Translational neuroimaging research in pediatric obsessive-compulsive disorder

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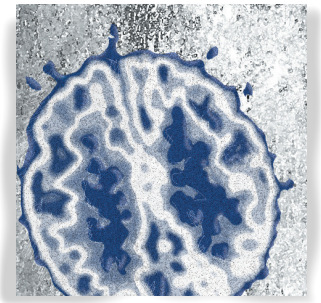

Obsessive-compulsive disorder (OCD) is a significant public health problem. Selective serotonin reuptake inhibitors (SSRIs) are the only FDA-approved medications for OCD. However, SSRIs are of limited efficacy in clinical practice. Given the persistence of symptoms and levels of treatment response, it is clear that the serotonin paradigm of OCD does not fully account for the neurobiology of the disorder, and that further translational research is needed. In this review, the glutamate hypothesis of pediatric OCD is explored, the neuroimaging evidence reviewed, and the translational impact highlighted. The traditional strategy of going from pharmacology to pathophysiology has failed to show real progress in our understanding of the neurobiology of psychiatric illness and, while still in the early stages, this work demonstrates the clear benefit of approaching psychiatric illness from the opposite direction.

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Obsessive-compulsive disorder (OCD) is a major public health problem. OCD is a severe and chronically debilitating disorder, affecting over 3 million people in the United States alone. People afflicted with OCD have distressing obsessions and compulsions that cripple their functioning in everyday life.[1,2] According to the World Health Organization, OCD is among the ten most disabling medical conditions worldwide.[3] The National Comorbidity Survey Replication found that, in anxiety disorders, OCD has the highest percentage (50.6%) of serious cases.[4] The estimates of its lifetime prevalence in pediatric and adult populations range from 1% to 3%.[4-6]

Why focus on pediatric OCD?

The clinical phenomenology, nosology, and treatment of pediatric OCD have been well described, making the illness a leading candidate for new and innovative neurobiological study. The two reasons to focus on pediatric OCD are, first, that OCD commonly has its onset during the developmental period,[7] and second, that pediatric OCD is continuous with adult OCD. The National Institutes of Mental Health considers OCD to be a neurodevelopmental disorder.[8] Estimates of the mean age at onset of OCD children range from 9 to 11 years in boys to 11 to 13 years in girls.[9,10] Evidence indicates that an early age of onset in OCD is associated with a poor outcome.[11,12] There is a strong genetic component to the illness, with estimates of the heritability of obsessive-compulsive symptoms in children and adolescents ranging from 45% to 65%.[13] Pediatric OCD is chronic and unremitting in up to 87% of cases.[12] Children with OCD are also at higher risk for other psychiatric disorders in adulthood.[9,14]

Why is translational research into pediatric OCD needed?

The biggest obstacles for people with OCD are getting a proper diagnosis and access to effective treatment.[15] Selective serotonin reuptake inhibitors (SSRIs) are the only FDA-approved medications for OCD. Treatment of OCD with SSRIs, while considered effective, has proven limited in practice. SSRIs are typically only effective in 40% to 60% of patients.[16] This leaves a substantial number still ill.[16] Indeed, many patients who are classed as "responders" are still markedly symptomatic after treatment; as studies define treatment response as a 20% to 40% reduction in symptoms.[16] In fact, typical OCD symptom severity scores, as measured by the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), post-treatment are 15 to 20 (test score range 0 to 40), indicating mild-to-moderate impairment.[17] In addition to medication, cognitive behavioral therapy (CBT) is also considered an effective treatment for OCD.[18] However, even the combination of CBT and medication still leaves approximately one third of pediatric patients markedly ill.[18] Furthermore, an earlier onset of OCD may be more associated with the illness being treatment-refractory.[18] Given the persistence of symptoms and limited levels of response to treatment, especially medication, it is clear that the serotonin paradigm of understanding OCD does not fully account for the neurobiology of the illness. In fact, our understanding of the biology of the disorder has been limited, until now.

How can brain imaging inform translational approaches?

