Part 1: Obsessive-Compulsive Disorder

Obsessive-Compulsive Disorder, or OCD, is a serious, chronic, and common psychiatric illness affecting 2-3% of the population worldwide(1, 2). OCD's namesake is derived from the nature of the illness. Those suffering from OCD experience distressing and intrusive thoughts (obsessions), which are usually complemented by ritualized and repetitive senseless behavioral acts that patients recognize as irrational or excessive (compulsions). The most common compulsions are checking, washing, sorting or counting, and hoarding. OCD is often young adult onset, and contains a familial component (~10%) and is often comorbid with other psychiatric illnesses, particularly anxiety and depression (~20% of cases).(4) Until recently OCD was classified as an anxiety disorder, but anxiolytics are ineffective in OCD treatment (6) and OCD is now considered part of the OC spectrum. (7)

OCD is currently diagnosed only through a constellation of symptoms in the DSM-V, there are no biomarkers for this disease. Consistent with the view of OCD as a psychiatric illness, the first line treatments are Cognitive Behavioral Therapy, and/or Pharmacotherapy. Currently SSRIs are the only proven monotherapy(8), but selective noradrenergic reuptake inhibitors have also proven useful in a select number of cases. CBT coupled with SSRIs are more efficacious than either treatment singular treatment.

However, around 30% of patients are treatment resistant.(4) Treatment regimens for resistant patients have recently shifted from psychiatric interventions to stimulation protocols. Deep Brain Stimulation (DBS) or Transcranial Magnetic Stimulation (TMS) have become the common next step. Stimulation protocols developed in the last 10 years, but show much promise. (9) These interventions can assist in the reduction of the compulsive behaviors in about 10-60% percent of treatment resistant cases, depending upon the stimulation location and protocols. This still leaves at least 15% of patients who are treatment resistant. As a last option, patients can opt for surgical resection. There is a current deficit of options for those who are treatment resistant.

Preclinical knowledge:

Much of our information surrounding OCD has come from human imaging studies and animal models. Obsessions, like other mental states, are extremely difficult to suss from animal models. Most animal models of OCD are reduced to studying the behavioral output of this disease: compulsive behaviors.(10) Compulsive behaviors indicate highly motivated, but unsatisfying, behaviors.(11) Some of the earliest work exploring the role of specific circuits in OCD arose from human PET and fMRI data.(12-14) Patients suffering from OCD displayed hyperactivity and volume changes of the circuitry containing the orbitofrontal cortex, anterior cingulate cortex, basal ganglia (especially the head of the caudate nucleus), and the thalamus (**C**ortex **B**asal **G**anglia **T**halamus **C**ortex, **CBGTC** or **CS**triatum**TC**).

Animal models of compulsive behaviors followed in the rat models of Schedule Induced Polydipsia (SIP) and cue checking. SIP is a non-essential ritualized act arising from a conditioning paradigm which can lead to functional impairment of the animal. (15) This aberrant behavior is relieved by SSRIs(16) and disruptions in CSTC regions reduce the development of these behaviors (17, 18) Thus SIP seems to have face and construct validity for compulsive behaviors. Susceptibility to SIP is influenced by a number of factors. It may be induced by social isolation, NMDA blockers, drug sensitization, and seems to coincides with striatum-based habitual learning.(10, 19) Immunostaining in SIP susceptible rats shows higher rates of ΔFosB/FosB staining in the mPFC and OFC, further implicating changes in cortical function in compulsive-like behaviors. (19)

In contrast, cue checking behaviors can be induced in two ways: pharmacologically (through quinpirole**, QNP**) and behaviorally (**SA**). In the better-studied QNP model, chronic treatment with a D2/D3 receptor agonist resulted in compulsive-like checking behaviors, similar to checking behaviors seen in humans. (20, 21) QNP-caused checking is relieved by serotonin receptor agonists(22), and SSRI's ameliorative effects are though to involve the desensitization of serotonin receptors.(23) The QNP

model of OCD allows for open ended analysis of spontaneous actions during situational uncertainty.(10) These abilities allowed for studies to divide compulsive behaviors have two components: vigor of behavioral performance and focus with which checks are performed as a goal-directed activity(11, 24). In these experiments, Nucleus Accumbens (NAc) within the Ventral Striatum (VMS) lesions were responsible for compulsive vigor, while the OFC mediated the compulsive focus of performing these actions in goal-directed settings. This QNP dysregulation in motivated behaviors points to the relevance of the dopaminergic system in the pathophysiology of repetitive behaviors.

