A CRH-HCN Theory of Obsessive-Compulsive Disorder (OCD)

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Abstract. I present the first complete theory of OCD. OCD occurs when excessive CRH is released in the prefrontal cortex, activating cAMP. cAMP is a major inducer of HCN channels, which promote repeated neural firing. The combination of CRH, which is strongly associated with stress, and chronic firing that cannot be controlled, explains all of the features of OCD, including obsessions and compulsions of all kinds.

Keywords. OCD; obsessions; compulsions; HCN channels; cAMP; CRH; cleanliness; hoarding; trichotillomania; excoriation; 'not just right'; guanfacine;

Theory

I present a **CRH-HCN theory of obsessive-compulsive disorder (OCD) (T*OCD)**. T*OCD is the first complete theory of OCD, explaining its etiology, symptoms, pathophysiology, and treatment.

The core cause of OCD is chronically increased release of corticotropin-releasing hormone (CRH), coupled with chronic activation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. HCN channels explain the mechanisms behind OCD symptoms, while CRH excites HCN channels and also explains the association with stress.

CRH is the major brain agent released following deviations from homeostasis (i.e., stress), conveying the need for restoration responses. It acts on two receptors, CRH1 and CRH2, with higher affinity for CRH1. Both receptors are G protein-coupled receptors that mainly bind Gs to induce cAMP, but also Gi/o and Gq.

Strong or chronic stress during sensitive developmental periods can induce persistent alterations to the stress response system. Such alterations commonly involve chronically increased release of stress-related agents, and can be heritable (e.g., via epigenetics).

According to T*OCD, **OCD occurs when chronically released CRH induces excessive activation of CRH1 and possibly CRH2**. This yields excessive cAMP, which induces chronic HCN channel activity as explained below. Alternatively, OCD can occur due to **CRH-independent chronic activation of HCN channels**.

HCN channels are activated by small hyperpolarization and inactivated by small polarization. They are permeable to Na^+ and K^+, and when open yield an excitatory current (Ih) that increases polarization close to the action potential threshold. Thus, their opening facilitates **intrinsic slow cellular oscillations**. HCN channels are crucial to heart rhythmic activity, and are strongly expressed in the brain, including in stress-related areas, cortical response neurons (layer 5 pyramidal neurons that project outside of cortex), the basal ganglia (BG), and the thalamus.

cAMP is a major stimulator of HCN channel opening. Thus, chronic CRH signaling induces chronic activation of HCN channels, which promotes repeated neural firing in stress-related areas (i.e., areas with CRHR expression).

Activation of CRH1 by CRH normally leads to its endocytosis and desensitization. However, in the presence of chronic CRH, this does not prevent chronic cAMP synthesis, because (i) if CRH does not bind CRH1, it accumulates and binds the lower affinity CRH2, which also stimulates cAMP, (ii) endocytosed CRH1 and CRH2 continue producing cAMP via lysosomes, and (iii) chronic CRH activates CRH1 receptors again when they are retransported to the plasma membrane.

According to T*OCD, **the obsessions exhibited by OCD patients are due to chronic neural firing driven by cAMP and HCNs**. Due to the increased push for HCN activation, it is very difficult for the brain to suppress repeated activations in paths that express CRHR-HCN. Thus, stress-related thoughts and actions are continuously reactivated without control.

OCD is strongly associated with a phenomenon called **'not just right'**, a feeling of **incompleteness** commonly manifesting as confirmation questions. This phenomenon results from the same chronic CRH-HCN process that drives obsessions. The need to answer a question/challenge (even simple questions), which is normally conveyed by CRH, continues reverberating due to HCN-induced oscillations, even after a response has been reached. **This also explains continuous rechecking behavior in OCD**.

Many OCD patients exhibit **strong binary views** and **rigid personality**. These occur because response neurons are sometimes not re-activated, making the person very confident in these responses (since patients are used to uncertainty). A lack of re-activation often results from inputs from valence areas (e.g., the amygdala), which provide strong excitation of cortical response neurons, especially to frontal layer 2 pyramidal cells, which are also the ones where CRH-HCN expression is highest. **This explains why the rigid personality in OCD is often related to moral issues**.

