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Neurobiology of obsessive-compulsive disorder: insights into neural circuitry dysfunction through mouse genetics

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Abstract

The precise causal factors for obsessive-compulsive disorder (OCD) are not known, however, decades of research have honed in on the cortico-striatal-thalamo-cortical (CSTC) circuitry in the brain as a critical pathway involved in obsessions and the intimately linked compulsive-repetitive behaviors. Recent progress in human and mouse genetics have led to the identification of novel candidate susceptibility genes, which in turn have facilitated a more focused approach to unraveling the nature of circuitry dysfunction in OCD. The ability to perform invasive techniques in genetic animal models of OCD will be crucial for rapid advances in this field, and as such we review the most recent developments and highlight the importance of searching out common circuitry defects underlying compulsive-repetitive behaviors.

Keywords

OCD; glutamate; glutamatergic; basal ganglia; CSTC; fronto-subcortical; synapse; neurotransmission; genetics; Sapap3; Tourette syndrome; trichotillomania; TTM; neuropsychiatric disorder; N-acetylcysteine; NAC; Slc1a1; EAAC1; Hoxb8; Slitrk5; Slitrk1; Shank3; MeCP2; corticostriatal; cortico-striatal; obsessive-compulsive spectrum disorder; OCD circuit

Introduction

Despite the fact that the causes of OCD remain elusive, in recent years this disorder, once considered relatively obscure, has experienced a reemergence in the public consciousness. This is underscored by the creation of not one, but two separate reality/documentary-style television shows dedicated to this topic within the past two years (“OCD Project” which aired on VH1 and “Obsessed” which aired on A&E). Perhaps this is the result of a growing acceptance that OCD is not obscure, but rather, ranks among the most prevalent neuropsychiatric disorders such as major depression, schizophrenia, and bipolar disorder.

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Conflict of Interest
None declared

It is estimated that the lifetime prevalence of OCD is 1–3% in the general population [1,2], suggesting that within each of our social networks we may find family members, friends, or colleagues that live with this often debilitating condition. While there are several treatment options currently available [3,4], the stark reality is that there remains a significant percentage of OCD sufferers that are either non-responsive or only partially responsive to the available treatment paradigms. Furthermore, last-resort invasive procedures such as deep brain stimulation or surgical procedures have had mixed success in alleviating severe symptoms [5], and thus these options remain an empirical art that is far from being mastered. This highlights the importance of continued research into the precise causes of OCD and continued exploration of novel targets that have promise to one day bring relief to all in need.

Theoretical framework for circuitry dysfunction in OCD

Diverse functional brain imaging technologies have allowed researchers to delve deep into the brains of OCD patients to seek out aberrations in neural circuits that control behavior. Over the past 25 years these noninvasive imaging approaches have consistently identified abnormal patterns of activity in a particular circuit, the CSTC loop [6] (Figure 1), and these studies have been highly influential in synthesizing the modern views on the neurobiology of OCD. Perhaps equally important over this span were emerging views on basal ganglia circuitry function, such as the description of numerous parallel and partially closed loops through the CSTC pathway proposed to sub-serve discrete motor or cognitive functions [7]. This model has been revised to incorporate the proposed opposing functions of the “direct” versus “indirect” projection pathways of the basal ganglia as well as compartmentalization of function with respect to neurochemically defined striosome and matrix [8–11]. One prominent hypothesis, which integrates the human OCD imaging findings with these earlier models on basal ganglia circuitry function, posits that hyperactivity of the orbitofrontal-subcortical loops caused by a disruption in the balance of activity through these opposing basal ganglia pathways (specifically, excessive direct pathway activation) underlies the manifestation of OCD symptoms [6].

While surely this represents an oversimplification of the neural circuitry that gates obsessions and compulsive behavior, it provides a useful theoretical framework for devising testable hypotheses on the mechanisms of circuitry dysfunction in OCD. Surprisingly, despite the accumulating evidence for the involvement of the CSTC circuit dysfunction and the proposed role of basal ganglia circuitry imbalance, there has been a marked absence of direct experimental evidence in the past two decades to support or refute this idea. The most likely explanations include ethical issues that preclude the majority of invasive procedures in human patients and the lack of well-established alternative animal models for exploring such detailed mechanistic insights. In this light, we concisely review the most recent progress specifically toward development of novel genetic animal models of OCD and explore intersections with recent human genetics studies on OCD. Comprehensive reviews on the various other animal models relevant to OCD-like behaviors have been covered elsewhere [12–16].

