Article

Thermoregulatory Fear of Harm Mood Disorder: In Depth Exploration of a Unique Juvenile-Onset Phenotype That Provides a Parsimonious Clinical Description of Certain Youths with Highly Comorbid Treatment Refractory Psychiatric Disorders

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ABSTRACT

Among aggressive youths with severe mood lability who frequently fail to benefit from mood stabilizers and antipsychotics there is a discrete subtype called 'Thermoregulatory Fear of Harm Mood Disorder' (FOH). This disorder is characterized by an underlying thermoregulatory deficit, a specific prodromal sequence and a unique constellation of symptoms. The underlying problem appears to be a deficit in thermoregulation resulting in excessive heat that manifests as thermal discomfort in neutral ambient temperatures and moderate to extreme cold tolerance, and produces REM sleep-related problems and parasomnias, such as night-terrors and hypnogogic hallucinations. Clinically, FOH is associated with the advent in childhood of frequent, recurrent, vivid nightmares with themes of pursuit and abandonment. The apparent psychological sequelae of exposure to this frightening imagery is fear sensitization and auto-traumatization. A developmental sequence of fear based defensive behaviors arises and includes obsessive bedtime rituals, fear of the dark, separation anxiety, contamination fears, hypervigilance, perfectionism, misperception of neutral stimuli as threatening, as well as reactive aggression in response to limit setting and perceived threat or loss. Ketamine, chosen as a potential treatment because of its effectiveness in reducing fear sensitization and dose-dependent lowering of body temperature in preclinical studies, has been associated with sustained

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improvement in otherwise refractory youths. We present a detailed description of this heritable disorder, link its clinical features to a potential disturbance in brain derived neurotropic factor (BDNF) and orexin, and indicate how ketamine rapidly affects BDNF through multiple mechanisms, to produce a dramatic beneficial response in youths with this disorder.

KEYWORDS: fear sensitization; juvenile bipolar disorder; aggression; ketamine; comorbidities

INTRODUCTION

This concept paper has three aims. The first is to further describe a novel clinical phenotype we call Thermoregulatory Fear of Harm Mood Disorder (FOH). The unique constellation of symptoms seen in FOH that are associated with fear sensitization can be frequently observed in some youths with early onset bipolar disorder [1,2]. These individuals experience intense fears related to abandonment, loss, injury and death, engage in aggressive behaviors directed toward self or others, undergo intense mood fluctuations, frequently require hospitalization and generally fail to respond to anxiolytics, antipsychotics, and mood stabilizers alone, but may experience sustained benefits from intranasal ketamine when combined with lithium salts. The second aim is to present a detailed neurobiological model that explains how a physiological abnormality—a deficit in thermoregulation—is both a critical etiological factor that initiates a prodromal symptom cascade, as well as a reliable marker for treatment response. Thirdly, we propose a molecular mechanism whereby a change in *Bdnf* gene expression, known to affect the development of fear sensitization and the establishment of a thermoregulatory set point, and alterations in orexin/hypocretin may underlie the development of this unique psychiatric phenotype. This understanding at the molecular level may also provide an explanation for the sustained effectiveness of the glutamate receptor antagonist, ketamine, in the treatment of this disorder.

CLINICAL PRESENTATION

Symptoms, Pathognomonic Features and Prodromal Sequence

FOH is a recently proposed clinical disorder that has been explored in seven published papers [1–7] and awaits independent validation. The modal FOH patient is a child between 6–12 years of age, who comes to clinical attention because of intermittent, rageful temper tantrums during which objects are broken and physical or verbal aggression is directed at self or others in response to separation from caretakers, unexpected changes in routine, perceived rejection or criticism, attempts to set limits or a parental “No” [1,2,4–7]. Clinical assessment reveals an

array of symptoms including affective lability with clear periods of sadness as well as a brief manic-like state characterized by increased goal-directed activity ("mission mode"), talkativeness and irritability if thwarted [1,2,4–7]. Comorbid symptoms of anxiety (separation anxiety, phobias with possible panic attacks), oppositional defiance, non-suicidal self-injury, violent obsession, inattention, impulsivity and features of post-traumatic stress disorder (PTSD) are present to varying degrees [1,2,4–7]. There are also some highly specific and potentially pathognomonic symptoms. The first is a thermoregulatory disturbance in which individuals feel uncomfortable (excessively hot, sweating) at neutral ambient temperatures and are moderate-to-extremely cold tolerant [2–4]. The second is a prominent sleep wake disorder with sleep onset insomnia, parasomnias (night-terrors, enuresis, bruxism, sleep-walking and sleep-talking), REM sleep-related problems (REM intrusions) and Nightmare Disorder (vivid, recurrent nightmares with themes of pursuit, death and abandonment) as well as morning sleep inertia [3,4,7]. The crucial features are the vivid nightmares and night terrors. Developmentally, a prodromal sequence of fear-based defensive behaviors arises and includes obsessive bedtime rituals, fearfulness of intruders, fear of the dark, separation anxiety, germ contamination fears, hypervigilence, misperception of neutral stimuli as threatening, and reactive aggression in response to limits, perceived threat or loss [2,4].

Auto-Traumatization

Our impression is that these individuals auto-traumatize to these terrifying nocturnal events and develop a posttraumatic reaction. A diagnosis of PTSD requires experiencing a Criterion A trauma defined as exposure to actual or threated death, serious injury, or sexual violence, which can be experienced, witnessed, or indirectly perceived (e.g., learning that the event occurred to a close relative or friend) [8]. Individuals with FOH repeatedly experience being severely injured, violated or killed in their nightmares, or experiencing doing these things to close family or friends [1,2,4,7], which we suspect may be quite traumatizing. In addition to experiencing trauma a DSM-5 diagnosis of PTSD requires at least 1 Criteria B and C and 2 Criteria D and E symptoms [8]. Individuals with FOH generally have: Criterion B intrusive symptoms consisting of emotional distress and physical reactivity to traumatic reminders; Criterion C avoidance symptoms, particularly attempts to avoid sleep; Criterion D negative alterations in cognition and mood, such as negative self-appraisal, shame, negative affect, feeling isolated and Criterion E alterations in arousal and reactivity including irritability and aggression, risky or destructive behavior, hypervigilance, heightened startle reactions, difficulty concentrating and difficulty sleeping [1,2,4–7]. Hence, a key component of FOH is the emergence during childhood or adolescence of an auto-traumatized variant of PTSD in addition to a

profound mood disorder, fear-based obsessions, aggressive behaviors, sleep disorder and thermoregulatory problems.

Impairment and Outcome

This is without doubt an extremely serious disorder. The child's symptoms typical increase to the point that they are no longer able to attend school because of their intense fears and have lost all or nearly all of their friends. Fifty-five percent of FOH youths in our recently reported sample had one or more psychiatric hospitalizations prior to successful treatment [4]. They received at various times one or more of the following diagnoses: major depression; bipolar disorder; separation anxiety disorder; simple phobias; social phobia; generalized anxiety disorder; disruptive mood dysregulation disorder; oppositional defiant disorder; nightmare disorder; ADHD and obsessive-compulsive disorder. Typically, they have been prescribed mood stabilizers (e.g., lamotrigine, lithium, oxcarbazepine, topiramate and valproate), atypical antipsychotics (e.g., aripiprazole, asenapine, clozapine, fluphenazine, olanzapine, quetiapine, risperidone and ziprasidone) and anxiolytics (e.g., clonazepam and lorazepam) with minimal benefit [4]. We have reported in both acute [6] and long-term [4] case series the clinically beneficial effects of intranasal ketamine in this population. After initiation and titration of intranasal ketamine they were often able to attend regular school, had ceased fighting with parents, were making new friends and were on a simpler drug regimen [4].