The behavioral induction of cue checking is cause through **SA** (signal attenuation). (25) This model derives from the theory that compulsive behaviors result from the disrupted feedback of goal-directed behaviors. Therefore, rats are exposed to variable ratio schedules in a food-reward lever-pressing paradigm. Animas are repeatedly exposed to the cue (lever) without the reward (food), and this leads to increased lever pressing without checking for food. The SA model of cue-checking is then a drug-free induction of compulsive-like behaviors.

Investigation of potential OCD therapies in both QNP and SA, can point to underlying commonalities in these aberrant behaviors. DBS to the lateral striatum ameliorated repetitive behavior in the SA, but not QNP, model. The QNP model was selectively ameliorated by DBS in the NAc. But DBS to the sub thalamic nucleus (STN) worked in both models, which suggests a potential commonality to compulsive behavioral outputs. In addition, GABA agonists into the thalamus decrease compulsion in both models further indicating a potential common path in both models.(26-28)

Through the correlational knowledge from human data, and the lines of evidence from rat models provide evidence for cortico-striatal dysfunction in compulsive behaviors, **new technologies were needed to probe and modulate these complex circuits related to compulsive behaviors.** Optogenetics presented a method of time-locked stimulation via unique receptors, and they are amenable to cell-type or circuit specific manipulations.

Part 2: Optogenetics

Optogenetics are an exciting technique in neuroscience which were demonstrated around 10 years ago from the Deisseroth lab at Stanford. Optogenetics allow temporal specificity in either stimulation or inhibition of relevant cells. This occurs, as the name suggests, using light. The channels used in optogenetics are 7 transmembrane domain proteins which achieve specificity through opsins, the light sensitive ion channels found in nature. Although the optogenetic toolkit contains many variants of these ion channels and more recently, mutated GPCRs, there are two frequently used opsins used in neuroscience research. These two channels are: Channelrhodopsins (ChR2) which are excitatory, non-selective cation channels opened with blue light, and Halorhodopsins (NpHR), which are inhibitory, chloride ion pump stimulated by yellow light. Despite the utility of optogenetics, applying them to psychiatric diseases without biomarkers has proved somewhat controversial. There no specific biological diagnostic criteria for many psychiatric illness, and assessing mental components of these diseases is always measured by proxy behaviors. Therefore, in OCD research, most work has focused on ability the probed cells/circuits to affect "compulsive" behavioral outputs to prove causal relevance of the circuit, and has not focused on anxiety phenotypes.

Orbitofrontal Cortex projections to the Striatum can cause repetitive behaviors:

CSTC circuit hyperactivity had been highly correlated with OCD, but the functional relevance of this hyperactivity in relation to disease manifestation was unknown. Ahmari et al used optogenetics to probe if stimulation of cortical projections to the striatum would cause OCD related behaviors (grooming) and if these behaviors were relieved by pharmacotherapy. (8)Their results show that glutamatergic stimulation from the Orbitofrontal Cortex (OFC) to the Ventromedial Striatum (VMS) is not sufficient to initially elicit compulsive responses, but chronic stimulation of this circuit caused

progressive increases in compulsive behaviors with repeated stimulation. While the authors were display compelling evidence for the causality of this circuit in compulsive behaviors, showed the relief of this phenotype with a physiologically relevant treatment, and carefully controlled for side-effects of their stimulation protocol, there are still some quibbles with these findings. This paper used a transgenic mouse line which was widespread throughout the forebrain, and the OFC has many projections to the midbrain, where the light was shone. Therefore, this paper lacks specificity and selectivity in the activation of terminals. In addition, this paper probed an indicated circuit which human therapies had already begun exploiting. Overall, we learn that glutamatergic stimulation from OFC to VMS was sufficient to cause neuroadaptations resulting in compulsive-like grooming behaviors.