OCD **compulsions** are a form of self-treatment in which patients voluntarily activate neurons. They do this because **neural activation induces moderate Ca^{2+} influx, which temporarily inhibits cAMP and relieves obsessions and the feeling of uncertainty**. With repeated execution, compulsions get desensitized, gradually losing their ability to stimulate Ca^{2+}

influx and prompting patients to increase compulsion complexity and/or number of repeats.

OCD behaviors related to **cleanliness** (e.g., hand washing) are very common. This occurs due to two reasons. First, CRH activates mast cells, and induces the release of histamine (both directly and via mast cells). Mast cells are innate immune cells activated by various pathogens. Histamine induces a feeling of itch, and a large variety of agents released by mast cells report the presence of pathogens and/or inflammation to the brain. Second, CRH yields ACTH release in skin. This can induce the production of beta-endorphin, which is known to induce itch via mu-opioid receptors. **The chronic CRH in OCD yields chronic activation of circuits conveying skin-related pathogen threats, and an uncomfortable feeling**. Hand-washing can temporarily relieve the problem as in other compulsions, and via the activation and desensitization of TRPV1 channels.

A similar account also explains **trichotillomania** and **excoriation**, OCD sub-types that involve hair pulling and skin picking, respectively, and nail picking in OCD. CRH1, mast cells and histamine are involved in hair growth. **Hoarding** is another OCD subtype. It is explained by the feeling of incompleteness applied to object use ('Am I finished with this object?' 'I'm not sure. I may need it in the future, so I won't throw it away').

From the patient perspective, OCD behavior is a rational response to the inputs that their brain receives. The problem in OCD is that these inputs are not connected to the real state of the organism, but result from erroneous release of a molecule. However, patients experience such inputs exactly as they experience real ones. This explains the (small) subset of patients who do not show **'insight'** as to their symptoms.

Beyond the biological logic related to the known effects of CRH and HCN channels, there is **empirical evidence** supporting T*OCD. CRH1 recruits the sympathetic nervous system (SNS) and the hypothalamus-pituitary-adrenal (HPA) stress axis (resulting in the release of the human glucocorticoid, cortisol). OCD patients show increased CRH, ACTH, and cortisol (indicating chronic CRH), reduced sensitivity to CRH challenge (showing chronic release), reduced cortisol-induced negative feedback (which is partly done via CRH1), reduced prepulse inhibition of the startle reflex (indicating primed CRH), and chronically higher activity in brain areas expressing HCN ('CSTC loops'). In addition, OCD is associated with genetic mutations in HCN and PDE (cAMP suppressor) genes, with increased allergies (indicating mast cell, histamine), and with trauma (supporting stress-related etiology). There is no contradictory evidence.

OCD patients have **trouble falling asleep**. This provides additional evidence for T*OCD, since CRH1 stimulates the SNS and cortical norepinephrine (NEP), both of which oppose sleep.

T*OCD is also supported by known OCD comorbidities. There is high comorbidity with **anxiety**, which is known to be linked to CRH.

OCD shows high comorbidity with **panic disorder**. T*OCD explains this by noting that the enhanced HCN channel and SNS activity in OCD are expected to increase the likelihood of panic attacks, due to their effects on the heart.

Supporting SNS dysregulation, OCD patients show higher rates of **cardiovascular disease**.

Traumatic brain injury (TBI) can induce a variety of psychiatric conditions, including

OCD. TBI increases CRH and affects HCN channels.

In summary, OCD involves both stress (CRH) and HCN channels. Most of the features that are unique to OCD stem from chronically active HCN channels rather than directly from CRH, but in many or most cases, chronic CRH is what produces the excessive cAMP that drives HCN channels.

Treatment

Cognitive behavioral therapy (CBT) is helpful in OCD, especially when combined with medication treatment. CBT teaches patients to reduce the attention given to OCD paths, thereby reducing their excitability and enhancing non-OCD paths.

The best drug treatment for OCD would be to **reduce CRH release**. Unfortunately, at present there is no selective drug that directly has this effect.