Diagnostic Criteria

Box 1 presents our latest version of a DSM-like set of diagnostic criteria for FOH intended primarily for clinicians who wish to identify individuals with this disorder in their patient population, and for researchers who wish to further study this proposed diagnosis. Criteria include: (A) the presence of a prominent mood disorder with episodic and abrupt transitions that fits within the broadest conceptualization of bipolar disorder [9]; (B) fear of physical harm with associated emotions and perceptions; (C) a characteristic disturbance in thermoregulation and heat dissipation; (D) a characteristic disturbance in sleep with nightmares and fear sensitization; and (E) reactive aggression directed towards self or others. The number of required symptoms within each category (and the number of required categories) should be taken as a guide that will likely be revised with further study, particularly as FOH may be better understood from a dimensional than categorical perspective [2]. Participants with FOH in prior studies [1–4,6] were diagnosed based on history of DSM-IIIR or DSM-IV bipolar disorder (bipolar I, bipolar II or bipolar NOS) and presence of aggressive obsessions on the Yale–Brown Obsessive Compulsive Scale (YBOCS) [10] (as captured in category B) and measures of extreme physical aggression towards self or others on the Overt Aggression Scale (OAS) [11], as

captured in category E. About 1/3 youths with pediatric bipolar disorder (PBD), or at high risk based on family history, had all, or nearly all, symptoms as originally conceptualized and 1/3 had none [11]. This suggests that many youths with PBD will have at least some symptoms of FOH. Further research is required to understand the prevalence and potential therapeutic implications of FOH symptoms in PBD in general, particularly alterations in thermoregulation and auto-traumatization which may be the most discriminatory features.

Box 1. Diagnostic criteria for thermoregulatory fear of harm mood disorder in DSM style format.

A–F are required for diagnosis and must be present most days for at least 6 months, without any symptom free periods that exceed 2 months in duration and cause functional impairment in one or more settings (e.g., significant behavioral problems at home but not necessarily in the school setting).

A. Mood Disorder. (Typically characterized by episodic and abrupt transitions in mood state accompanied by rapid alternations in levels of arousal, emotional excitability, sensory sensitivity, and motor activity).

1. Meets DSM-5 criteria for any form of bipolar disorder (bipolar I, bipolar II, mixed episodes, major depression with short duration mania, major depression with insufficient criteria hypomania, hypomania without major depression, cyclothymia). Manic, hypomanic and mixed episodes are defined by DSM-5 symptom criteria but not by DSM-5 duration criteria.

B. Fear of Harm. (Fear that physical harm will come to self or others; easily misperceives and experiences neutral stimuli such as tone of voice or facial expression as threatening; obsessive bedtime rituals; fear of the dark; fear of intruders; separation anxiety; contamination fears; hyper-vigilance).

Three (or more) of the following are required:

1. Obsessive fears that something awful may happen to self or significant others
2. Obsessive fears that they will harm themselves or others
3. Reacts with excessive anxiety and fearfulness in novel situations or with strangers
4. Reacts with excessive anxiety in situations involving separation
5. Is self-conscious and feels easily humiliated in social situations
6. Easily misjudges other people as threatening, intimidating or critical

C. Thermoregulatory Disturbance. (Experiences thermal discomfort such as feeling hot, or excessively sweating in neutral ambient temperature environments, as well as little or no discomfort during exposure to moderate or extreme cold, and alternates noticeably between being excessively hot in the evening and cold in the morning).

Two (or more) of the following are required:

1. Feels excessively warm/hot at bedtime or overheats during the night
2. Feels cold in the morning having felt hot at bedtime
3. Feels excessively warm during day in neutral temperatures
4. Has moderate to extreme cold tolerance (able to go out into the cold without a jacket)
5. Overheats or sweats profusely with exertion

Box 1. *Cont.*

D. Sleep Disorder. (Most specifically characterized by highly disturbing nightmares or night terrors resulting in fear of going to sleep and auto-traumatization).

Two (or more) of the following

Frequent night-terrors or nightmares – often containing images of gore and mutilation
Fear of going to sleep because of disturbing dreams
Hypnogogic hallucinations
Excessively restless sleep

(Note insomnia/hypersomnia and other parasomnias not included as they are often occur in mood disorders without FOH).

E. Aggression. (Territorial and reactive aggression in response to limit setting and perceived threat or loss including aggressive fight-based speech or actions or self-directed aggression such as head banging, cutting or scratching self, suicidal thoughts or actions).

Two (or more) of the following are required:

1. Excessively aggressive or controlling speech (critical, sarcastic, demanding, "bossy")
2. Excessive anger and oppositional/aggressive responses to situations that elicit frustration
3. Self-directed aggression (head-banging, skin-picking, cutting, suicidal ideations or actions)
4. Temper tantrums
5. Often threatens or breaks objects, slams doors, smashes walls

F. Symptoms are not due to a general medical condition (e.g. hypothyroidism). Criteria may overlap with symptomatology from other DSM classifications.

G. Family history of bipolar disorder. Lends further support to the diagnosis.

Research Domain Criteria (RDoC) were developed by NIMH to provide a means of understanding the nature of mental health and illness in terms of dysfunctions in specific psychological/neurobiological systems [12]. RDoC was not designed to serve as a diagnostic guide, nor to replace current diagnostic systems. However, we thought that it would be helpful for researchers if we delineated the RDoC systems, constructs and subconstructs that appear to be affected in youths with FOH. These are outlined in Table 1 and include nearly all systems, though the major alterations appear in the Arousal and Regulatory, Negative Valence and Social Processes Systems.

Table 1. RDoc Domains and Categories (in bold) that Appear to be Implicated in Thermoregulatory Fear of Harm Mood Disorder (FOH).

Domains	Categories
Negative Valence System	1. Frequent, inappropriate and sustained states of **Acute Threat ("Fear")** (e.g., in restaurants, school or at bedtime). 2. Characteristically in state of **Potential Threat ("Anxiety")** or **Sustained Threat** when not experiencing **Acute Threat**. 3. Periods free from **Threat** are rare and short-lived. 4. Episodes of extreme **Frustrative NonReward**–as manifest in temper tantrums and rages.