Recent insights from genetic mouse models

Sapap3 null mice

SAP90/PSD95-associated protein 3 (SAPAP3) belongs to a family of four homologous genes encoding SAPAP proteins that are widely yet differentially expressed in the nervous system [17]. SAPAP3 is localized to the postsynaptic density (PSD) at excitatory synapses and is the only family member strongly expressed in the striatum. Genetic deletion of *Sapap3* in mice caused behavioral abnormalities consisting of increased anxiety and

compulsive self-grooming to the point of facial hair loss and skin lesions [18]. *Sapap3* null mice were also found to have defects in glutamatergic transmission at cortico-striatal synapses, and both synaptic and behavioral defects were rescued by virus-mediated reintroduction of SAPAP3 specifically into the striatum [18], thus confirming the critical role of cortico-striatal circuitry function to the expression of compulsive grooming behavior. Repeated administration of fluoxetine (which is known to be effective in treating human OCD) successfully alleviated compulsive grooming and anxiety.

These findings on *Sapap3* null mice prompted two recent genetic studies of *Sapap3* and OCD. Züchner *et al.* [19] performed *Sapap3* gene re-sequencing analysis in OCD and trichotillomania (TTM) case samples. This study identified seven rare non-synonymous heterozygous *Sapap3* variants. The combined load of these rare *Sapap3* mutations was significantly higher in OCD/TTM cases compared to controls. These findings await further validation, including analysis of the functional relevance of these rare mutations. Additionally, a relatively large family-based gene association study of *Sapap3* in OCD and grooming disorders has also been conducted [20]. The evidence suggests that multiple variations in the *Sapap3* gene are associated with grooming disorders. No direct association between *Sapap3* variants and OCD was reported, although it is noteworthy that grooming disorders without OCD were uncommon in this study. With this in mind the authors suggest the possibility that *Sapap3* variants may be involved in a subtype of OCD involving pathological grooming behaviors.

Slitrk5 null mice

Slit and Trk-like proteins (Slitrks) represent a relatively newly discovered family of structurally related transmembrane proteins that are predominantly expressed in the CNS and regulate neurite outgrowth and neuronal survival. Although not consistently replicated, prior work supports a link between Slitrk1 and Tourette syndrome [21] as well as TTM [22], and Slitrk1 was shown to be highly expressed in significant portions of the CSTC circuitry [23]. However, Slitr1 null mice display only limited behavioral abnormalities such as moderately elevated anxiety [24]. In contrast, more recently described mice in which the Slitrk5 coding region was replaced with the LacZ reporter gene (a null/reporter allele) exhibit compulsive self-grooming and increased anxiety [25]. The LacZ expression allowed unequivocal determination of the predominantly neuronal expression pattern throughout cortex and striatum. Slitrk5 was found to localize to the PSD and mutant mice further displayed significant alterations in striatal ionotropic glutamate receptor subunit expression in PSD enriched fractions and functional disruption of cortico-striatal glutamatergic transmission. The compulsive grooming was corrected by chronic fluoxetine treatment. These findings bear striking similarity to those reported for the *Sapap3* null mice, and in both models virtually all homozygous mutants develop overgrooming-induced facial lesions at 3–6 months of age, with less severe defects including delayed appearance of lesions in heterozygous mice [18,25]. In addition, the Slitrk5 mice had reduced striatal volume and dendritic complexity of striatal medium spiny neurons, and elevated neuronal activity (indicated by elevated FosB expression) specifically in orbito-frontal cortex, providing further evidence to strengthen the relevance of this model to OCD in humans. The collective findings on Slitrk1 and Slitrk5 may point to a common pathway to neuropsychiatric disorders through disruption of Slitrk gene function in the CNS [26].