Selective serotonin reuptake inhibitors (SSRIs) increase brain serotonin (SER) levels. In high doses, SER opposes the low CRH mode and CRH1 signaling. Moreover, SER reduces HCN currents via PKC. Thus, SSRIs can significantly help OCD. However, in lower doses, SER cooperates with the high CRH mode and CRH2 signaling. Thus, SSRIs only help when provided at the right doses (especially when coupled with antagonists of the CRH2-related SER2 receptors, such as atypical antipsychotics). In practice, this only works in a subset of patients, because it is very difficult to continuously calibrate the doses required, and because the effect of SSRIs is non-selective and indirect.

Alpha2 adrenergic (NEPa2) receptor agonists cross the blood-brain barrier and oppose brain HCN channel activation, and hence might be beneficial in OCD. **NEPa2 agonists such as guanfacine and clonidine** are routinely used to treat ADHD, a disorder with substantial comorbidity with OCD. There are some indications from a small number of case reports that these drugs are helpful in OCD. **Usage of these drugs to treat OCD, alone or with SSRIs, should be seriously explored**.

Guanfacine is preferable over clonidine, because it is more selective to the NEPa2a subtype, which has a higher expression in stress-related areas such as the prefrontal cortex, amygdala, hypothalamus, and locus coeruleus.

When used for ADHD, NEPa2 agonists commonly induce sleepiness and sedation due to suppression of NEP (and possibly epinephrine (EPI)) release. **In OCD, reducing NEP and EPI may actually be desirable**, because the chronic CRH problem in OCD induces chronic NEP and EPI release (see above).

SSRIs and guanfacine can be used alone or in combination. **For patients with minimal anxiety symptoms (i.e., with relatively 'pure' OCD symptoms), guanfacine may suffice**, due to its direct suppression of HCN channels. SSRIs may be essential for addressing patients with higher anxiety symptoms.

In summary, I believe that guanfacine can provide substantial help to OCD patients, and that it might be better than SSRIs for a large subset. Guanfacine is approved for treating ADHD,

and since there is some symptom overlap between OCD and ADHD, physicians are allowed to start treating OCD patients with guanfacine.

Key References

General OCD background. OCD symptoms, epidemiology, pathology and treatment have been the subject of several large reviews [1, 2]. A 'not just right' feeling and confirmation questions have been increasingly recognized to be core to the disorder, with components that are not directly explained by stress. Area-wise, OCD involves areas beyond the classical ones of orbital frontal cortex, cortico-striatal-thalamo-cortical loops, ACC, and amygdala (note that these are valence/stress areas) [3].

General HCN channels & cAMP background. HCNs have been extensively reviewed [4, 5]. At rest, they counter both hyperpolarization and depolarization, and dampen amplitude and duration of EPSPs and IPSPs. They promote non-burst oscillations (heart, thalamus). Crucially, they can be activated with cAMP, which facilitates their activation by shifting activation voltage to more positive values [5]. Both CRH receptors dramatically increase cAMP [6]. The HCN current Ih increases neural excitability [7].

HCNs are expressed in PFC dendritic spines, colocated with the a2a-adrenergic receptor (NEPa2a) [8]. NEPa2a closes HCN channels and suppresses cAMP [8], which will be important for our proposal of guanfacine treatment. In the ventral tegmental area, NEPa2 agonists (possibly NEPa2c) decrease HCN currents and slow their activation rate [9].

CRH can induce OCD symptoms. OCD is associated with the propensity to move (a large part of the compulsions are physical). CRH induces defensive burying, grooming, mounting, and locomotion. Increased CRH1 yields non-coping and aggression [10]. A thorough review summarized how CRH increases locomotion [11]. CRH increases self-biting and grooming, (self licking and scratching) much higher in novelty (i.e., under stress) [12].

Early life stress (sexual abuse and harsh punishment in early life) are associated with more OCD symptoms in adults [13]. Adult nonhuman primates exposed to early life stress show persistent CSF CRH [14].

There is a very large literature on CRH and early life stress that I assume is well-known and does not need to be cited here.

CRH in OCD. OCD symptoms worsen following childbirth in most women w OCD, and in almost half of men. This we explain by the fact that CRH dramatically rises just before childbirth in women [15]. A genetic association has been found in OCD with the CRH2 receptor (as well as with some others) [16].