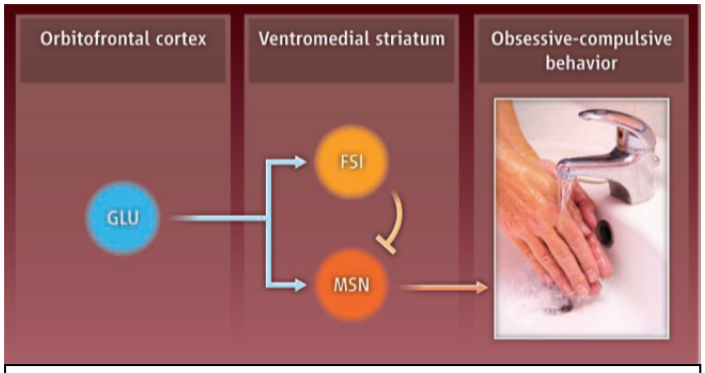

Figure 1: Schematic of proposed functional circuitry in of OFC to the Striatum, from Rauch et al 2013.(5)

Burguière et al complements Ahmari's paper, by further probing the effects of OFC projects to striatal circuitry in a mutant mouse model with OCD-tendencies. Burguière had several questions concerning the cellular and circuit mechanisms underlying the mouse model's behavior(29). Initially they probed if mice would demonstrate repetitive behaviors in response to a formerly neutral stimulus, similar to SIP or SA paradigms. They then utilized electrophysiology to investigate the neuronal basis of this behavioral maladaptation, and optogenetics to assay circuit stimulation would ameliorate these repetitive behaviors. Indeed, their mutant mouse developed an inhibition deficit in their conditioned responses, interpreted as compulsive grooming. They investigated Local Field Potentials in both the OFC and Centromedial Striatum (CMS) of animals at baseline and throughout the conditioning task in accordance with CSTC's association with compulsive behaviors. They found that OFC firing rates were

similar between mutants and wildtype animals throughout the conditioning task, but there were significant differences in both baseline and training-induced CMS Medium Spiny Neuron (MSN) activity. MSNs in mutant had higher firing basal firing rates, and displayed a tuning deficit during conditioning, as compared to their wildtype counterparts. This suggests either increased excitation of striatal MSNs or a reduction of inhibitory input (Fast-spiking interneurons, FSIs) onto MSNs. Optogenetic stimulation of OFC to CMS projections caused increased inhibition of striatal MSN spiking, which was preceded by increased FSI spiking. Stimulation of the circuit did indeed restore wild-type firing patterns in MSNs. This circuit stimulation also ameliorated the aberrant cued and spontaneous compulsive-like behaviors in the mutant mouse. This paper demonstrates that reducing hyperexcitability of striatal MSNs is sufficient to reduce aberrant compulsive-like behaviors, and suggests this is through cortical glutamatergic signaling onto inhibitory interneurons. This paper also shows that compulsive behaviors can arise from inappropriate signaling in the striatum itself and makes a case for the importance of FSI's in maintaining appropriate behaviors. However, the authors did not address any measure of anxiety behaviors, nor show resolution of these OCD-like symptoms through SSRIs thus failing to show this is indeed an OCD model. In addition, several experiments did not include a wild-type control group forcing potential over interpretation of the amelioration effects of stimulation. Most seriously, the group did not determine the type of MSN they were stimulating within the striatum, which leads to difficulty interpreting if these effects were modulated through direct or indirect pathways.

Together Burguière and Ahmari make the case for OFC glutamatergic projection to (FSIs) and MSNs within the medial striatum, where FSIs inhibit MSNs (see **Fig 1**). Deficits in this circuit result in increased MSN activity and compulsive-like grooming behaviors, consistent with the CSTC hyperactivity found in humans.

The Striatum is highly heterogeneous, fine-tuning of targeting within the striatum:

Ahmari and Burguière established causality of the OFC to Striatal circuit to elicit compulsive-like behaviors, and demonstrated that this occurred at the level of the striatum. The striatum is prime neuroanatomical location for investigating OCD, as the striatum is the site of integration for emotional information, decision-making, and behavioral outputs and patients report the known irrationality of their behaviors and the accompanying emotional distress and anxiety. The striatum is a large brain area and more information concerning the neuroanatomical structure of the striatum and it functional outputs is needed to provide better understanding of compulsive-like behaviors. A report by Friedman et al 2015 sought to illuminate the function of the neuroanatomical grouping of neurons called "striosomes" using optogenetics .*(3)* The projections from the PFC and OFC preferentially target striosomes, which are located most prominently in the head of the caudate nucleus.(3, 30)