Hoxb8 null mice

The investigations focused on Hoxb8 mutant mice over the past decade have provided unexpected discoveries and striking insights concerning the causes of compulsive grooming in mice. In 2002, the Capecchi lab reported that *Hoxb8lox* mutant mice exhibited compulsive grooming and fur loss with 100% penetrance [27]. The mutant mice engaged in

excessive self-grooming as well as excessive grooming of wildtype cage-mates, and this phenotype was identical on two different genetic backgrounds, thus providing strong evidence for a specific role of *Hoxb8* in normal grooming behavior. This was unexpected given that *Hoxb8* is a member of a large family of transcription factors best known for their important roles in establishing body patterning during embryonic development. However, *Hoxb8* expression is detected in adult brain, including regions comprising the CSTC circuitry. It was not until 2010 that we learned the expression of *Hoxb8* which is evident *in* brain did not in fact originate *from* brain, but rather, came from bone marrow-derived microglia that migrate into the brain in the postnatal period [28]. Cell-type specific disruption of *Hoxb8* restricted to this microglia progenitor population fully recapitulated the grooming defects. Remarkably, bone marrow transplantation from *Hoxb8* mutants into wildtype mice led to increased grooming and fur loss in a subset of mice, while bone marrow transplantation from wildtype mice into *Hoxb8* mutants completely rescued the pathological grooming in a subset of mice. Further studies are needed to clarify exactly how *Hoxb8* deficient microglia impact neural circuitry involved in grooming behavior, although it is already recognized that microglia have diverse roles in regulating brain function [29]. The evidence on *Hoxb8* in mice reminds us that although OCD is believed to be a disorder caused by dysfunctional neurons within CSTC circuits, the underlying causal insults need not be exclusively neuronal or even waged by cells that originate in the brain at all. This finding adds food for thought in the ongoing debate concerning a subtype of childhood-onset OCD that is thought to be precipitated by autoimmune dysfunction following streptococcal infections [30].

***Slc1a1/EAAC1* null mice**

The neuronal excitatory amino acid transporter EAAC1 has a dual role in regulating neuronal function through limiting glutamate diffusion in extrasynaptic regions [31], and mediating neuronal cysteine transport, an essential rate-limiting step in the production of the endogenous antioxidant glutathione [32]. EAAC1 null mice exhibit a range of neuronal defects largely due to increased vulnerability to oxidative stress in multiple brain regions [32,33]. Given that the strongest and most well-replicated findings of genetic linkage in OCD center on *Slc1a1* [34], the gene that encodes EAAC1, it is of great interest whether EAAC1 null mice exhibit OCD-like behaviors. It has been reported that EAAC1 null mice beyond one year of age exhibit increased aggression and excessive self-grooming, and approximately 30% of these mice develop fur loss [32] (Dr. Raymond Swanson, personal communication). This is intriguing given the neuronal perisynaptic localization and strong expression in the CSTC circuitry [35]. In addition, EAAC1 functionally interacts with NMDA receptor subunits [36], which is interesting given that a GRIN2B variant was previously reported to be associated with OCD [37], and since NMDAR subunit expression in the PSD fraction is significantly altered in *Sapap3* null mice [18]. One rare variant in *Slc1a1* has been identified in a single OCD family to date [38]. EAAC1 homozygous loss-of-function mutations are exceedingly rare in humans and cause the renal condition dicarboxylic aminoaciduria. It is provocative that one such patient self-reported lifelong obsessive-compulsive behaviors but declined formal psychological evaluation [39].

The elevated widespread oxidative stress observed in EAAC1 null mice was alleviated by treatment with N-acetyl-cysteine (NAC), a cell-permeable amino acid that can normalize neuronal glutathione levels [32,33]. It is of great interest that NAC is currently being explored in clinical trials for the treatment of OCD on the basis of putative anti-glutamatergic properties relating to transporter activity [4], and recent studies indicate an improvement in symptom severity with NAC treatment in SSRI-refractory OCD and TTM patients [40,41]. It would seem the importance of EAAC1-dependent glutathione synthesis may be under-appreciated in this context. In light of the weak evidence to support EAAC1

null mice as a *bona fide* model for OCD-like behaviors but strong evidence of genetic linkage for *Slc1a1* in OCD, EAAC1 functional deficits may confer broad susceptibility when coincident with other rare mutations in a variety of genes important for CSTC circuitry function.

