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Obsessive-compulsive disorder, insulin signaling and diabetes – A novel form of physical health comorbidity: The sweet compulsive brain

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ABSTRACT

Background: While a growing body of research highlights a bi-directional link between diabetes and mood disorders, little is known about the relationship between diabetes and obsessive-compulsive disorder (OCD). The aim of the present review is to investigate current evidence linking OCD, insulin-signaling and diabetes.
Methods: A PubMed search was conducted to review all the available studies assessing diabetes, glucose metabolism and insulin-signaling in OCD patients and vice versa.
Results: Some clinical and epidemiological studies show a higher prevalence of diabetes in OCD and vice versa compared to the general population. Animal and genetic studies suggest a possible role of insulin-signaling in the pathophysiology of OCD. Deep brain stimulation (DBS) studies suggest that abnormal dopaminergic transmission in the striatum may contribute to impaired insulin sensitivity in OCD. While DBS seems to increase insulin sensitivity, a possible protective role of serotonin reuptake-inhibitors on diabetic risk needs further studies.
Conclusion: Despite their preliminary nature, these data highlight the importance of further investigations aimed at assessing metabolic features in OCD patients and OCD symptoms in diabetes patients to understand the impact of each condition on the pathophysiology and course of the other. Understanding the role of insulin in the obsessive-compulsive brain could open new treatment pathways for OCD.

1. Introduction

Diabetes, especially type 2 diabetes mellitus (T2DM), is a widely prevalent and disabling condition worldwide [1]. Diabetes is more and more recognized as a frequent comorbid condition across psychiatric disorders especially in mood and psychotic disorders [2,3]. The relationship between diabetes and psychiatric disorders is complex and bi-directional. Longitudinal population-based studies show an almost double risk of cardiovascular diseases and type 2 diabetes in psychiatric patients with a diagnosis of schizophrenia, bipolar disorder or depression relative to the general population, even after controlling for the use of psychotropic medications [4]. Conversely, large-scale multicenter trials show that moderate-severe depressive symptoms are present in up to 17% of diabetic patients, and 10% of diabetic patients have a diagnosis of major depression [5]. Also, recent meta-analyses show that bipolar patients have a double risk of T2DM relative to non-psychiatric populations and around 20% of bipolar patients have a diagnosis of diabetes while 30% have a pre-diabetes condition [6].

Several hypotheses have been proposed to explain the link between mood disorders and diabetes highlighting a putative role of inflammation, hypothalamic-pituitary-adrenal (HPA)-axis dysregulation, gut microbiota alterations, circadian rhythms dysregulation, genetic and lifestyle factors [7]. In fact, all these factors have been suggested to influence glucose metabolism and insulin signaling. In this perspective, the role of insulin and insulin-signaling in the brain gained a lot of attention in the last years. Insulin has relevant non-metabolic functions in the brain, including neural survival, synaptic and dendritic plasticity, learning and memory, neural circuitries formation and dopaminergic transmission modulation in the striatum and brainstem [8–16]. To exerts these functions, insulin reaches the brain from the periphery through the blood-brain barrier binding to specific insulin receptors in both neurons and glial cells [8]. Also, insulin can directly alter white matter microstructures in both type 1 and 2 diabetic patients and adults with hyperglycemia [17].

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While the literature on diabetes and mood disorders has grown in the last decades, little is known about the link between diabetes, insulin-signaling and obsessive-compulsive disorder (OCD). Factors mediating mood disorders in diabetes, such as Inflammation, HPA-axis dysregulation and gut microbiota alterations, have also been associated to OCD [18–24]. Also, OCD has been related to dysfunctional dopaminergic transmission in the striatum and insulin is known to modulate dopaminergic mesolimbic pathways and vice versa [8,25]. Therefore, the aims of the present study are to: (a) review the current clinical and biological evidence linking insulin-signaling, diabetes and OCD, (b) review current hypotheses about the interconnections between impaired insulin-signaling, dopaminergic transmission, inflammation, HPA-axis dysregulation and gut microbiota alterations as hypothetical mechanisms involved in the co-occurrence of diabetes and OCD, and, finally, (c) discuss the literature gaps, open issues and implications for future research in this field.

2. Methods

In this narrative review, we aim to include all the available data in the field of OCD, insulin-signaling, diabetes and glucose metabolism. For this purpose, a PubMed search was conducted by two independent reviewers (GG and AP) using terms related to OCD ("obsessive-compulsive disorder" OR "obsessions" OR "compulsions") combined through the Boolean operator AND with terms related to diabetes ("diabetes", "insulin", "insulin-signaling" "glucose metabolism" "metabolic disorders"). We included English papers published in peer-review journals without restrictions related to publication date. In each section we review the data on the relation between OCD, insulin-signaling and glucose metabolism, while in the last section we discuss future implications and needs for further study.

