. Although the effect sizes were small ($d < 0.5$), they were significantly different from healthy controls for executive function. This is particularly true for speed dependent measure of executive functions, a possible marker of abnormality of WM structure as speed of information processing relying on the efficiency of the whole brain network of cortical fibres connections. Interestingly, some evidence shows that a state of elevated inflammation that in turn led to elevated glutamatergic neurotransmission correlate with poor processing speed **(25),** implying an

interaction between inflammation, increased brain glutamate levels and cognitive impairments in BD subjects.

**Learning and memory**

Among cognitive functions, verbal memory deficits were consistently found in BD. Deficits of verbal learning and memory was found in euthymic bipolar patients providing evidence for the state independence of this dysfunction. Verbal learning deficits during the euthymic phase are associated with work disability and poorer clinical and functional outcomes, representing a major contributor to the overall burden of disability.Unaffected twins of BD patients also showed reduced short-term and long-term verbal learning and memory. This corroborates with deficits in verbal long-delay free recall and verbal recognition in URS of BD patients. However, evidence from meta-analysis studies in URs is conflicting. Indeed, some studies showed significant deficits in verbal memory, whereas a recent meta-analysis found no difference in verbal learning and memory between URs of probands with BD and controls **(26).**

In healthy subjects, verbal learning and memory were found to have a particularly high heritability with a genetic component explaining 56% of total variance found in a twin study on memory functions. In particular, this study demonstrated that monozygotic intraclass correlation was significantly larger than the dizygotic correlation for verbal learning and memory but not for response discrimination, learning strategy, and recognition. Neurobiological mechanisms that are potentially involved in the synaptic plasticity required for learning and memory include glutamatergic neurotransmission and changes in gene expression brought about by neurotrophic factors, such as cyclic adenosine monophosphate response element binding protein (CREB) and BDNF **(27).**

The presence of verbal learning and memory deficits in BD patients as well as in first-episode patients and HR subjects, suggest that these deficits are already evident early in BD and that these neurodevelopmental abnormalities have genetic underpinnings.

**Dysregulation of emotion and reward**

Individuals with BD are characterized by a dysregulation of the reward system. Heightened incentive motivation and compulsiveness toward reinforced behaviors are characteristic symptoms of the manic phase of BD, whereas loss of interest, lack of reactivity to positive events, and anhedonia are core features of the depressive phase of the disorder. First evidence of a dysregulation of the dopamine reward system came from observations that dopamine agonists induce mania-like behaviour in healthy individuals. Euphoria has been related to amphetamine-induced dopamine release in human ventral striatum. Enhanced rewarding effects of psychostimulants in patients with affective illness and induction of mania in individuals with BD has been proposed as a trait-like dysfunction of the dopaminergic system associated with impairment of the brain reward function **(2).**

Evidence of the heritability of reward abnormalities includes a functional polymorphism of the *COMT* gene that has been associated with the individual variation in the brain response to dopaminergic challenge **(28).**

Many studies investigating the dysregulation of the behavioural activation system (BAS) and found that individuals along the bipolar spectrum exhibit higher BAS sensitivity than controls even in a euthymic state. A prospective study also found that adolescents with no prior history of BD who exhibited an ambitious goal-striving cognitive style at baseline had a greater likelihood and shorter time to first lifetime onset of BD than those without this cognitive style. These findings suggest that the high reward sensitivity may be independent of mood state and a potential reward-related endophenotype **(2).**

Neuroimaging findings point to dysregulation of ventral striatum and mesial prefrontal cortex functions in BD. Increased metabolism in the striatum in both depressed and manic BD patients have been found, suggesting that elevated metabolic activity in the striatum may be a state-independent illness marker. Interestingly, an fMRI study found a greater ventral striatal and right-sided orbitofrontal (OFC) activity during anticipation, but not outcome, of monetary reward, in euthymic BD patients relative to healthy controls. Interestingly, there was no difference in neural activation between bipolar I and healthy control subjects during anticipation or receipt of monetary loss, suggesting specificity for reward-related fronto-striatal activity as putative trait-like endophenotype in BD **(29).**