Table 1. *Cont.*

Domains	Categories
Positive Valence System	1. Basal state of low **Reward Responsiveness** and low **Reward Valuation**. 2. Occasional brief spontaneous periods of high **Reward Responsiveness** and high **Reward Valuation**.
	Cognitive System
	Occasional brief spontaneous periods of impaired **Cognitive Control** in which **Goal Selection** and **Response Selection** become fixated on a narrow set of goals and actions.
	Social Processes
	1. Disrupted **Affiliation and Attachment** characterized by overattachment to parental figure, deficient affiliation with others and social withdrawal; resulting in limiting and constrained friendships. 2. Impaired **Social Communication** in which **Reception of Facial and Non-Facial Communication** are misconstrued as threatening or disapproving. 3. Impaired **Perception and Understanding of Others** in which the **Actions** and **Mental State** of others are misconstrued as threatening or disapproving. 4. Impairment in P**erception and Understanding of Self** > **Self Knowledge** characterized by unshakable, highly negative or critical thoughts about self (abilities, self-worth).
Arousal and Regulatory Systems	1. In state of high **Arousal**, particularly when experiencing **Acute Threat.** 2. Oversensitivity to environmental stimuli producing state of high **Arousal**. 3. Disruption in **Circadian Regulation** of temperature / heat dissipation as manifest by feeling excessively warm at night and cold in the morning with moderate to extreme tolerance to cold and intolerance of heat. 4. Disruption in **Circadian Regulation** of temperature as manifest in deficient heat transfer from core to proximal extremities while endeavoring to fall asleep, resulting in delayed or absent DPG^0 during sleep initiation. 5. Prominent disturbance in **Sleep Wakefulness** as characterized by difficulty falling asleep, difficulty arising, frequent intense nightmares, REM intrusions and other parasomnias.
Sensorimotor Systems	Motor actions match **Negative** and **Positive Valence Systems** and **Arousal** states.

IDENTIFICATION OF THE PHENOTYPE

Heritability of Clinical Features in Youths with Bipolar Disorder

Thermoregulatory Fear of Harm Mood Disorder (FOH) emerged from an effort to identify the genetic associates of pediatric bipolar disorder (PBD) [5] using an endophenotype approach similar to Cheng *et al.* [13] and Faraone *et al.* [14]. The Child Bipolar Questionnaire (CBQ) [15], a 65 item, self-administered, parent report measure derived from Depue *et al.*'s [16] dimensional approach to the identification of adults at risk for bipolar disorder, was used to assess the range and severity of symptoms seen in a large sample of youths who had been given a community diagnosis of bipolar disorder or were at high risk for developing this disorder based on an enriched family history [5]. A factor analysis of the CBQ was conducted using N = 2795 children who screened positive for PBD on the CBQ. The resulting factors were used in a concordance analysis between N = 260 proband/sibling pairs and N = 260

proband/matched comparison pairs. Factors extracted included: fear of harm, depression, aggression, mania, sleep-cycle problems, anxiety and executive function deficits. Of the ten factors extracted from the CBQ the strongest concordance coefficients (rho) between probands and siblings, and the widest contrasts between proband/sibling *vs.* proband/comparison pairs, were for the Fear of Harm factor, that implicates this as an important heritable trait [5].

Fear of Harm Index

The CBQ was then used to further elucidate FOH in children with community diagnoses of PBD or at risk for the illness because of on enriched family history (*N* = 5335). Included were all subjects who had >40 positively endorsed CBQ symptom items at frequencies of very often, almost always, and always and were diagnosed with all forms of PBD (e.g., BPI, BPII and BPNOS). This group was divided randomly into two groups, an exploratory group (*N* = 2668) and a hypothesis testing (study) group (*N* = 2666) [2]. A FOH Index was created using six items from the Yale–Brown Obsessive Compulsive Scale (YBOCS) and two items from the Overt Aggression Scale (OAS) [11]. The YBOCS items were measures of aggressive obsessions (*i.e.*, fear might harm self, fear might harm others, fear harm might come to self, fear harm will come to others—may be because of something the child did or did not do, fear of acting on unwanted impulses and fear they will be responsible for something else terrible happening). The OAS items were measures of extreme physical aggression (*i.e.*, mutilates self, causes deep cuts, bites that bleed, internal injury, fracture, loss of consciousness, loss of teeth and attacks others causing severe physical injury). The score consisted of the number of YBOCS items rated by parents as occurring “often”, “very often” or “almost constantly” and number of OAS items rated 2 or higher. It was found that 1/3 met all criteria for the phenotype (FOH index ≥_7), 1/3 had no symptoms of FOH (FOH Index = 0), and 1/3 had symptom severity somewhere between these extremes. Compared to children with PBD who have no or low FOH, children with high FOH had significantly higher indices of severity of mania and depression and greater number of hospitalizations. The groups did not differ in age of onset, age at first diagnosis or age at first hospitalization. FOH therefore constitutes a large proportion of children diagnosed with cycling mood disorders who are among those that demonstrate the most significant levels of pathology.

THERMOREGULATION AND SLEEP

FOH and Temperature Sensitivity

In addition to the CBQ items that defined behaviors linked to FOH, a cluster of symptoms were identified during clinical evaluation that are highly suggestive of a disturbance in temperature sensitivity and regulation. Patients with FOH were noted to experience thermal

discomfort (e.g., feeling hot, excessive sweating in neutral ambient temperatures or on exercise) but no discomfort during exposure to moderate or extreme cold. Further, they would noticeably alternate between being excessively hot in the evening and cold in the morning. Individuals with FOH typically wear few layers of clothes in cold temperatures, and frequently complain of being hot even when others are comfortable. Overheating and the sequelae of peripheral vasodilation; facial flushing, deep red, warm pinnae of the ears and dark circles under the eyes often accompany “affective storms”, panic or aggressive behaviors in response to stressors, which has been labeled as psychogenic or emotional hyperthermia [17].

This unique group of seemingly independent traits, associated with an aberrant response to a perceived threat and a disturbance in thermoregulation, are considered central to the clinical presentation of the phenotype. We believe that the temperature-related symptoms associated with FOH are overt manifestations of an impaired ability to dissipate heat, particularly in the evening hours near the time of sleep onset and thereby interfere with the circadian sleep initiation process as well as transitions between sleep arousal states that typically have a 1–2 h ultradian periodicity [3].

Brain Temperature Homeostasis

This makes sense as temperature has a critical impact on sleep as well as on a vast array of other brain functions. The homeostatic imperative to maintain core body temperature has been well known since the time of Claude Bernard and Walter B. Cannon. However, there is increasing awareness that there is also a more specific homeostatic challenge of maintaining brain temperature as CNS function can be dramatically affected by slight shifts in temperature and the brain is more vulnerable to hyperthermic damage than other organs. Further, the brain, like a computer CPU, has a tremendous potential to run hot and overheat. Brain cells utilize 300–2500 times more energy than the average body cell [18] causing the brain to consume 20% and 25% of total body oxygen and glucose though it only accounts for about 2% of body weight [19]. Intense heat production is an essential feature of brain metabolic activity as all energy used for brain metabolism is eventually transformed into heat [18].

In general, brain regions at rest are about 1 °C warmer than arterial blood, though different brain regions maintain different specific temperatures [18,19]. Sensory stimuli, such as tail pinch or change in cage placement of rats, produces a very rapid ~1–2 °C rise in the temperature of specific brain regions and the subsequent increase in blood flow may play an important role in cooling as well as increasing delivery of oxygen and glucose [18]. Further, natural occurring fluctuations in brain temperature affect membrane potentials, burst firing rates, and the release and reuptake of neurotransmitters [18]. Temperature sensitive neurons, critical for thermoregulation, were

initially identified as a discrete population of cells in the preoptic/anterior hypothalamus (POA). They have since been identified in visual, motor and somatosensory cortex, hippocampus, brain stem and substantia nigra [18]. The medial thalamus and suprachiasmatic nucleus actual have a greater percentage of thermosensitive neurons than the POA [18]. A wide range of sensitivity is achieved through the participation of distinct types of channels that are each sensitive to narrow yet overlapping ranges in temperature [20,21]. A great deal more needs to be learned regarding brain processes responsible for brain temperature homeostasis and the clinical consequences that might ensue from abnormalities in heat dissipation from the brain.