3. Clinical evidence for a link between diabetes, insulin signaling and OCD

3.1. Epidemiological studies

An early Italian cross-sectional study showed a 21,2% prevalence of metabolic syndrome (including the presence of obesity, hypertension, diabetes and dyslipidemia) in a sample of 104 OCD patients [26]. This prevalence rate was higher than those reported in the Italian general population, although the confidence interval encompasses the general population estimate reported. In this study, the presence of metabolic syndrome was associated with lifetime exposure to antidopaminergic drugs [26]. A subsequent Italian study reported a similar rate of metabolic disorders (19,8% of metabolic syndrome and 6,2% of diabetes) in a sample of 162 OCD patients and a correlation between the presence of any medical condition and older age and the absence of physical activity [27]. A large longitudinal population-based study in Sweden on more than 25.000 OCD patients followed for 40 years showed that OCD patients have a higher risk (up to 45% higher) of obesity, type 2 diabetes mellitus and circulatory system diseases compared to their relatives and the general population (odds ratio of 1.22 for T2DM). Results remain largely similar when different groups of psychiatric comorbidities were excluded and the increased risk of metabolic and circulatory disease for OCD patients was evident from the beginning of the follow-up. In this study, selective serotonin reuptake inhibitors (SSRIs) (with or without antidopaminergic augmentations) reduced the observed risk in a dose and time-dependent manner [28]. However, the authors are cautious to attribute the observed risk reductions to medications alone, since the design of the study did not allow to exclude an indirect effect of SSRI on metabolic risk (e.g. the effect of lifestyle changes that follow a sustained symptom reduction associated with evidence-based treatment in general) [28].

These European data are consistent with a large epidemiological study in Singapore showing that OCD patients have an increased risk of diabetes relative to the general population (odds ratio of 3.1) [29]. Interestingly, another large epidemiological survey in Singapore, examining changes in the prevalence of comorbidity of mental and physical disorders between 2010 and 2016, found a significant increase of the prevalence of diabetes in OCD patients (from 4.1% in 2010 to 10.9% in 2016) and of the prevalence on OCD in diabetic patients (from 1.4% in 2010 to 3.9% in 2016) [58].

On the other hand, a previous large international cross-sectional survey on DSM-IV mental disorders and a series of physical chronic diseases, found an association between only depression, eating disorders, intermittent explosive disorder and type 2 diabetes [59]. However, respect to the Swedish study, this survey was not longitudinal, the OCD sample was almost one quarter of the Swedish one and the diabetes diagnosis was only retrospectively self-reported. Of note, a German survey on the general population did not found a correlation between OCD symptoms and diabetes but found that subjects self-reporting both OCD symptoms and physical diseases (including diabetes) reported a higher number of days of disability due to physical or psychological problems relative to subjects with only OCD symptoms [30].

Sparse studies focused on OCD in diabetic patients. An early study in 1990 reported a higher prevalence of obsessive-compulsive symptoms in insulin-dependent diabetic patients relative to healthy controls (41% vs 21.3%) [31]. A study on pregnant women showed that type 1 diabetic women have higher rates of OC symptoms (a mean difference up to 40%) during pregnancy compared to women with gestational diabetes without a previous history of diabetes [32]. Also, a small sample study comparing patients with a history of rheumatic fever (a population suggested to have higher rates of OCD by a subsequent larger study [60]) and type 1 diabetic patients found low but similar rates of OCD and OC symptoms across the two groups [33]. Of note, a Norwegian epidemiological study on mental health in adolescents with diabetes did not find differences between OCD symptoms and other psychiatric disorders between subjects with or without type 1 diabetes [34]. However, this study failed to include a validated tool for the assessment of OC symptoms.

Evidence of a link between OCD and diabetes in the literature also exist for type 2 diabetes. A large study on more than 9000 Chinese adults found a higher prevalence of obsessions in newly diagnosed diabetic and pre-diabetic subjects relative to non-diabetic controls (odd ratios of 1.20–1.29) [35]. Also, a Brazilian study on insulin-dependent type 2 diabetic patients found a higher prevalence of anxiety disorders and OCD relative to healthy controls (with and odd ratio of 2.47 for OCD) [38]. Finally, two independent studies showed higher prevalence of OC symptoms (OCS) in uncontrolled respect to controlled diabetic patients and a correlation between OCS and levels of HbA1c (a medium-term glycemic index with higher levels indicating an uncontrolled diabetes) [36,37]. In the first study the correlation was especially evident in women [36], while in the second study uncontrolled diabetic patients, independently by gender, have a 5.5 higher risk of having OCS [37]. Of note, this latest study showed a prevalence of OCD symptoms (expressed as a Y-BOCS score higher than 15) in more than 50% of the sample (with a total sample of 400 T2D patients) and a double risk of having OC symptoms in women [37].