In search of a common neural circuitry defect

Despite the varying degrees to which each genetic mouse model recapitulates core aspects of the human condition of OCD, some notable commonalities have emerged. First, no single model is sufficient to recapitulate the entirety of the human condition of OCD. This is especially true given that the presence and content of obsessional thinking that is intimately tied to compulsive behavior is perhaps impossible to assess in a mouse [12]. Thus, it is important to focus on robust and easily quantifiable behaviors—in this case compulsive grooming—for which we can pinpoint and probe the underlying neural circuitry defects. Second, with respect to the genes that are disrupted in the genetic mouse models described herein, there is a striking degree of overlap in the endogenous expression patterns throughout the brain, and the regions of overlap are the same regions strongly implicated in human OCD (Figure 1). Third, mounting functional evidence from these recently developed genetic mouse models also demonstrates convergence on CSTC circuitry in OCD-like behaviors, including evidence for cortico-striatal synaptic dysfunction and orbito-frontal hyperactivity, which are highly consistent with earlier functional imaging data from human OCD cases. Sustained intensified effort on this front will be necessary to fill in crucial gaps in our understanding of the origins of common circuitry defects in OCD, such as elucidating how glial and immune system dysfunction might perturb neuronal function in the CSTC circuitry.

The core feature of compulsive-repetitive behavior is not unique to OCD. In fact, this feature is central to an extensive group of broader neuropsychiatric disorders. Some such disorders (TTM, Tourette syndrome, and compulsive skin picking) fall into the obsessive-compulsive spectrum of disorders, while others (Autism, Asperger syndrome, Fragile X syndrome, and Rett syndrome) fall into a category called autism-spectrum disorders (ASDs) (Figure 2). Importantly, it is estimated that as many as 30–40% of autistic patients are also diagnosed with OCD [42], and there are high rates of co-morbidity with OCD in other ASDs. The recent development of novel genetic mouse models of autism and ASD-like behaviors that specifically exhibit robust compulsive-repetitive behaviors [43,44] will no doubt help researchers to search out common circuitry defects and improve our understanding of these presently perplexing human conditions.

Conclusions and future perspectives

Searching out common circuitry defects in genetic animal models of OCD and various other disorders with overlap in the domain of compulsive-repetitive behaviors represents one of the most promising directions for future research in this field. In this respect it is important to urge inclusive (yet with tempered skepticism) as opposed to dismissive views concerning novel animal models. No animal model will adequately capture all aspects of a complex human disorder, yet significant aspects of specific core features can reasonably be investigated in a salient neurobiological context. Furthermore, genetic animal models represent an exceptionally attractive platform for carrying out detailed investigations on the functional impacts of novel candidate gene mutations identified from genetic studies of human OCD. Given the polygenic and heterogeneous nature of OCD and related disorders, we should welcome the availability of diverse genetic animal models and actively explore interactions across multiple mutations that may converge on a common pathway of brain function. This strategy should hasten progress in the search for genes that may be causal and

genes that may confer susceptibility to the expression of compulsive-repetitive behaviors. Elucidation of common circuitry mechanisms will greatly facilitate the development of more effective treatments for these debilitating disorders.

Research Highlights

- OCD is a prevalent neuropsychiatric disorder
- Cortico-striatal-thalamo-cortical circuits are central to OCD core features
- Several recently described genetic mouse models exhibit OCD-like behaviors
- Genetic mouse models may help researchers identify common circuitry defects in OCD
- Common circuitry defects may also help to explain key aspects of autism spectrum disorders

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44. Chao HT, Chen H, Samaco RC, Xue M, Chahrouh M, Yoo J, Neul JL, Gong S, Lu HC, Heintz N, et al. Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. *Nature*. 2010; 468:263–269. [PubMed: 21068835] • This study describes autism-like stereotypies resulting from deletion of *Mecp2* from GABAergic neurons. In particular, *Viaat-Mecp2*^{-y} mice exhibited excessive self-grooming leading to fur loss and skin lesions. These mice also displayed a significant increase in the number of sequential nose-pokes in a hole-board assay for compulsive-repetitive behavior.