Sleep and Body Temperature

The relationship between sleep and core body temperature however, is reasonably well understood. Sleep is governed by both a circadian process, most clearly reflected in the ~24-h rhythms in core body temperature and melatonin release, and a homeostatic process in which sleep debt progressively accumulates during wakefulness and is paid down by time spent in restorative slow wave sleep (SWS) [22]. Core body temperature decreases during the normal sleep onset period in humans as part of the underlying circadian rhythm and sleep further facilitates this reduction. The primary mechanism driving the reduction in core body temperature is increased blood flow to the skin, which is rich in arteriovenous anastomoses that play a critical role in thermoregulation [23]. These anastomoses open when noradrenergic vasoconstrictor tone declines, shunting blood from arterioles directly into the venous plexuses of the limbs [23], promoting greater inflow of heated blood from the core and facilitating heat loss to the environment through the skin surface [23,24]. This selective vasodilation of distal skin regions promotes the rapid onset of sleep and is strongly associated with melatonin secretion [24]. After sleep onset, core temperature continues to gradually decline while distal and proximal skin temperature remain elevated [24]. Higher measures of skin temperature are associated with increased sleep efficiency and time spent in SWS [24].

Homeothermic animals need to thermoregulate during sleep but capacity to do so varies by sleep stage. Shivering during sleep, as a defense against cold, is confined to stages 1 and 2. Sweat rate and heat dissipation are maximal during SWS. REM sleep is most significantly influenced by ambient temperature but during this stage thermosensitivity is markedly reduced and there is a delayed onset of sweating, decreased sweat rate, diminished evaporative heat loss and reduce heat tolerance [24]. To compound matters brain activity during REM is metabolically demanding. Previously known as paradoxical sleep, REM is characterized by rapid eye movements, cortical activation resembling wakefulness, vivid dreaming and skeletal muscle paralysis (atonia) [25]. Playing a central role in REM is the subcoeruleus nucleus

(part of the locus coeruleus/subcoeruleus complex), which produces REM paralysis through glutamineric connections to neurons in the ventromedial medulla and spinal cord that inhibit motor neurons through the combined action of GABA and glycine [25]. This sleep paralysis is critical as otherwise REM would be accompanied by vocal outbursts and violent arm and leg movements as seen in REM behavior disorder. Hence, both brain and core body temperature increase during REM and can pose a hyperthermic challenge if heat is not adequately dissipated. Conversely, core body and brain temperature fall to their lowest levels during SWS.

Body Temperature and Waking

Waking at normal times occurs in conjunction with rising core body temperature and falling peripheral temperature [26]. Two ascending pathways stimulate wake maintenance. One is a cholinergic pathway from the pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei to the thalamus that activates thalamic relay neurons crucial for information transmission to the cortex [22]. These cells are active during waking and REM sleep and much less active during NREM. The second branch originates from monoaminergic cell groups in the locus coeruleus (LC), dorsal and medial raphe, ventral periaqueductal grey (vPG) and tuberomammillary (TM) neurons that provide noradrenergic, serotonergic, dopaminergic and histaminergic projections to the lateral hypothalamus, basal forebrain and throughout the cerebral cortex. These neurons are most active during waking, less activity during NREM sleep and are silent during REM [22]. The cell groups involved in wakefulness are reciprocally interconnected with the ventrolateral preoptic area which is primarily active during sleep and releases the inhibitory neurotransmitters galanin and GABA. Together these regions function as a ‘flip-flop’ switch toggling between sleep and wakefulness. This type of self-reinforcing loop produces relatively abrupt transitions between sleep and wakefulness but is inherently unstable [22]. Orexin projections from the hypothalamus with prominent connections to LC, raphe, vPG and TM promote wakefulness and stabilize the system by orchestrating the interaction between the various cell body regions involved in wakefulness [27]. Loss of orexin neurons in narcolepsy result in unstable shifts between wakefulness and sleep as well as bouts of cataplexy that stem from the intrusion of the REM sleep paralysis mechanism into wakefulness [25].

One might assume that alertness would be optimal shortly after awakening due to diminished sleep debt. That however is not the case as there is a significant degree of sleep inertia following waking that persists from minutes to hours. Interestingly, the decline in subjective sleepiness correlates very strongly with the rate at which the extremities cool and heat transfers from the periphery to the core in a process that mirrors the shift in temperature during sleep initiation [26].

Impaired Regulation of Nocturnal Temperature and Sleep in FOH

The presence of a thermoregulatory disturbance was confirmed in children with FOH via thermal skin patches placed on the child's lower left calf (distal) and subclavicle region (proximal) prior to and following sleep onset, which was assessed using actigraphs [3]. The key metric was the distal-to-proximal (DPG) thermal gradient defined as distal-minus-proximal temperature. This gradient has been validated as a measure of heat dissipation and it is well-known that distal temperature is lower than proximal temperature prior to sleep, that distal temperature rises and proximal temperature falls and that distal temperature generally exceeds proximal temperature until shortly before awakening. Interestingly, the point where proximal and distal temperatures meet and cross over (DPG^0) is highly coincident with sleep onset and plays an important permissive role in sleep initiation and awakening [28–31]. Proximal temperatures in children with FOH tended to run high throughout much of the night, delaying the onset of DPG^0 by nearly an hour and in some children with FOH DPG^0 failed to occur at any time [3]. In short, children with FOH appear to have a problem dissipating heat during the night and this disturbance was associated with delayed sleep onset, and serves as a risk factor for REM intrusions, nightmares, parasomnias and morning sleep inertia. We consider this thermoregulatory deficit a potential biomarker for FOH with possible causal implications.

These findings are consistent with our hypothesis that alterations in neural processes that underlie thermal regulation sets the stage for the development of sleep disorders, fear sensitization and poor modulation of aggression and other survival-based behaviors that are the manifest phenotypic features of FOH. Disturbances in all of these functions may be linked to a compromised orexin system that no longer provides appropriate regulation of the expression of these behaviors, nor smoothly executes survival based homeostatic functions [32]. Indeed, many of the aberrant behaviors seen in youths with FOH, for example separation anxiety and fear based aggressive responses to perceived threat, are best understood as responses to existential threat. Individuals with these phenotypic features appear to have a very similar pattern of response to psychopharmacological treatments, suggesting that this is a relatively homogeneous disorder with a common molecular basis.