There is a large body evidence showing dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis in OCD, which can be explained via chronically increased CRH release that triggers increased cortisol, followed by increased negative feedback on CRH, optionally now followed by decreased cortisol [17, 18, 19, 20, 21, 22, 23, 24, 25].

HCN channels in OCD and stress. Chronic social defeat increases VTA DA spontaneous firing rates, bursts, Ih (in resilient animals too), and avoidance behavior. This behavior can be reversed by Ih inhibitors [26]. HCN inhibitors induced ketamine-like rapid and sustained antidepressant effect in a chronic social defeat stress model [27].

Panic disorder is very common in OCD [28]. Note that panic disorder involves repeated heart beats that are driven by heart HCN channels. In the same direction, OCD involves increased risk of metabolic and cardiovascular disease in a large Sweden cohort [29].

Interoceptive heart inputs reach the insula. Supporting overactivity of HCN channels, OCD involves increased insula activity to unpleasant but also pleasant odors. This is correlated with disgust sensitivity and symptoms [30].

Three HCN4 SNPs are associated with OCD and depression [31]. A PDE4D (cAMP suppressor) SNP is associated with female late-onset (>18y) OCD [32].

CRH, OCD, and allergy. OCD patients show very high (>50%) allergy disorders [33, 34], and there is high incidence of OCD among people with systemic autoimmune diseases [35]. Importantly, the skin expresses the full HPA axis, including CRH and cortisol [36], and skin-related CRH promotes stress-enhanced nasal allergy and mast cell proliferation [37]. Mast cells are central in conveying the feeling of itch to the brain [38].

In one report, a 1st generation anti-histamine (diphenhydramine (benadryl)) unexpectedly helped OCD (it was used as control in another experiment) [39].

Traumatic brain injury (TBI). TBI can induce OCD, depression, anxeity, panic, and PTSD [40, 41]. The parsimonious account of how this happens is that it induces a large stress response involving CRH and HCN. Indeed, blast-induced mild TBI increases anxiety and spontaneous firing frequency of CRH neurons in the paraventricular hypothalamus [42]. Moreover, TBI is specifically known to drive HCN channels [7], and CRH1 mediates stress-induced high-frequency oscillations in TBI [43].

Guanfacine and clonidine. Guanfacine is a NEPa2a agonist, and clonidine is a general NEPa2 agonist. Clonidine rapidly decreased compulsions in one woman [44], and significantly decreased symptoms in others [45]. More recently, clonidine rapidly and significantly improved OCD following SSRI sertraline failure in a 16yo female [46]. Clonidine augmentation to SSRIs or clomipramine significantly helped vs. baseline, but with only a trend vs. placebo, in an RCT with n=57 [47].

8 weeks guanfacine significantly decreased repetitive behavior (CYBOCS-ASD) in autistic patients with ADHD [48]. There is also a negative result [39].

OCD patients showed a blunted growth hormone response to clonidine, with higher basal plasma NEP and MHPG. This was interpreted as increased presynaptic NEP with decreased receptor responsiveness, according with desensitization of NEP (the SNS) [49]. We add that this can be due to chronic CRH.

Not specific to OCD, chronic guanfacine protects rodent PLmPFC L2/3 pyramidal dendritic spines and working memory from chronic stress [50]. Guanfacine extended release helped symptoms related to traumatic stress [51].

Guanfacine has been used to treat TBI-induced cognitive deficits [52], including working memory [53].

An additional possible treatment direction is via **retigabine**. This opener of potassium channel Kv7 decreased the long term effect of repetitive blast TBI [54].

SSRI. SSRIs decrease hippocampus CRH and increase weight gain [55]. High dose SSRI is safe for treating OCD, but with side effects including sexual dysfunction, weight gain, sedation, sweating, and tremor tremor [56]. Thus, SSRIs help some patients oppose the stress driving the disorder. There is even one report in which fluoxetine downregulated HCN2 in the hippocampus (but not the prefrontal cortex, where OCD matters) [57]. Nonetheless, due to the side effects, the lack of efficacy on about 50% of patients, and the highly indirect action on the core OCD problem (HCNs), there is strong motivation to search for other drugs.

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