The traditional, but not exclusive, strategy in psychiatry has been to go from the pharmacology to the pathophysiology of a given disorder. The development of the serotonin hypothesis of OCD is an example of this approach, where medications were applied first and a physiological explanation shaped around that. This approach has failed to show real progress in our understanding of the neurobiology of psychiatric illness.[19] However, developing an understanding of the physiology of psychiatric disorders has been difficult. That is, until the development of brain imaging methodologies that have allowed for the in vivo examination of the living brain. Postmortem work, while informative, does have its limits, and samples in pediatric populations with psychiatric illness are rare. There have been 2 decades since the application of brain imaging to the study of OCD, and tremendous progress has been made. Bringing these advances from the "bench" however, has been difficult.

Translational research has in two basic hurdles to jump.[20] The first hurdle is in transferring new understandings of the mechanisms of the disorder into novel treatments, diagnostic tools, and prevention. The second hurdle is in taking these novel therapies, diagnostic and preventative methods, and implementing these protocols in the actual clinic *(Figure 1)*. As out-

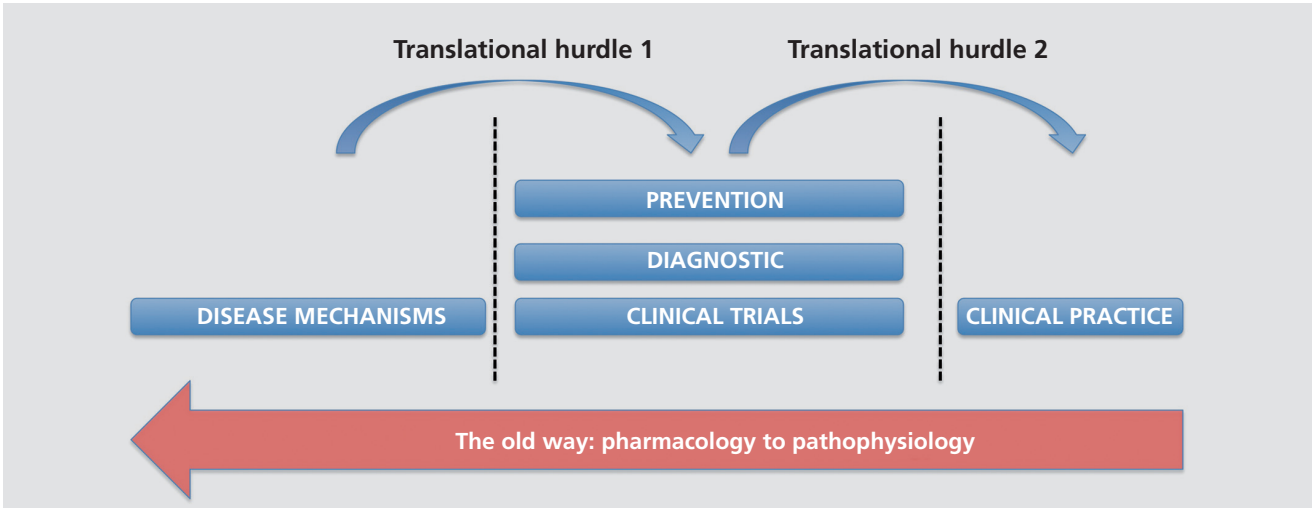

Figure 1. Basic pathway of translational research and the two main hurdles that need to be crossed to make research clinically relevant. The standard method in psychiatry has been to move from pharmacology in clinical practice to theories of pathophysiology.

lined in the following section, significant progress has been made in increasing our understanding of the neurobiological substrates of pediatric OCD. These advances have directly led to the novel application of agents to treat pediatric OCD. This is one of the rare instances in psychiatric research where knowledge has indeed moved from the "bench" and closer to the "bedside."