Friedman found that striosomes fit with the cortico-striatal circuitry of behavior proposed above within the DMS. When cortical efferents to striosomes were inhibited, this relieved inhibition of SPNs (MSNs), and increased SPN activity lead to risk prone rats during a motivationally conflicting task. This effect was specific for the motivationally conflicting tasks. The authors interpret these results as SPN activation causes a decrease in cost sensitivity of the context (See **Fig 2).** *While this work does not directly probe compulsive behaviors, it displays a context-specific functional relationship between the cortex and striosomes of the DMS. That this context involves motivational conflicts suggests striosomes integrate value judgements with mood states and state-dependent control of motivation, and this is controlled through inhibitory interneurons of striosomes***.** However, the electrophysiology did not have cell

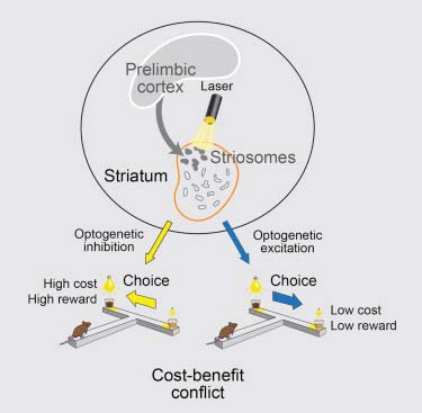

Figure 2: Inhibition of cortical inputs to striosomes leads to risk tolerant behavior, while activation of these inputs increases risk adverse behavior. From Friedman et al 2015.(3)

identity associated with them, so the relevance of direct and indirect pathways of the stratum are still unknown. In addition, the motivational conflict context was only tested with light, so it is unknown if these finds will generalize to all motivational conflict contexts. Despite these short comings this study exquisitely controlled for many variables including: the interrogation of other PFC associations and striatal regions, the differing contexts of activation, effects of both stimulation and inhibition of PFC on behavior, and inhibition of projections from other brain regions which project to striosomes. All of these controls increases the confidence in these results and interpretations of these data.

From Friedman 2015 we learn that while the striatum is heterogeneous, focal targeting of striosomes can induce specific behavioral outcomes dependent upon context. Given the knowledge of OFC innervation of striosomes in the head of the caudate nucleus, and the shown context-specific functional relationship between the cortex and striosome in goal-directed behaviors, these locations would be an ideal location for therapeutic interventions obsessive compulsive disorders, as striosomes also receive functional integration limbic systems and goal directed behaviors in these locations.

However, in each of the aforementioned studies, researchers stimulated a different region of the rodent striatum**.** The striatum is complex and heterogeneous but can generally be divided into the dorsal and ventral striatum. Generally, unlike the ventral striatum which is anatomically connected to limbic structures and involved in reward-related learning, the dorsal striatum receives inputs from the substantia nigra and cortex and is primarily involved in action selection and movement. But recent work using optogenetics showed that illuminating ChR2-expressing dMSNs in the dorsomedial striatum was sufficient to induce intracranial self-stimulation, whereas activating iMSNs punished the same behavior(31), identical to findings in the ventral striatum. This indicates that neurons in dorsal striatum are still a component of the reward system. So interventions at the dorsal striatum may provide a better location for therapeutic intervention, since striosomes effects are specific to contexts, instead of altering all value-encoding and goal-directed behaviors in the NAc containing Ventral Striatum.

To further examine subregions of the striatum in behaviors, a study by Gremel et al, (32) investigated the role of OFC, DMS, and dorsal lateral striatum (DLS) in habitual versus goal directed actions via optogenetic stimulation. Stimulation of OFC correlated with amounts of goal-directed behavior, and its activity changed in response reward outcome. The OFC and DMS fired more during goal-directed behaviors and the DLS became active during habitual behaviors. These results were dissected using a shifting task to differentiate OFC activation been repetitive habitual actions and goal-directed behaviors, honing in on differenced noticed in early rat models of OCD. However, these researchers also did not identify if the striatal neurons were dMSNs or iMSNs. These results display a role of OFC in action revaluation and goal-directed behaviors, which provides further context in compulsive behaviors without satiation(11).