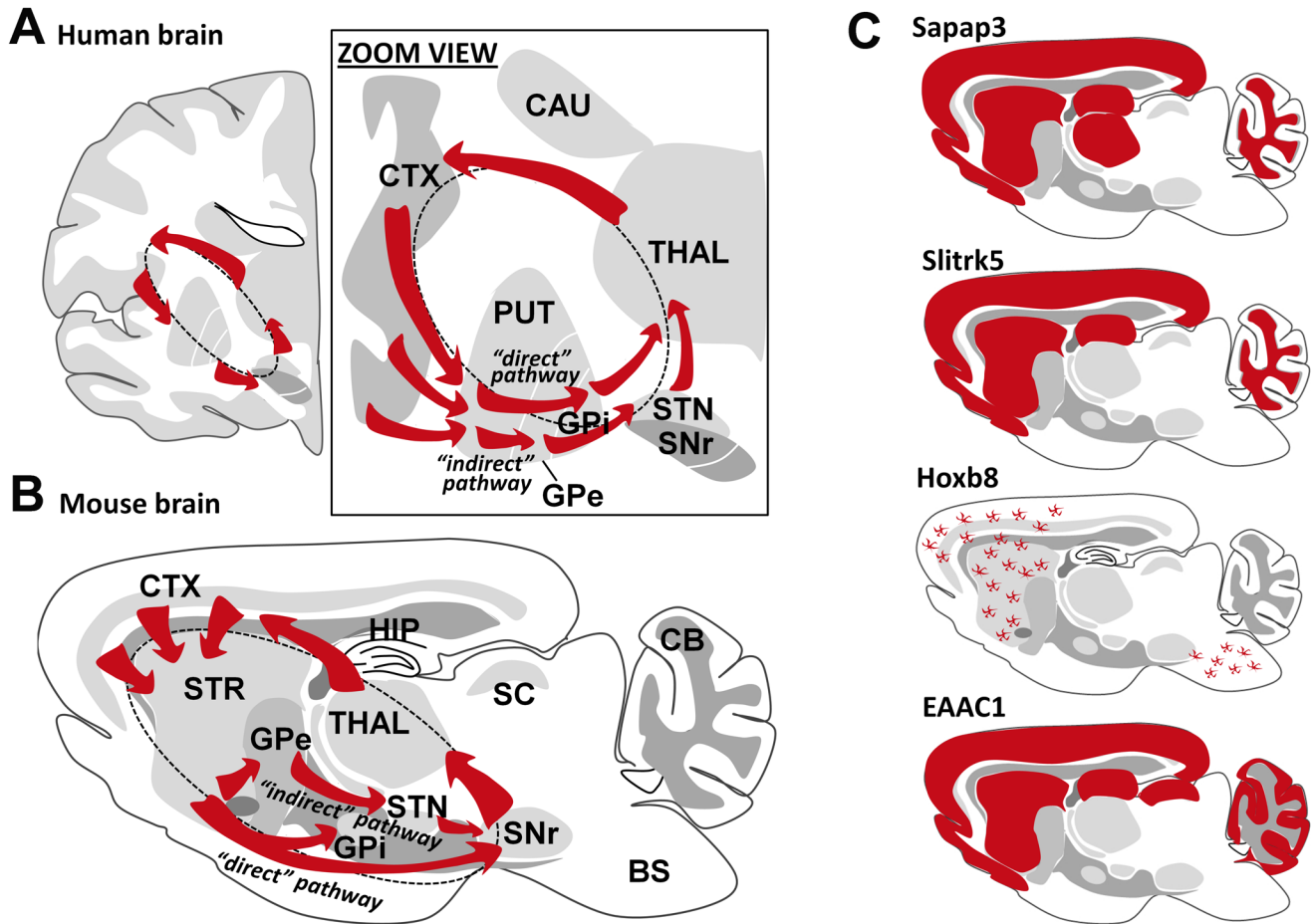


Figure 1. Central role of the CSTC circuitry in obsessive-compulsive disorder in humans and compulsive-repetitive behaviors in mice