Basic neurobiological model of pediatric OCD

In this section, we will outline the basic neurobiological model of OCD *(Figure 2)*. The cortical-striatal-thalamic circuit has been the most consistently implicated in OCD.[21,22] In the striatum, 80% of all synapses are cortical inputs.[23] The cortical regions projecting to the striatum can be divided into "motor" and "limbic associative." Motor projections include somatosensory, motor, and premotor cortex. More pertinent to OCD, the "limbic associative" projections are derived from the amygdala, hippocampus, orbital, frontal, cingulate, parietal, temporal, entorhinal, and association cortex.[24] One can subdivide the cortical-striatal connections into circuit loops. There are sensorimotor, oculomotor, dorsal cognitive, ventral cognitive, affective/motivational loops that extend from the cortex to the striatum to the thalamus and back to the cortex.[22] The anatomy and organization of the cortical-striatal circuits have been reviewed in depth elsewhere.[25-30] These circuits progress through distinct parts of the frontal cortex, basal ganglia, substantia nigra, and the thalamus in a self-repeating loop.[25] Two of the pathways act to regulate output from frontal cortex to insure appropriate behavioral responses to stimuli.[25] The "direct" pathway facilitates thalamic stimulation of the cortex. The "indirect" pathway acts to inhibit the thalamus—thus permitting the cortex to shift sets and respond to novel stimuli. OCD may result from excessive neural tone in the direct pathway relative to the indirect pathway.