FOH AND THERAPEUTIC RESPONSE

First Line Treatment *versus* Ketamine

Although FOH was initially recognized as a severe variant of juvenile onset bipolar disorder it became clear that individuals fitting this clinical description rarely experienced a meaningful clinical response to first-line treatments including atypical antipsychotics and mood stabilizers. Ketamine was selected as a tertiary treatment for these

severely ill and refractory youths based on success in adults with refractory mood disorders [33] and because of its effectiveness in reducing fear sensitization and dose-dependent lowering of body temperature in preclinical studies [34,35]. Remarkably, almost all experience a robust and sustained clinical response to intranasal ketamine administered approximately every 3 days. Indeed, we recently reported in a detailed assessment of individuals receiving extended treatment with intranasal ketamine for FOH, that these individuals were currently taking an average of 3 psychotropic medications prior to ketamine [4]. Overall, 80% were taking one or more atypical antipsychotics, 60% mood stabilizers, 29% antidepressants and 17% anxiolytics. Despite these treatments, they were seen as severely ill (Clinical Global Impression = 5.7 ± 0.7), with 10 of 48 patients rated as "amongst the most severely ill" by at least one of the two raters, and 53% had one or more psychiatric hospitalization prior to initiation of ketamine. Following ketamine, 21% were rated as very much improved and 67% were rated as much improved, with no subsequent hospitalizations over a more than 2 year follow up period [4].

To date we have restricted treatment with intranasal ketamine to youths with clear features of FOH and do not know how efficacious ketamine would be in refractory youths with bipolar disorder but without FOH. Overall, there is a pressing need for randomized, double-blind, placebo-controlled trials of ketamine in refractory PBD both with and without FOH.

It is important to note that the effects of ketamine were holistic and not limited to effects on mood. Indeed, an almost immediate effect of intranasal ketamine is to foster heat dissipation and patients often notice facial flushing, reddening and warming sensation in the pinna of the ears, and that the soles of their feet become quite warm during treatment. Effectively treated individuals typically lose much of their cold tolerance and the return of heat sensitivity and cold tolerance over the next few days heralds their need to receive another ketamine treatment in order to maintain benefits. Overall, pre-post differences in ratings were strongest for the factor that included the core FOH phenotypic features [4]. Hence, understanding the mechanism of action of ketamine may provide insight into the pathophysiology of FOH.

Direct Effects of Ketamine

Initial reports of a rapid and sustained antidepressant effect of ketamine, and subsequent studies showing its benefits in treatment refractory depression, anxiety, bipolar disorder, PTSD and suicidality [33,36–39], has stimulated a great deal of interest in the potential mechanism of action. Briefly, ketamine is a 50–50 racemic mixture of *R*- and *S*- optical enantiomers that act as non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonists. The simplest theory is that ketamine works through direct NMDA receptor inhibition. Interestingly,

while ketamine would be expected to block excitatory glutamatergic neurotransmission via NMDA inhibition, it actually increases prefrontal cortical activity in healthy volunteers; likely due to a preferential inhibition of NMDA receptors located on GABAergic interneurons leading to a disinhibition of pyramidal neurons and enhanced glutamatergic firing [40]. In addition, ketamine blocks extra-synaptic NMDA receptors which are tonically activated by low levels of ambient glutamate [40] and it inhibits NMDA receptor-dependent burst firing activity of the lateral habenula, which is associated with depressive symptomatology [41]. However, while these actions may contribute to ketamine's antidepressant effects it appears that these are not the primary mechanism of action. We know this, in part, because other NMDA channel-blocking antagonists do not provide antidepressant effects of comparable magnitude, immediacy or duration [40]. Similarly, there is reasonable evidence that the R-enantiomer of ketamine has a superior and longer lasting antidepressant effect then the *S*-enantiomer, though the later has a 4-fold higher affinity for the NMDA receptor [40]. Further, deuteration of ketamine at the C-6 position, which does not affect NMDA receptor binding, but does inhibit conversion to (2*S*,6*S*;2*R*,6*R*)-hydroxynorketamine (HNK), blocks its antidepressant effects in animal models, suggesting that this metabolite is an essential component. Consistent with this finding is the observation that (2*R*,6*R*)-HNK is a more effective antidepressant than (2*S*,6*S*)-HNK, though the *R* enantiomer does not appear to have any effect on NMDA receptors at therapeutic doses [40]. Rather enantiomers of HNK appear to facilitate signaling through the α-Amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) glutaminergic receptor, which are the primary receptors responsible for the transduction of fast synaptic neurotransmission in the brain [40].

Downstream Effects of Ketamine on Brain Derived Neurotrophic Factor

Although ketamine and its HNK metabolite have a multitude of direct effects at least four of these exert convergent downstream effects on brain derived neurotrophic factor (BDNF). The disinhibition of glutamate release through ketamine's effect on GABAergic interneurons stimulates post-synaptic AMPA receptors that are also facilitated by (2*S*,6*S*;2*R*,6*R*)-HNK resulting in enhanced release of BDNF [40]. Further, ketamine inhibition of extrasynaptic NMDA receptors, which are tonically activated by low levels of ambient glutamate, serves to disinhibit phorphorylation of eukaryotic elongation factor 2 kinase (eEF2K) resulting in an increase in protein translation in general and BDNF translation in particular [40]. Similarly, (2*R*,6*R*)-HNK also suppresses eEF2K phosphorylation and increases BDNF translation through a non-NMDA mediated mechanism [40]. The net result is that within minutes ketamine produces a marked and sustained increase in BDNF levels. Antidepressants also produce an increase in BDNF but only after several

weeks of treatment. Blocking the effects of ketamine on BDNF, or the downstream molecular effects of BDNF, blocks antidepressant response to ketamine in animal models [40]. Hence, this is likely a key effect of ketamine and leads in turn to the question regarding the relationship between BDNF and the phenotypic features of FOH.

BRAIN DERIVED NEUROTROPHIC FACTOR AND FOH

Function and Structure of BDNF

BDNF is a critically important protein that is synthesized and released by neurons in the brain and cells in the periphery. It exerts a vast array of effects that depend on location and stage of development. During development BDNF supports neuronal survival, growth and differentiation while promoting connectivity, neuroplasticity, neurogenesis as well as synapse, spine and dendrite formation in the mature brain. BDNF acts within minutes to enhance glutamatergic and reduce GABAergic synaptic transmission in CNS neurons [42]. Chronic exposure to BDNF enhances the formation and functional maturation of glutamatergic and GABAergic synapses [42] and has widespread effects on the serotonin systems [43,44]. It also plays a critical role in cycling of synaptic vesicles in rapidly firing neurons and is a crucial mediator of long-term potentiation (LTP) in multiple brain regions [42].

The human *Bdnf* gene has a complex structure consisting of 11 exons in the 5' end and nine promoters [45,46]. The coding sequence resides in exon 9, with eight upstream promoters regulating regional and cell-type-specific expression [46,47]. Each of the different *Bdnf* transcripts encode the exact same BDNF protein [45,46]. However, the selective expression of distinct *Bdnf* transcripts, that are specific to various tissues or cell types and responsive to different stimuli, explains how BDNF can effectively mediate such a wide array of behavioral and molecular functions [44].

As indicated above FOH is characterized by a deficit in thermoregulation, sleep disturbance, extensive periods of depression and brief periods of mania, intense fear-based obsessions, aggression towards self and others and characteristic features of PTSD. Many youths with FOH also experience carbohydrate craving. There is good support for BDNF playing a role in all of these aspects of the disorder.