A. Diagram of a human brain section (coronal) illustrating a simplified CSTC loop. Right panel, zoom view of the CSTC loop illustrating the intermingled but functionally distinct “direct” and “indirect” projection pathways of the basal ganglia that are thought to exert opposing control over selection of motor behaviors. B. Diagram of a mouse brain section (sagittal) illustrating the equivalent CSTC loop in the corresponding rodent brain structures. Abbreviations: CTX, cortex; STR, striatum; CAU, caudate; PUT, putamen; HIP, hippocampus; THAL, thalamus; STN, sub-thalamic nucleus; SNr, substantia nigra pars reticulata; GPe, globus pallidus externa; GPi, globus pallidus interna; SC, superior colliculus; BS, brain stem; CB cerebellum. C. Highly simplified diagram of candidate OCD gene expression patterns throughout the mouse brain demonstrating extensive overlap of expression in brain regions composing the CSTC circuitry. NOTES: The Sapap3 expression pattern is based on in situ data as reported in [17]. The Slitrk5 expression pattern is based on LacZ activity as reported in [25]. The Hoxb8 expression pattern was inferred from [28], and importantly this pattern is intended merely to reflect the regions of highest concentration of Hoxb8-expressing microglia rather than all Hoxb8-expressing microglia in the brain. The EAAC1 expression pattern is based on anti-EAAC1 antibody staining in brain slices as reported in [35].

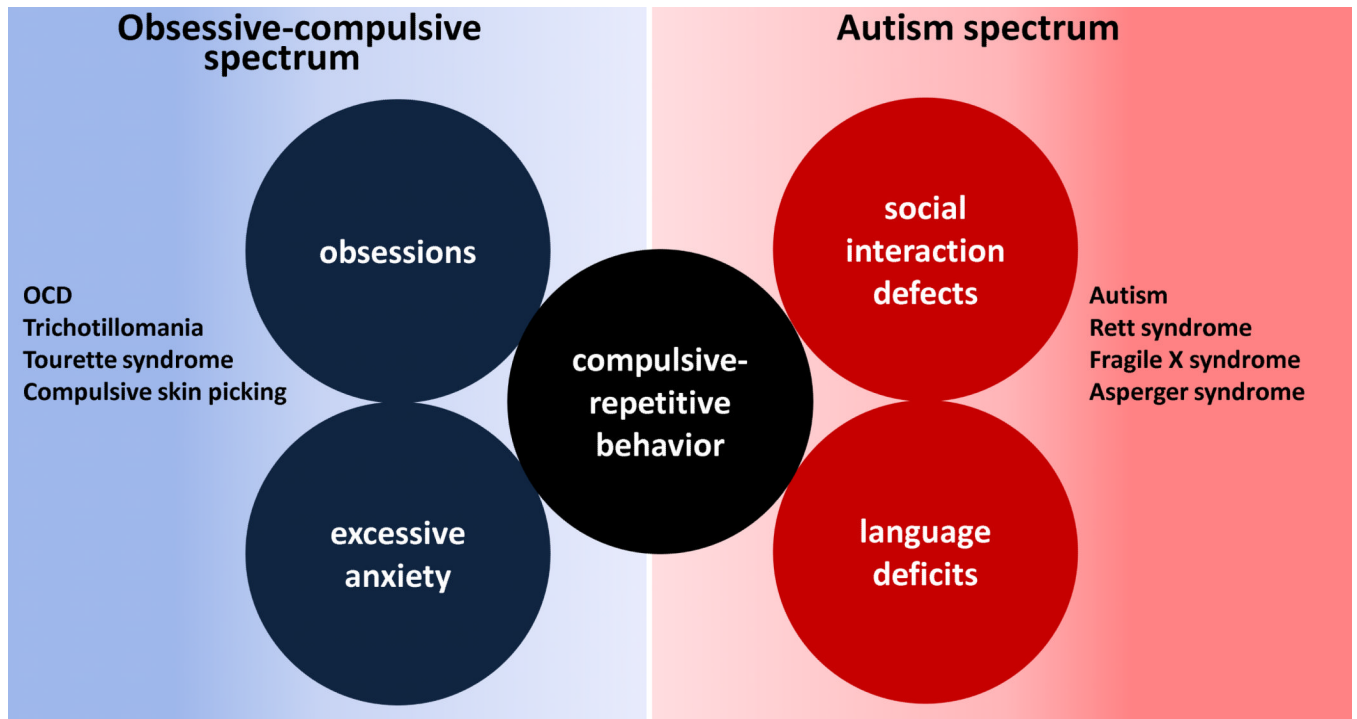


Figure 2. Compulsive-repetitive behavior is a core feature that is shared between obsessive-compulsive spectrum disorders and autism spectrum disorders
Specific features of obsessive-compulsive spectrum disorders include obsession and excessive anxiety; whereas specific features of autism spectrum disorders include social interaction defects and language deficits.