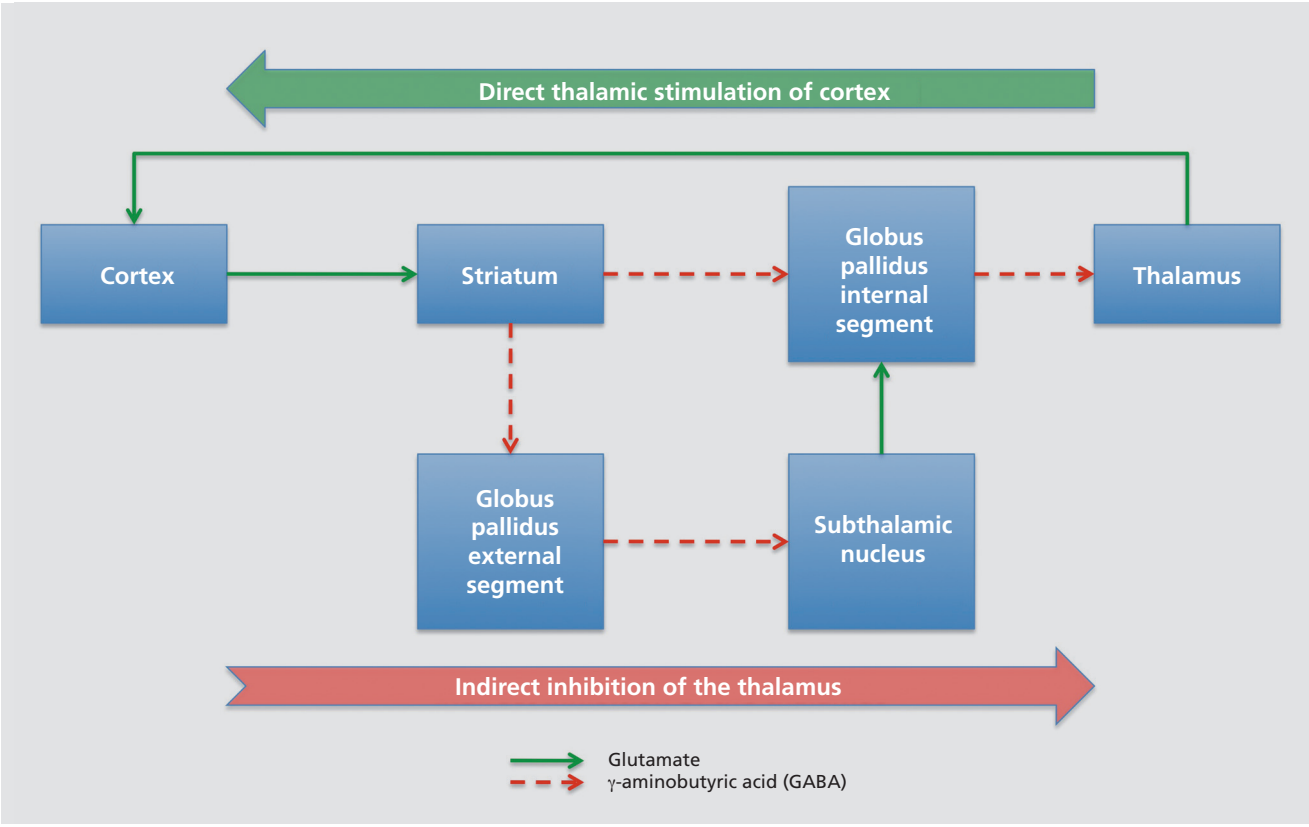

Figure 2. Basic schematic of the cortical-striatal-thalamic-cortical loop pertinent to pediatric obsessive-compulsive disorder.

Neuroimaging studies of pediatric OCD

Below is a brief review of neuroimaging studies of pediatric OCD. The aim is provide enough background to highlight the move to a translational approach from an investigative one. Reports relevant to the translational research approach are in the following section.

Frontal cortex

Rosenberg et al[31] did not find any significant difference in prefrontal cortex (PFC) volume between pediatric OCD patients and age- and sex-matched controls. However, the measurement of total PFC volume may have been too gross a measure, and more subtle abnormalities in specific subregions lost. Indeed, the genu of the corpus callosum, which connects aspects of PFC across the hemispheres, was found to be larger in pediatric OCD subjects.[32] Larger anterior cingulate volumes were also noted, consonant with the larger genu finding.[33] Anterior cingulate volume was correlated with OCD symptom severity (r=0.73, obsessive subscale). This was replicated in a second sample.[34] This is noteworthy as replication is rare in psychiatric research. Developmentally, the normal increase in anterior cingulate volume with age (r=0.45) was absent in patients with OCD (r=-0.12). Rosenberg and Keshavan[33] hypothesized that increased anterior cingulate volumes correlating with reduced basal ganglia volumes (r=-0.46) in pediatric patients with OCD is suggestive of neural network dysplasia—characterized by alterations in postnatal pruning. Developmentally, the greater anterior cingulate volume and lack of a correlation with age in pediatric patients with OCD may reflect delayed or reduced neural pruning, while reduced striatal volume might reflect increased pruning. No differences in posterior cingulate or dorsolateral prefrontal cortex (DLPFC) volume were noted.[33]

Subcortical and other regions

Smaller basal ganglia volumes have been reported in treatment-naïve pediatric OCD patients.[31] Furthermore, greater ventricular brain ratios have been observed in adolescent patients with OCD compared with healthy controls, which would be expected with decreased basal ganglia volume.[35] The thalamus was found to be larger in pediatric OCD patients as compared with controls, a difference that resolved with SSRI treatment[36] but not cognitive behavioral therapy.[37] Also in the thalamus, greater medial but not lateral thalamic choline was observed in pediatric patients with OCD compared with both healthy controls and patients with major depressive disorder (MDD).[38] The choline resonance is derived primarily from membrane lipid compounds, and the increase may be related to the volumetric alteration noted earlier.[36] Greater creatine concentration was also noted[39] in patients, perhaps reflecting a greater metabolic demand in the medial thalamus. Amygdala volume decreased with effective SSRI treatment in pediatric OCD patients.[40] Interestingly, the change in amygdala volume was not related to a change in OCD symptom severity, but correlated with SSRI dosage. Pituitary gland volume was significantly smaller in pediatric OCD patients as compared to matched controls.[41] This was especially apparent in males, highlighting a possible sex difference in OCD.