Dysmodulation of reward and emotion processing and emotion regulation, including failure to down-regulate emotional reactivity to positive stimuli, may represent a specific endophenotype of BD given evidence of co-segregation of these traits in families at risk for BD. Behavioural studies have found that BD patients and URs compared to healthy controls showed a reduced ability to modulate risk taking in the face of certain types of stressors and increased trait impulsivity and impulsive decision-**making (30).**

Fronto-limbic disconnection during emotion and reward processing is a putative neuroimaging endophenotype for BD as it could mediate the relationship between the underlying susceptibility genes and the clinical expression of BD **(24).** Imaging studies have linked the behavioural features to WM integrity in cortico-limbic connectivity with possible deficient top-down regulatory mechanisms during anticipation of reward and deficient emotion regulation during anticipation of losses. In the reward circuitry, youth offspring of parents with BD exhibit altered patterns of frontal activation and ventrolateral prefrontal cortex-striatal functional connectivity than offspring of non-bipolar parents and of healthy parents. High-risk offspring had weaker functional connectivity between the pregenual cingulate and the right ventrolateral prefrontal cortex while anticipating rewards than did low-risk offspring, but had a stronger connectivity between these regions while anticipating losses. These studies joint to aberrant prefrontal activations and connectivity during reward processing in URs. Compared to health comparison subjects, BD patients and URs showed increased activity of the orbitofrontal cortex and the amygdala, related to heightened sensitivity to reward and deficient prediction error signal and in particular WMA coupled with a significant increased number of errors during set shifting and increased risk taking. This suggests that an altered myelination during development plays a role in the pathophysiology of BD **(31).**

**Impaired facial expression recognition**

Impairments in affective cognition are increasingly recognized as part of the neurocognitive profile and possible treatment targets in BD. Affective cognition may partially reflect neurocognitive functioning in social contexts and moderate the association between neurocognitive impairments and socio-occupational difficulties in BD. State- and trait-related affective cognitive impairments in BD have been observed across the three phases of the illness and the most consistent findings were trait-related difficulties in facial emotion recognition. Specifically, a recent systematic review by the International Society of Bipolar Disorder (ISBD) targeting cognition task force, identified global or selective facial emotion recognition deficits in 77% of studies of remitted patients and in 71% of studies of symptomatic BD patients **(32).**Both remitted and symptomatic patients showed difficulties in facial emotion recognition indicating that this may be a trait-related impairment in BD.

At the same manner, URs exhibit abnormalities at the behavioural and neural levels of emotion processing and regulation, including deficits in the recognition of emotional faces. Several studies showed consistent non-specific deficits in the recognition of facial displays of emotion in URs [for a review see **Miskowiak et al. (32).** These facial expression recognition problems in URs have been shown to be accompanied by aberrant frontal and/or limbic activation. Unaffected youths have been shown to exhibit decreased amygdala and inferior frontal gyrus response to angry facial expressions and exaggerated amygdala response to fearful (but not happy) faces. In contrast, a study of adult URs showed exaggerated amygdala response to happy (but not fearful) faces coupled with increased mPFC reactivity to both happy and fearful faces **(33).**

Taken together, there is consistent evidence for aberrant fronto-limbic activity to emotional faces in URs. The discrepancy in the direction the activity changes may be due to different experimental paradigms across studies (i.e., passive viewing vs. task-directed processing of faces), or could indicate age-related differences in individuals at familial risk for BD **(32).**

Notably, a pivotal study including 196 adolescent twins (47 monozygotic and 51 dizygotic pairs) provides the first evidence for heritability of neuroelectric indicators of face emotional processing and suggests that event-related brain potentials (ERPs) components sensitive to emotional expressions can potentially serve as endophenotypes. In particular, the amplitude of the ERP components N240 and P300 showed heritability to emotional response to happy, fearful and neutral faces. This study showed that a substantial proportion of the observed individual variation in these ERP responses can be attributed to genetic factors (36–64% for N240 and 42–62% for P300 components, respectively) **(34).**

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