Taken together, these data might suggest a possible bidirectional association between OCD and diabetes. Except for one study correlating OCD metabolic dysfunctions with antidopaminergic treatments, large epidemiological evidence suggests that pharmacological treatment with SSRIs may be protective (at least indirectly) against metabolic and cardiovascular diseases. However, data on the effect of possible moderators such as psychiatric and medical comorbidities, life-style, age at onset and duration of illness are still largely lacking.

4. Biological evidence for a link between diabetes, insulin signaling and OCD

4.1. Genetic studies

In 2016 van de Vondervoort and colleagues conducted a study aimed to identify the molecular mechanisms underlying OCD by integrating the top-ranked results from the existing GWAS association studies with genes implicated in OCD through other evidence (e.g. a gene associated with OCD in at least a human and an animal genetic study). The authors selected the top-ranked GWAS finding (89 genes presenting the most significant *p* values) and other 26 candidate genes (selected from other genetic studies) and therefore conducted a literature search in order to define the (putative) function and neuronal expression of these genes. The results of this study show that more than 40% of the proteins encoded by the selected genes (implicated in OCD pathophysiology) functionally interact within a distinct "hypothetical" molecular landscape. This molecular OCD landscape contains a number of signaling cascades that are involved in the endogenous synthesis, secretion and extracellular signaling of insulin in and around postsynaptic dendritic spines and that regulate the formation of these spines, which in turn affects and regulates synaptic plasticity. Also, in this molecular landscape, two additional signaling cascades centre around receptors for the neurotransmitters glutamate and serotonin (both linked to OCD pathophysiology), and both cascades regulate the secretion of insulin that can have autocrine or paracrine effects on (neighbouring) neurons, leading to the modulation of dendritic spine formation. The authors, concluded that this model suggests that OCD is associated to genes regulating postsynaptic dendritic spine formation and function through insulin-dependent serotonergic and glutamatergic signaling [39].

In line with this model, a recent study by the same group identified a shared genetic risk between OCD/OCS and insulin related traits [40]. In this study, the authors compared the polygenic risk scores of 51 CNS insulin-linked genes (extracted from the molecular landscape mentioned above), five peripheral insulin-signaling related traits (presence of T2D, increased Hb1Ac levels, increased fasting insulin levels and increase fasting glucose levels and increase level after 2 h of a glucose challenge) and OCD-related genes (extracted from previous large GWAS association studies) in a population-based sample of 650 children and adolescents and in a second replication sample of more than 5000 adolescents (aged 7–17 years) [40]. The results showed a correlation between both CNS and peripheral insulin-linked genes and OC symptoms. Also, the authors found a shared genetic risk between two of the four T2D blood markers (increased blood levels of fasting insulin and increase 2 h glucose levels) and OCD [40].

4.2. Preclinical studies

TALLYHO/JngJ (TH) mice are a reliable murine model for diabetes since these mice develop hyperglycemia, hyperinsulinemia, and enlargement of the islets of Langerhans [41]. In a recent study, TH mice showed increased compulsive-like and anxiety behaviors (expressed by reduced spontaneous alternation behavior and reduced time spent in the open arm respectively) relative to control mice [17]. Interestingly, compulsive-like behaviors in TH mice were correlated to blood glucose levels. TH mice showed increased levels of glucose in the dorsal-medial striatum (DMS) as measured with magnetic resonance spectroscopy (MRS) and again these levels correlated with compulsive-like behaviors (e.g. the higher glucose levels correlated with reduced spontaneous alternation behavior). Also, diffusion tensor imaging (DTI) showed altered structural connectivity (reduced fractional anisotropy) in the DMS (and other brain regions) that was correlated to behavioral flexibility, therefore suggesting the hypothesis that increased glucose levels in DMS may increase compulsive-like behaviors through altered structural connectivity (despite the authors did not report any correlation between MRS and DTI results). Moreover, TH mice had higher levels of glutathione, whose production is stimulated by insulin, in the anterior cingulate cortex (a region previously implicated in OCD). Finally, the authors found decreased levels of insulin grow factor 1 (IGF-1) in the mice's cerebellum and increased IGF-1 blood levels [17]. This latter result is particularly intriguing in the light of two recent studies showing increased blood levels of IGF-1 in adult OCD patients relative to controls and a positive correlation between baseline IGF-1 levels and SSRIs response in drug-naïve OCD patients [42,43].