Glutamate and pediatric OCD proton magnetic resonance spectroscopy studies (1H-MRS)

The core excitatory neurotransmitter of this cortical-striatal-thalamic circuit mentioned earlier is glutamate. It was in 1998 that Rosenberg and Keshavan[33] first hypothesized a role for glutamate in pediatric OCD, and evidence of glutamate abnormalities in OCD has been mounting since. In the first report on glutamate in OCD, Rosenberg et al,[42] using proton magnetic resonance spectroscopy (1H-MRS), observed above-normal striatal glutamate + glutamine (Glx) concentrations in psychotropic-naive pediatric OCD patients as compared with controls, which normalized after effective treatment with an SSRI. This decrease in striatal Glx may endure after SSRI discontinuation.[43] Interestingly, the other treatment considered effective for OCD, CBT, did not alter caudate Glx concentrations in pediatric OCD patients despite a reduction in symptoms.[44] Conversely, in the anterior cingulate, a single-voxel 1H-MRS study found lower Glx concentrations in pediatric OCD patients than in healthy controls.[45] This was replicated in adults with OCD, where below normal anterior cingulate Glx was observed in female patients.[46] Lower anterior cingulate glutamate correlated with symptom severity in this sample. Again in adult OCD patients, Whiteside et al[47] observed elevated Glx/PCr+Cr (crea-

tine) levels in the orbital frontal white matter in patients as compared with controls. These effects appear to be regionally specific, with no effect noted in the occipital cortex, an area not typically implicated in the pathophysiology of OCD.[42] In conclusion, in vivo studies of the cortical-striatal-thalamic circuit in OCD have implicated glutamate directly. It is important to note, however, that correlation does not indicate causation and the overall weight of the evidence implicating glutamate should be considered.

Animal models and peripheral marker studies

These neuroimaging findings have been bolstered by studies using other methods and models. Chakrabarty et al[48] studied cerebral spinal fluid (CSF) concentration of glutamate in 21 psychotropic-naïve adults with OCD and 18 healthy controls. CSF glutamate concentration was significantly greater in OCD patients as compared with control subjects. Indirect support for glutamate involvement in OCD has also been provided by rodent models of obsessive-compulsive[49,50] and stereotypic behaviors.[51]

Glutamate transporter polymorphisms

Three independent groups have found that the 3' region of *SCL1A1* may contain a susceptibility allele for OCD, predominantly in male offspring.[52-54] The protein product is the high-affinity neuronal and epithelial transporter (EAAT3, EAAC1) for L-glutamate, L- and D-aspartate, and cysteine.[55,56] EAAT3/EAAC1 is found in cortex, basal ganglia, and hippocampus, and has been detected in all parts of the neuron.[57] In the adults, glutamate transport helps to keep extracellular glutamate below neurotoxic concentrations.[58] EAAT3/EAAC1 exhibits rather low expression and makes a minor contribution to the removal of synaptic glutamate as compared with EAAT1 and EAAT2.[59] During early brain development, it is expressed before astrocytes are functional. This is suggestive that EAAT3/EAAC1 is involved in the developmental role of glutamate.[59] A critical role of EAAT3/EAAC1 in neurodevelopment is consistent with the linkage and association findings supporting *SLC1A1* as a primary candidate gene in not only pediatric OCD,[52-54] but also in autistic spectrum disorders.[60] Testosterone and prolactin regulate the expression of EAAT3/EAAC1.[56] The increase in expression of EAAT3/EAAC1 by testosterone is consistent with the association of OCD with *SLC1A1* being strongest in males.[52,53] As for the possible function of the polymorphism, mice deficient in EAAC1 develop impaired self-grooming.[55] This suggests that EAAT3/EAAC1 knockouts in pediatric OCD may be associated with increased rather than with decreased EAAT3 expression.