BDNF and Thermoregulation

Translational studies indicate that BDNF is involved in two key aspects of thermoregulation. First, BDNF in the anterior hypothalamus has been reported to play an essential role during a critical developmental phase in the fine-tuning of a thermal-response set point in chickens [48]. Antisense attenuation of *Bdnf* in this region at this critical stage produces an enduring deficit in thermoregulatory capacity [48]. The critical step involves the epigenetic methylation and histone

modification of *Bdnf* gene promoters in the hypothalamus [49,50]. Presumably specific epigenetic modifications to *Bdnf* promoters during this critical period serve to regulate the emerging balance between warm and cold sensitive neurons in this region [48]. Second, these warm-sensitive neurons (WSNs) within the mammalian preoptic hypothalamus function to orchestrate the homeostatic response to heat [51] as their optogenetic excitation triggers rapid hypothermia, mediated by reciprocal changes in heat production and heat dissipation, as well as dramatic cold-seeking behavior [51]. BDNF likely plays an import role in their function as these neurons are molecularly defined by their co-expression of BDNF and pituitary adenylate cyclase-activating polypeptide (PACAP) [51].

BDNF and Sleep

Both clinical and translational studies show that BDNF plays a crucial role in the homeostatic regulation of REM and non-REM (NREM) slow-wave sleep (SWS). First, translational studies show that the homeostatic increase in sleep pressure for restorative SWS that builds during wakefulness is further moderated by the amount of exploratory behavior and cortical activation that occurs during this time, and that this is mediated by the degree of cortical BDNF expression [52–54]. More specifically it appears that activity-dependent BDNF expression increases sleep pressure by acting through tropomyosin receptor kinase B (TrkB) receptors on a subset of cortical and hippocampal GABAergic interneurons that express the neuropeptide cortistatin, which plays a critical role in regulating cortical inhibitory balance and degree of SWS activity [55,56]. Mice in which TrkB was selectively deleted from cortistatin-expressing interneurons sleep less and due to insufficient cortical inhibition become hyperactive and develop spontaneous seizures [56].

Second, translational studies indicate that BDNF also plays an essential role in the homeostatic regulation of REM sleep through a similar mechanism. Selective REM deprivation leads to an increase in BDNF protein expression in the pedunculopontine tegmentum (PPT) and the subcoeruleus nucleus (SubC) that regulate REM sleep, but not in the medial preoptic area, which regulates NREM sleep [57]. The increase in REM rebound following REM deprivation requires BDNF stimulation of TrkB receptors [58,59]. More detailed molecular analysis reveals that BDNF activation of TrkB receptors promotes extracellular-signal-regulated kinase 1 and 2 (ERK1/2) activity in cholinergic neurons within the PPT which, in turn, leads to the transcription of the *Bdnf* gene [60]. Pharmacological inhibition of s1/2 activation in the PPT prevents REM rebound and suppresses BDNF expression [60]. Orexin, in turn, serves as the master regulator of sleep/wakefulness states.

These findings are supported by clinical studies. In particular a very recent study by Deuschle *et al.* [61] measured morning serum BDNF levels followed by sleep polysomnography in a significant number of

participants with either primary insomnia, restless legs syndrome, idiopathic hypersomnia or narcolepsy as well as healthy controls. Across all disorders low BDNF levels were associated with a low percentage of SWS and REM sleep [61] consistent with translational studies indicating the importance of BDNF in generating the homeostatic drive for SWS and REM. Conversely, full or partial sleep deprivation, which increases sleep pressure and has been reported in several studies to produce a rapid reduction in depressive symptoms, leads to a rapid increase in BDNF levels [62]. This is highly consistent with preclinical findings and indicates that the rapid antidepressant effect of sleep deprivation and the rapid antidepressant effect of ketamine are both mediated by increasing levels of BDNF [62].

BDNF and Mood Disorders

There is strong clinical as well as translational support for an important role of BDNF in both depression and bipolar disorder [63]. First, as reviewed above there is compelling preclinical support for BDNF and its primary receptor TrkB as essential components in the mechanism of antidepressant action of ketamine [40] as well as in the mechanism of action of traditional antidepressants [64,65], electroconvulsive therapy [64,65], sleep deprivation [62] and exercise [66]. Similarly, genetic manipulations of the BDNF/ERK kinase pathway alters affective-like behaviors in mice in multiple ways, with most changes consistent with manic-like behavior [67]. Second, there is good evidence that peripheral BDNF levels are reduced in patient with major depression, though this may be moderated by severity and history of abuse or neglect [68–70]. Similarly, there is good evidence for reduced peripheral BDNF levels during depressed, manic and mixed phases of bipolar disorder [71–74] though this also may be moderated by degree of exposure to traumatic events [75]. More definitively, there is also evidence for reduced BDNF and TrkB mRNA expression in specific brain regions of post-mortem samples from individuals who had unipolar and bipolar disorders [76–78].

Pandey *et al.* [79] studied this association in PBD and found decreased levels of BDNF in platelets and decreased BDNF expression in lymphocytes in N = 26 unmedicated youths with PBD versus N = 21 controls. Moreover, BDNF measures increased to near normal levels after 8-weeks of treatment (N = 19). On the other hand, more recent studies have not found differences in BDNF serum levels between PBD and controls [80–82] nor an association between BDNF levels and symptoms of mania or depression [83]. These studies though did report associations between BDNF in serum and inflammatory markers [83], amygdala volume [81], risk factors for cardiovascular disease and measures of executive function [82]. They do not however, refute Pandey *et al.* [79] as they measured BDNF in serum versus lymphocytes and participants in these latter studies could be euthymic or medicated.

What is less consistent in clinical studies is the relationship between BDNF levels and clinical response. Some studies have reported a significant rise in BDNF levels with successful treatment [79,84] but other studies have not [85] or found no relationship between degree of rise and clinical response [86]. There are also several inconsistent reports regarding the relationship between the Val66Met functional polymorphism of BDNF and risk for mood disorders or prediction of antidepressant response [87–97]. It seems likely, at this point, that reduced BDNF levels in individuals with mood disorders does not generally arise from a specific polymorphism but may stem from genotype dependent environmental effects (particularly childhood maltreatment) leading to epigenetic modifications to promoters regulating different slice variants of *Bdnf* [98–110]. A key question in FOH is whether the potentially auto-traumatizing effect of frequent intensely disturbing nightmares acts as a form of childhood adversity that results in new or additional epigenetic alterations to the *Bdnf* gene.

BDNF and Fear

Fearful obsessions and defensive fear-based behaviors are hallmarks of this disorder. Both the formation and the extinction of fear memories requires *Bdnf* gene expression and activation of its high-affinity TrkB receptor [111,112]. FOH may be similar to PTSD in that the formation of fear based emotional memories appears to be intact but the ability to extinguish fear memories is severely impaired [111,113]. An overall defect in BDNF expression would affect consolidation as well as extinction suggesting that FOH and PTSD are associated with more circumscribed alterations in BDNF signaling.

Briefly, there are three key components to the fear circuit [112,114,115]. The first is the amygdala, particularly the basolateral nucleus, central nucleus and intercalated cells which together serve as the fear acquisition and expression hub. The second is the prelimbic and infralimbic subdivisions of the medial prefrontal cortex, which are respectively involved in the expression and extinction of fear memories. The third is the hippocampus which modulates these prefrontal regions and helps provide contextual information [112,114–116]. The prelimbic subdivision promotes fear by activating the basolateral nucleus, which stores fear-based associations, and has excitatory projections to the central nucleus. In contrast, the infralimbic portions projects to the intercalated cells and lateral division of the central nucleus, which contain GABAergic neurons that inhibit the output neurons of central nucleus [112,114,115]. There are also reciprocal connections between the basolateral nucleus and prelimbic cortex that become active during states of high fear and between basolateral nucleus and infralimbic cortex that are active during extinction [112,117]. Coordinated electrophysiological oscillations and neuronal synchrony facilitate communication between these regions and regulates synaptic plasticity.