Another study revealed that streptozotocin (STZ)-induced diabetic mice show increased compulsive behaviors (expressed as increased marble burying behaviors) compared to non-diabetic mice[44]. Treatment with both metformin and genistein (an isoflavonoid phytoestrogen known to have neuroprotective, anti-inflammatory and antidiabetic effects) significantly reduced compulsive behaviors to a comparable degree as did fluoxetine [44].

4.3. Deep brain stimulation studies

In 2018, a study in OCD patients undergoing deep brain stimulation (DBS) of the ventral anterior limb of the internal capsule (vALIC) highlighted a putative role of striatal dopamine transmission in glucose metabolism and insulin sensitivity [45]. This study started from the observation of increased peripheric insulin sensitivity in an OCD patient with insulin-dependent diabetes after vALIC-DBS. Subsequently, the authors found that vALIC-DBS increased hepatic and peripheral insulin sensitivity in a sample of 14 non-diabetic OCD patients. The authors argued that these effects could be potentially related to an increase of dopamine transmission in the striatum. Indeed, the same group demonstrated in previous work that vALIC-DBS increased striatal dopamine transmission as confirmed by reduced dopamine D2/3 receptor availability in the striatum after acute and chronic DBS [46]. The authors assessed insulin sensitivity in a group of healthy controls after the induction of an acute dopamine depletion, through a pharmacological inhibition of tyrosine hydroxylase, the rate-limiting enzyme in endogenous dopamine synthesis. Acute dopamine depletion decreased peripheral insulin sensitivity in this sample of healthy subjects supporting the role of central dopamine in insulin sensitivity. Finally, these results were further corroborated by a preclinical investigation in which optogenetic activation of dopamine D1 receptor–expressing neurons in the nucleus accumbens (NAcc) increased glucose tolerance and insulin sensitivity in mice [45]. All together, these findings point toward a central role of striatal dopamine transmission in glucose metabolism and insulin sensitivity. A potential mechanism for Nacc modulation of glucose metabolism discussed by the authors is a Nacc-hypothalamus interaction. DBS of the the shell of the Nacc increases peripheral glucagon and glucose levels in mice that is coupled to an activation of the lateral hypothalamic area [47].

5. Hypotheses linking diabetes, insulin signaling and OCD

Several factors could be implicated in a potential link between diabetes, insulin-signaling and OCD.

Lifestyle factors associated with OCD could potentially play a role in the emergence of metabolic disorders. For example, reduced physical activity, disruption of circadian rhythms and sleep disorders are associated to OCD and these factors have a negative impact on glucose metabolism and insulin sensitivity [48,49]. In line with this, one of the presented studies showed a correlation between absence of physical activity and the presence of a general medical condition (including metabolic disorders) [27]. Also, mood and anxiety comorbidities are common in OCD and have been associated to diabetes and impaired insulin-signaling, both directly and indirectly through changes in lifestyle habits [1,6,50]. Unfortunately, not all of the reviewed studies controlled for these factors and therefore these hypotheses should be addressed in future studies.