Glutamate receptor polymorphisms

In addition to the glutamate transporter, the 5072T/G variant of NMDA subunit 2B gene (*GRIN2B*) has been associated with OCD in pediatric patients.[61] Specifically, the 5072G–5988T haplotype was associated with OCD. GRIN2B, on chromosome 12p, encodes for the NR2B subunit of the ionotropic glutamate receptor. It is expressed mainly in the striatum and the prefrontal cortex.[62] This consistent with regions demonstrating glutamatergic abnormalities in pediatric OCD patients.[42,45] Furthermore, GRIN2B has been linked to schizophrenia,[63] attention deficit hyperactivity disorder[64] and bipolar disorder.[65] During cortical development, GRIN2B is thought to play a role in plasticity.[66] In addition, neurotoxic levels of glutamate during the neonatal period increase the expression of NMDA NR2B in the striatum and cortex.[67] Functionally, the increased expression of GRIN2B in reaction to excess glutamate[68] suggests that pediatric OCD is associated with greater GRIN2B expression in the striatum. Most recently, a significant association was identified between the rs1019385 polymorphism of *GRIN2B* and decreased anterior cingulate cortex Glx but not with occipital Glx in pediatric OCD patients.[69]

Limitations to the glutamate hypothesis of obsessive-compulsive disorder

Clearly, a solitary neurochemical hypothesis of a psychiatric disorder is limited, as neurotransmitters do not operate in a vacuum. The preferential response of OCD patients to SSRIs has spawned the "serotonin" hypothesis of OCD. There is also neurobiological evidence to substantiate that assertion. For example, the serotonin transporter protein (5-HTPR) capacity indexed in platelets by 3H-paroxetine is reduced in pediatric OCD patients compared with controls.[70] However, the persistence of symptoms despite targeting serotonin pharma-

cologically indicates limits of the serotonin hypothesis of OCD.[16,17] Indeed, glutamate and serotonin interact on a number of levels in the frontal striatal circuit. For instance, Becquet et al[71] found that glutamate exerts a potent inhibitory effect on serotonin release in the caudate nucleus. In addition, the orbitofrontal cortex sends projections to dorsal raphe nuclei, which in turn sends serotonergic input to the striatum. The orbitofrontal cortex also has direct glutamate projections to the striatum, which play a role in the release and turnover of serotonin and regulation of serotonin receptor number in the striatum. Given the above evidence, we believe that glutamate is a logical choice for a biomarker and possible translational focus, as it may play a role in the pathophysiology of the disorder, the mechanism of action of the proposed medication, and its interplay with serotonin, the target of currently approved OCD medications.

Translational impact

Indeed, the glutamate hypothesis and consequent evidence have lead to the application of glutamate-modulating agents for the treatment of pediatric OCD *(Figure 3)*. Given the previously mentioned limitations of SSRI treatment for OCD, the search for novel medica-