From optogenetic interrogations of compulsive behaviors, we now understand that OFC is important in action revaluation(32), stimulation of the OFC results in neuroadaptations driving compulsive behaviors (8), and that the OFC projects to striosomes. Striosomes use an inhibitory interneuron circuit onto SPNs (MSNs) to drive behavior(3), consistent with circuitry described in compulsive behaviors(29). Decreases in striosomal SPN activity drive risk aversive decisions during motivational conflict (3), perhaps such as obsessions driving irrational behaviors. And intervention within the DMS is more selective, and in line with human imaging data, than in VMS or STN (30, 31, 33). However, how could it be possible to modulate functional inhibitory circuits into the human brain? We can't use cell specific genetics to introduce optogenetic via viral vectors as used in animal studies.

Recent advances answer some of these technical hurdles. In Henderson et al 2014, researchers explored if functional inhibitory circuits from optogenetically transfected exogenous stems cells could be established to reduced hyperactivity in model of seizures. (34) This study quantified longer term effects of stem cell therapy, and in-depth analysis of the interneurons variety and interconnected that resulted from stem cell injections, but only quantified results two months out and potential tumors could still

develop in these models. Researchers found that injections of interneuron stem cells containing opsin channels differentiate into several different subtypes of GABAergic interneurons, and the presence of new cells temporarily reduce hyperactivity (seizures). This basal seizure level may rebound, but these newly integrated interneurons are responsive to optogenetic activation to selectively inhibit hyperactive circuits in the hippocampus. The similarities between the hyperactivity and interneuron death in seizure models, and in the finds of animal models of OCD(29) suggest a similar method is feasible in human rOCD, if human interneuron precursors are available and optogenetics work in human tissue.

Extremely recently, Andersson et al 2016 showed that opsins can expressed in live human tissue, a heretofore untested hypothesis.(35) This study was the first to demonstrate that optogenetics work in live human neurons and this allow light-based control of human neuronal firing. But the tissue was ex vivo from epileptic patients who opted for surgical resectioning, and so the basal properties of these neurons may not be physiologically the same as normal human tissue. This induction of ChR2 was through a lentiviral vector. This study shows that optogenetics do work in human tissue, and recent work by Liu et al 2013 (36) describes protocols for directed differentiation of forebrain GABA interneurons from induced pluripotent stem cells (iPSCs).

Thus we know that injections of stem cells temporarily reduce hyperactivity of a region, and develop into multiple types of mature interneurons and integrate into existing functional circuitry. Light stimulation affects these new functional circuits, and so optogenetic approaches may be feasible in rOCD patients.

Part 3: Specific hypothesis about a potential novel therapeutic

After Ahmari et al 2013 showed that increases in PFC stimulation were sufficient to induce OCD-like behavioral adaptations, signifying downstream neuroadaptations, clinical researchers modified TMS protocols from their initial usage in the SWA (37), and instead used TMS in the prefrontal cortex. This

was well tolerated by participants and was efficacious for 50% (>50% improvement on a scale)(38). However, this large proportion of non-responders is not being served adequately, as the more invasive DBS of subcortical areas stimulate the regions indiscriminately and the surgeries themselves are inherently risky.(39)

Novel Therapeutic Approaches:

My hypothesis is that remodeling PFC efferent, inhibitory circuits within the striatum via optogenetics would be sufficient to reduce compulsive behaviors in OCD. This is consistent with current treatment courses. To address patients suffering from refractory OCD, I propose an optogenetic approach as an alternative to DBS to increase the selectivity and efficiency of stimulation, which may increase odds of success in rOCD*. I predict that injecting human stem cells containing channelrhodopsins, fated for interneurons, into the caudate head of the striatum would induce remodeling of FSI interneurons enhancing inhibition of SPNs. Activation of ChR2 on these interneurons would inhibit SPNs, leading to risk aversive behaviors during motivational conflicts, and reduction of compulsive behaviors on-demand. Enhanced stimulation of these interneurons may induce neuroadaptations relieving compulsive behaviors.*