States of high fear and anxiety are associated with increased theta power and synchrony between hippocampus, prefrontal cortex and amygdala, whereas extinction is characterized by decrease in phase synchrony and after successful extinction, with shift in directionality so that prefrontal theta oscillations now 'lead' amygdala theta oscillation [118,119].

BDNF signaling and regulation of synaptic plasticity are critically involved in all components of the fear circuit. Behavior deficits from impaired BDNF signaling depend upon the brain regions affected [112]. Decreasing BDNF signaling in the amygdala significantly impacts fear learning and consolidation [112,120–122] as does a deficit in prelimbic BDNF [123]. In contrast, diminished BDNF signaling in HPC or infralimbic cortex is associated with impairments in fear extinction [124,125].

Specific polymorphisms in the *Bdnf* gene can also lead to a selective deficit in fear extinction. For example, females are twice as likely to develop PTSD as males and female mice are more resistant than males to fear extinction. This appears to be due to increased DNA methylation of *Bdnf* exon IV and a concomitant decrease in mRNA expression within the medial prefrontal cortex [113]. Similarly, *Bdnf-e4* mice, in which the activity-dependent promoter in exon IV is disrupted, have impaired fear extinction and decreased hippocampal–medial PFC theta phase synchrony during extinction learning [126]. Conversely, exposure during adolescence to predictable chronic mild stress facilitates fear extinction and this appears to be related to increased BDNF/ERK1/2 signaling in infralimbic cortex in adulthood resulting from decreased DNA methylation of the *Bdnf* gene at exons IV and VI.

Clinical studies are also consistent with translational studies in showing that individuals with the low expression Val66Met single nucleotide polymorphism of *Bdnf* have impaired ability to extinguish learned fears [127], a diminished response to extinction-based therapies, and enhanced risk for developing fear-related disorders such as PTSD [128–130]. The Val66Met polymorphism is associated with reduced activity-dependent secretion of mature BDNF (mBDNF) [131,132] and it has been proposed that the corresponding decrease in mBDNF bioavailability results in reduced BDNF–TrkB-dependent signaling that affects the development of fear circuit plasticity during a sensitive period in early adolescence such that alterations in BDNF expression exert a persistent impact on fear behaviors and fear-related disorders [133].

However, that specific molecular mechanism has recently been challenged by the finding that the BDNF prodomain, which is cleaved off from BDNF along with mBDNF, is also secreted in an activity-dependent manner from neurons [134]. Further, it is structurally modified by the presence of the Met 66 amino acid and serves as a potent ligand that triggers disassembly of mature mushroom spines on ventral hippocampal CA1 neurons that project to prelimbic cortex and eliminates synapses by mobilizing actin regulators [134]. The net molecular effect of the BDNF Met prodomain is to keep the projections from ventral

hippocampal CA1 to prelimbic cortex in an immature developmental state thus attenuating their capacity for subsequent circuit modulation necessary for fear extinction [135]. Hence, the consistent cross-species effect of the BDNF Val66Met polymorphism on anxiety may not be due to reduced BDNF activity dependent release but to a specific pro-anxiety effect of the BDNF Met prodomain.

BDNF and Aggression

Most of what we know regarding the role of BDNF in aggression comes from preclinical studies. In one of the earliest reports, Lyons *et al.* (1999) [43] found that heterozygous BDNF(+/−) mice with reduced BDNF levels developed prominent intermale aggression, hyperphagia and weight gain, which were attributable to alterations in the expression of 5-HT receptor subtypes in the cortex, hippocampus, and hypothalamus and could be ameliorated by administration of selective serotonin reuptake inhibitors. Further studies showed that conditional knockout mice in which BDNF expression was disrupted either prenatally or postnatally became dramatically hyperactive and aggressive. BDNF depletion from the fetal brain had more pronounced effects on aggression and was associated with deficits in 5-HT(2A) receptor content in medial frontal cortex [136].

In general, *Bdnf* heterozygote knockouts or mice with forebrain-restricted full *Bdnf* deletions show elevated aggression, but also experience other changes such as increased anxiety [137]. Another important means of studying selective effects of *Bdnf* alterations is to produce mutant mice in which BDNF production from one of the major promoters (e.g., I, II, IV, or VI) is selectively disrupted. Mice with promoter I or II disruptions (*Bdnf* -e1 and -e2) displayed heightened aggression, increased sexual behavior, alterations in serotonin signaling [44] and hyperphagia [138]. In contrast, *Bdnf* -e4 and -e6 mutants were not aggressive or hyperphagic but displayed widespread impairments associated with GABAergic gene expression [44].

Clinical studies have reported a significant association between peripheral BDNF levels and aggression in a small sample of unmedicated participants with Obsessive-Compulsive Disorder and healthy controls [139] and in individuals with amnestic mild cognitive impairment or Alzheimer's disease [140]. The association between Val66Met polymorphism and aggression however is unclear. One study reported a significant association between number of BDNF 66Met alleles and overt aggression scores in patients with schizophrenia [141]. Another reported a significant G × E interaction in which childhood participants in the large Avon Longitudinal Study who affiliated with aggressive peers at age 10 showed increased risk for aggression at age 15 if they carried the BDNF Met-Met variant compared to Val-Val wildtype [142]. On the other hand, two studies failed to find a significant association between Val66Met polymorphisms and aggression in individuals with

schizophrenia [143,144]. This lack of consistency is not surprising given the complexity of human aggression, reliance on peripheral BDNF measures that can be problematic [145] and focus on the Val66Met polymorphism as we are unaware of any reports of increased aggression in mutant mice engineered to mimic this polymorphism.

BDNF, Orexin/Hypocretin and FOH

Overall, there is a wealth of data linking the beneficial psychiatric effects of ketamine to BDNF and altered BDNF levels within specific brain regions to the phenotypic features of FOH. We suspect however that the story does not end here, and a critical question remains as to why do alterations in BDNF levels within these regions produce this array of symptoms? Our leading hypothesis is that the orexin/hypocretin (orx/hcrt) system is also fundamentally involved and interacts with BDNF-TrkB to regulate these behaviors. Briefly, orx/hcrt neurons, colocalized with glutamate and other co-transmitters are expressed in a limited region of the hypothalamus comprised of the dorsal-medial hypothalamus (DMH), lateral hypothalamus (LH) and perifornical area (PFA) [146] but innervate a wide array of regions. Orexin 1 receptor mRNA is preferentially located in locus coeruleus, prefrontal and infralimbic cortex, hippocampus (CA2) and anterior hypothalamus. Orexin 2 receptor mRNA is located in the tuberomammillary nucleus, arcuate nucleus, dorsomedial and lateral hypothalamus, paraventricular nucleus, hippocampus (CA3) and medial septal nucleus [147]. Both receptor mRNAs can be found in the amygdala, bed nucleus of the stria terminalis, paraventricular thalamus, dorsal raphe, ventral tegmental area and laterodorsal tegmental nucleus (LDT)/pedunculopontine nucleus (PPT) [147,148]. The orx/hcrt system serves as a central mediator of reward/aversion [149–160], sleep/arousal [27,161–179], thermoregulation [180–184], energy homeostasis [185–196], motor control [197–200] response to stress or threat [201–213], and production of theta band oscillations that synchronize neuronal networks [27,214–216]. It is this circumscribed area of the hypothalamus, with only about 1000 cells, that coordinates diverse, contextually appropriate survival behaviors linked to homeostatic functions that cycle within the circadian day and oscillate in parallel with ultradian frequencies of arousal states during wake and sleep [32].