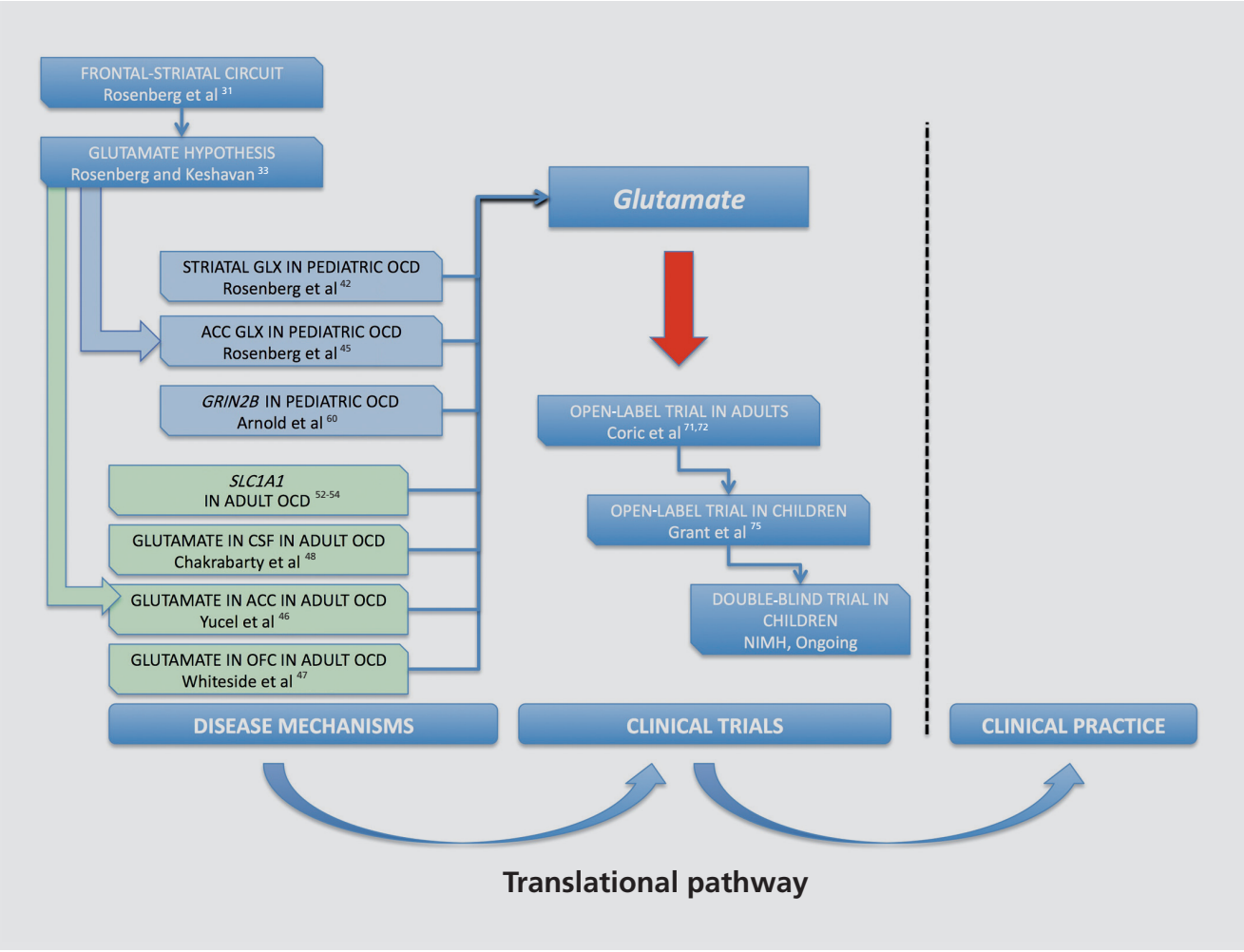

Figure 3. From initial findings to hypothesis to evidence and impact. The first hurdle in translational research has been crossed with neurobiological evidence being translated to clinical trials. ACC = anterior cingulate, Glx = glutamate + glutamine, *GRIN2B* = glutamate receptor gene, OCD = obsessive-compulsive disorder, *SLC1A1* = glutamate transporter gene

tions/applications and drug combinations is warranted. Recently, the glutamate modulating agent riluzole (1-amino-6-trifluoromethoxybenzothiazole) has shown promise in psychiatric disorders.[72-76] Riluzole is typically well tolerated by patients and is FDA-approved for the treatment of amyotrophic lateral sclerosis (ALS).[77-79] The mechanism of action of riluzole is not entirely clear. Riluzole can act in three ways: (i) as an inhibitor of glutamate release; (ii) inactivating voltage dependant sodium channels in cortical neurons; and (iii) acting to block γ-aminobutyric acid (GABA) reuptake.[80-82] In both a case report and an open-label trial in adults with OCD,[72,73] riluzole demonstrated an ability to reduce the symptoms of OCD. More recently, an open-label trial in pediatric OCD patients (8 to 16 years) found that riluzole was both beneficial and well tolerated.[76] Currently, a National Institutes of Mental health-sponsored large double-blind clinical trial is under way. Given the above neurobiological findings and clinical reports, glutamate modulating agents like riluzole offer particular promise as an anti-OCD therapies.