To test if this is a feasible therapy for rOCD the essential experiment would ideally require at least 60 individuals with rOCD of at least 18 years of age. Participants should not have any comorbid schizophrenia or substance use disorders, as this would cloud interpretation of the results. Participants should not have had previous brain surgeries nor neuroprostheses. Women who are pregnant will also be excluded. This essential study would be 3 months long, with 6 month follow-ups pending the success of the study. The timelines would go as follows: an initial fMRI and intake evaluation prior to surgical injection of stem cells (or placebo) and an optode. This would be followed by a 2-month quiescent monitoring period to allow maturation and integration of the cells. At the end of 2 months there will be

another self-report. Then we will test optode stimulation in a clinical setting. Blue light from the optode will directly stimulate the ChR2 channels on the exogenous interneurons. If well tolerated, this stimulation will continue daily for seven days followed a quiescent seven days, and an assessment after these two weeks. This stimulation protocol will be repeated once more. Following these described three months, there will be another fMRI and evaluation. In total, each patient will receive 2 weeks of optogenetic stimulations, 2 fMRIs, 4 assessments, over the course of 3 months.

There ideally will be four groups of 15 participants, and two variables I would like to test. The first being the type of surgical injection. One group will receive GABA progenitor cells derived from human iPSCs, generated as described in (36). Another group will receive GABA progenitor cells transfected with ChR2. A third group will undergo a sham surgery, with no cells or optode implanted. The fourth group will be a pure control group, continuing their treatment region without manipulation. The second variable I will test is the effect of optode stimulation using blue light or no stimulation. The block design of the experiment means that patients serve as their own controls for the stimulation protocol.

Assessment measure and limitations:

We will use several measures to account for treatment efficacy. First and foremost, Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Quality of Life (QOL) survey, Beck Anxiety Inventory (BAI), Barratt Impulsiveness Scale (BIS) and inquiry into any motor effects. We will use the fMRI to measure changes in functional connectivity after intervention, and to monitor at for any potential tumor growth within the head of the caudate nucleus.

But this study does have many limitations. The first of which is the potential for the inject precursor cells to continue to divide, forming tumors. Secondly, the longevity of optogenetic ion channels within humans are unknown. Thirdly, injections of stem cells are not as specific as desired.

Perhaps with new technologies we could more directly target OFC striosomes directly. And lastly, this intervention is targeted at reducing compulsive behaviors and may not address to co-commitant feelings of anxiety.

Despite these challenges, this therapy mimics DBS protocols already in place, but refines these stimulation protocols to uniquely manipulate inhibitory interneurons within the head of the caudate nucleus. These treatments can be paired with CBT and pharmacotherapies, and provide on-demand selective stimulation of cells, many of which are known to be essential in action selection and compulsive behavior. This therapy is subcortical, in regions known to integrate dopaminergic, thalamic and cortical signals, this is makes it an ideal location to target maladaptive and compulsive actions across endophenoypes of OCD, and less dangerous than stimulation of deeper structures, such as the thalamus.

Implementation:

Hurdles to this clinical trial include finding the appropriate number of participants, a number of essential pilot studies, and ethical concerns. Various ethical concerns arise from the ability to "mind control" via stimulating specific neurocircuitry of humans to the irreversible nature of stem cell implementation, and there is no easy address for these concerns. In relation the number of participants, sufficient numbers of rOCD patients may not be feasible. If enough participants cannot be found, we could eliminate our non-treatment and sham surgery control groups. This would reduce our ability to interpret our results as a result of optogenetic stimulation, stem cells treatment, or the placebo effect. Because of within-subject design, we will still be able to measure treatment outcomes and determine if optogenetic stimulation increases therapeutic benefit, relative to new interneurons alone. Some necessary pilot studies should assess if transfection of ChR2 into human stem cells is viable, and assess the range of stem cell migration and light penetration from the optodes in the human brain. An

important fine-tuning may be required in injection site. Although much of the theoretical basis for this therapy focuses on the control of compulsive behaviors through the DMS and analogous head of the caudate nucleus, we might opt for the VMS which contains the Nucleus Accumbens. The VMS is more closely tied to the limbic system. The VMS is responsible for more than behavioral outputs, and modulation of this region may alter more than the desired compulsive behaviors. Nevertheless, it may provide therapeutic results for rOCD patients. Building off of the knowledge from optogenetic studies in animal models of OCD is already underway in non-invasive stimulation paradigms. (38) This proposed treatment will act on rOCD patients by an on-demand fine-tuning of specific cells and neurocircuitry responsible for compulsive behaviors.

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