We particularly suspect that abnormalities within the orx/hcrt system may play a fundamental role in the emergence of FOH given its critical importance in thermoregulation [180–184] and sleep wakefulness [27,161–179]. Loss of orexin in knock out mice results in elevated nocturnal temperature due to inadequate activation of heat loss mechanisms or sustained activity in heat-generating systems and is associated with sleep fragmentation [182]. We propose that FOH, at its core, is a disorder involving the impaired homeostatic regulation of certain survival functions, the most dramatic being the dysregulation in threat perception and development of fear-based obsessions of harm

befalling the individual that may be initiated or induced by a disturbance in thermoregulation. We envision orx/hcrt as the output of a hypothalamic command center that orchestrates and coordinates between these various survival-based behaviors. In contrast, BDNF is locally expressed in the regions involved in generating these homeostatic processes and likely plays an important role in bringing these behaviors about once signaled by enhancing synaptic transmission, shifting the balance between excitatory and inhibitory neurotransmission and facilitating rapid plastic transformations. We suspect that FOH may represent a cluster of highly similar ketamine-responsive disorders involving a primary disturbance in either orx/hcrt or BDNF, though this remains to be determined.

DISCUSSION

In 1972, Feighner, Robins, Guze and Winokur [217] laid out a strategy for establishment of a psychiatric taxonomy. In their view psychiatric disorders could be distinguished by their symptoms, age of onset, clinical course, family history and laboratory measures. FOH readily emerges as its own unique disorder or subtype by this strategy. While FOH shares with bipolar disorder a severe and pervasive problem with mood dysregulation characterized by depression, irritability and at least brief periods of mania [9] it stands apart because of the thermoregulatory abnormality and the prodromal sequence of nightmares and REM intrusions leading to fear-based obsessions and an auto-traumatized state resembling PTSD. Further, a 'fear of harm' factor was found to be even more heritable than depression or mania factors [5] and the measurable disturbance in distal/proximal skin temperature at bedtime that results in delayed or absent DPG^0 could emerge, with further study, as a potential biomarker [3]. An important lesson is that the recognition of more homogeneous clusters within broad diagnostic categories may benefit from assessment of features, such as impaired thermoregulation, that go beyond our customary focus.

There is also increasing recognition that the Feighner *et al.* [217] approach, which has led us from DSM-III to DSM-5, is insufficient. As Insel *et al.* [12] articulated, symptom-based classifications must inevitably be flawed as two fundamentally different medical disorders can share the same syndromic manifestations and a common underlying cause may manifest in distinctly different ways. In the end a taxonomy for brain-based psychiatric disorders will require a specific understanding of the underlying molecular, cellular and circuit-based neurobiology. Hence, we have leveraged what we have learned regarding therapeutic effectiveness to hypothesize how ketamine may work to address the myriad symptoms of FOH and how they may arise from a disturbance in BDNF or the orx/hcrt system. Given the complexity of these systems it is also likely that FOH may have more dimensional properties than cross categorical boundaries [2].

We need to emphasize that while FOH is not listed in the DSM or ICD and relatively few clinicians may be aware of it, it is not a rare disorder. According to our data up to a third of youths who present with symptoms suggestive of bipolar disorder may have FOH [2]. Clinicians treating children, adolescents and emerging adults with severe highly comorbid treatment-refractory disorders will have likely encountered several without necessarily being aware of their unique features. Inquiring about heat sensitivity and cold tolerance, fear-based obsession, defensive aggression and nightmares may be revelatory. Though randomized controlled trials have not been conducted, clinical experience and blind chart review have found that these individuals typically have a good to excellent response to intranasal ketamine, which appears to work optimally when combined with lithium, and the benefits have endured for as long as the patients have been followed [4]. Hence, it is well-worth identifying these individuals as it may lead to a crucial change in therapeutic approach.

A number of important limitations need to be acknowledged. First, published information on FOH consist primarily of seven peer-reviewed articles [1–7] and there is need for independent replication. Hence, we strongly encourage colleagues who treat youths with severe mood disorders to screen for symptoms of FOH and report their results. Second, assessment of distal/proximal temperature gradients and actigraph-assessed sleep onset identified a potential biomarker, but this needs to be replicated and assessed for its capacity to distinguish FOH from other psychiatric disorders with disrupted sleep. Third, our hypotheses about the potential role of BDNF and orx/hcrt systems is based on clinical response to intranasal ketamine and literature review regarding the relationship between these neurotransmitter systems and the deep phenotypic features of FOH. We have not collected samples and do not have genetic, epigenetic or clinical chemistry findings to support these hypotheses.

In short, there is a tremendous amount of work that needs to be done. On the other hand, the patients that we have seen have been in dire straits—compelling us to apply what we have learned, rather than waiting for definitive pathophysiological answers. The identification of an underlying disturbance in thermoregulation and heat dissipation has been a critically important insight as it has led to complementary strategies such as use of cooling baths and bedside fans to improve sleep and overall well-being. We have also learned that individuals with FOH tend to become more symptomatic when exposed to abrupt changes in weather pattern so we can adjust accordingly and not mistake a transient weather-related disruption for a more fundamental change in their condition.

It is interesting that critical components of FOH are found in specific DSM disorders. Nightmare disorder captures the frequent, intensely disturbing dreams that wake the sleeper and the subsequent emergence of dysphoria without recognizing the risk for auto-traumatization and

symptoms of PTSD. DSM-5 now includes an "*anxious distress*" specifier for bipolar disorder or major depression which stems from the recognition that these individuals may have an increased risk for suicide and a particularly poor response to treatment. However, this specifier includes individuals with relatively mild symptoms of anxiety (feeling keyed up, unusually restless, difficulty concentrating) as well as individual who fear that something awful may happen or fear that they might lose control, which comes close to the concept of fear of harm that we propose is the overt manifestation of the underlying problem responsible for their poor prognosis. Overall, individuals with FOH typically receive an expanding list of DSM diagnoses throughout childhood. An advantage of the FOH construct, and focus on neurobiology, is the ultimate recognition that the diverse array of disparate appearing symptoms that constitutes their deep phenotype come together in a meaningful way and stem from a specific underlying cause rather than from an unfortunate combination of unrelated comorbidities. Ongoing studies should further clarify our understanding of this disorder.

AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization and organization of the paper and to the description of the phenotype. DP, SM and MHT conducted key literature reviews linking FOH to BDNF and orexin. DP and MHT primarily wrote the paper with critical input from all authors.

CONFLICTS OF INTEREST

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