Other glutamate and GABA-modulating agents have shown some promise as well. For example, topiramate has shown some promise in treating OCD in adults.[83-85] However, there are case reports indicating that some glutamate modulating medications (lamotrigine, topiramate) have induced OCD-like behaviors.[86-88] Furthermore, the occurrence of skin rash with lamotrigine treatment is also a concern.[89] Aside from safety, the mechanism of action is also important in choosing which glutamatergic agent. While topiramate enhances GABA activity and lamotrigine is a sodium channel blocker, riluzole acts primarily to inhibit glutamate. Given the above neurobiological findings and clinical reports, glutamate modulating agents like riluzole, offer particular promise as an anti-OCD therapies.

Conclusions

There is converging biological evidence indicating a role for glutamate in the symptoms of OCD.[42,45,47-49,52-54,61,90] Additionally, pharmacologically modulating glutamate has been shown to have an effect on OCD symptoms.[72,75,76] Hence, 1H-MRS, CSF, genetic, animal, and clinical studies have all implicated glutamate in OCD, indicating a clear conceptual link between glutamate and OCD symptoms. Indeed, the work on the glutamate hypothesis in pediatric OCD fits with Dr Tomas Insel's call for "rational therapeutics" for psychiatric illness.[91] Considering the large number of nonresponders and residual symptoms in even patients classed as responders to SSRI treatment, there is a pressing need to find better therapies. This work may have high clinical impact as it may stimulate the wider application of glutamate modulating agents for pediatric OCD. As mentioned earlier, the traditional strategy of going from pharmacology to pathophysiology has failed to show real progress in our understanding of the neurobiology of psychiatric illness.[19] New approaches, such as discussed here, may allow for progress that is more substantial. Given the findings regarding glutamate and OCD, and the development of novel safe agents that modulate glutamate, we could be on the cusp of breakthrough. As with any new medication intervention, there is the risk of failure. However, the payoff is enormous, as a much-needed new avenue of treatment will be developed. ❑

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La investigación translacional de neuroimágenes en el trastorno obsesivo-compulsivo pediátrico

El trastorno obsesivo-compulsivo (TOC) es un importante problema de salud pública. Los inhibidores selectivos de la recaptura de serotonina (ISRS) son los únicos medicamentos aprobados por la FDA para el TOC. Sin embargo, los ISRS en la práctica clínica son de una eficacia limitada. Considerando la persistencia de los síntomas y los niveles de respuesta terapéutica, es claro que el paradigma serotoninérgico del TOC no da cuenta totalmente de la neurobiología del trastorno y se requiere de más investigación translacional. En esta revisión se explora la hipótesis glutamatérgica del TOC pediátrico, se revisan las evidencias de las neuroimágenes y los impactos translacionales más destacados. La estrategia tradicional de ir desde la farmacología a la fisiopatología no ha podido mostrar el real progreso en nuestra comprensión de la neurobiología de la enfermedad psiquiátrica y, aunque sea en las primeras etapas, este trabajo demuestra el claro beneficio de una aproximación a la enfermedad psiquiátrica en el sentido opuesto.

Recherche translationnelle en neuro-imagerie dans le trouble obsessionnel compulsif de l'enfant

Le trouble obsessionnel-compulsif (TOC) est un important problème de santé publique. Les inhibiteurs sélectifs de la recapture de la sérotonine (ISRS) sont les seuls médicaments pour le TOC approuvés par la FDA, bien qu'ils soient peu efficaces en pratique clinique. Étant donné la persistance des symptômes et les taux de réponse au traitement, il est clair que le modèle sérotoninergique du TOC ne rend pas vraiment compte de la neurobiologie du trouble et qu'une recherche translationnelle supplémentaire est nécessaire. Nous examinons dans cet article l'hypothèse glutamatergique du TOC chez l'enfant, nous passons en revue la neuro-imagerie et nous insistons sur l'impact translationnel. La stratégie classique allant de la pharmacologie à la physiopathologie n'a pas réussi à montrer un vrai progrès dans notre compréhension de la neurobiologie de la maladie psychiatrique et, alors qu'il en est encore aux premiers stades, ce travail démontre le véritable bénéfice d'une approche inverse de la maladie psychiatrique.

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