Conversely, several biological factors could play a role in mediating

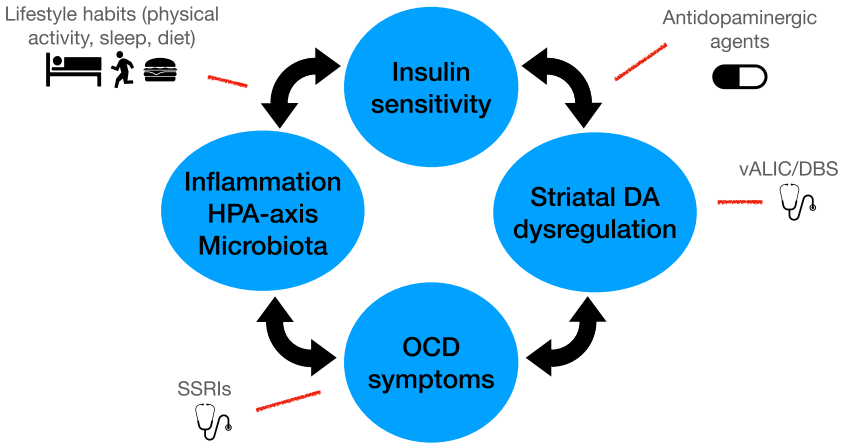

Fig. 1. Hypothesized interconnections between insulin signaling dysregulation, dopaminergic dysregulation, inflammation, HPA-axis dysregulation and gut microbiota. In this model striatal dopamine, inflammation, HPA-axis and gut microbiota are hypothesized to influence both OCD symptoms and insulin-signaling. vALIC-DBS increases peripheral insulin sensitivity through increase of striatal dopamine release. Antidopaminergic agents worsen insulin sensitivity (through striatal dopamine blockade and/or other pathways). SSRIs acts on OCD symptoms and may lower the risk of diabetes. Lifestyle habits (physical activity, sleep habits and diet) may influence insulin-sensitivity directly or through other factors (e.g. increasing inflammation, altering HPA-axis and/or gut microbiota). DA: dopamine; HPA-axis: hypothalamic-pituitary-adrenal axis.

insulin-signaling alterations in OCD. First, according to human and preclinical studies, insulin is known to modulate dopaminergic transmission in the mesolimbic circuitry and vice versa [8]. OCD is associated to impaired dopaminergic transmission which may impair insulin sensitivity similar to what has been found in healthy controls [25,45]. In line with this hypothesis, non-overweigh OCD patients treated with vALIC-DBS (known to increase dopaminergic transmission in the striatum) showed increased insulin sensitivity after treatment [45]. Additionally, dopamine blockade induced by antidopaminergic medications for OCD could also contribute to dysregulated insulin-signaling [26]. Second, the presence of inflammation, HPA-axis dysregulation and gut microbiota alteration, factors that all have been related to OCD, have also been related to insulin-signaling dysregulation and impaired peripheric insulin sensitivity through different mechanisms [18,23–24,49,51–55]. Indeed, stress-related activation of the HPA-axis is known to alter insulin-signaling (through the release of cortisol) and to induce inflammatory response, as well as inflammation has been linked to both HPA-axis dysregulation and insulin resistance [49,54]. Also, alteration of gut microbiota can play a role in this triangle by increasing systemic inflammation and altering insulin-signaling and brain functions [55]. Although the role of inflammation, HPA-axis dysregulation and gut microbiotia alteration on diabetes and metabolic disorders' pathophysiology has been largely studied [61], their potential role in OCD pathophysiology and neuroinflammation remain speculative. However, it could have several potential treatment implications. For instance, it will be interesting to understand if anti-inflammatory agents (e.g. non-steroidal anti-inflammatory drugs, NSAIDs, that show preliminary positive effects in OCD trials) may induce a more robust improvement on OCD symptoms in the context of a metabolic illness [51]. On the other hand, it will be interesting to investigate the potential anti-obsessive effects of anti-diabetic drugs. In this latest perspective, one animal study showed an anti-compulsive effect of metformin and at least one case report in the literature showed improvement of OC-like symptoms in an autistic patient after treatment with liraglutide, a glucagon-like peptide-1 analog [62]. Similarly, future research might explore the effects of cognitive-behavioral therapy (CBT) on metabolic features in OCD patients, as data from samples with chronic disorders showed that CBT outcomes may be associated with an improvement in the function of immune system [64,65] and brain-gut-microbiome axis [66].

Finally, we argue that the presented biological factors may all be interconnected and modulated by life-style factors, leading to a different impact on each individual patient and causing an insulin dysregulation up to diabetes in a subset of patients (see Fig. 1).

6. Clinical implications and open issues

Taken together, the epidemiological, clinical and animal studies presented in this review seem to converge toward a link between insulin-signaling, glucose metabolism and OCD. This preliminary evidence makes a relevant point that has been partially neglected in the literature: the relevance of metabolic assessments in OCD patients. Clinician should assess familial risk of metabolic disorders and monitor metabolic parameters (such as body mass index, blood glucose levels, dietary habits, physical activity and sleep patterns) during the course of treatment (especially when prescribing antidopaminergic agents), in order to understand and prevent their impact on OCD severity and trajectory. Also, this literature once again confirms the importance of providing OCD patients with a proper treatment. Indeed, while the metabolic impact of SSRIs is still debated (with several studies showing a negative metabolic impact [63]), OCD patients treated with medium-high doses of SSRIs seem to show a reduced metabolic risk over time, suggesting at least an indirect positive metabolic effect of a proper pharmacological treatment of the disorder (for example inducing lifestyle changes that follow a sustained symptom reduction). Moreover, vALIC-DBS (an established treatment for refractory patients) show a positive effect on insulin sensitivity and glucose metabolism. Finally, current data also support the importance of lifestyle interventions (widely used for metabolic disorders) in the management of OCD. Some studies have already demonstrated that physical activity (mainly moderate aerobic activity) significantly reduces OCD symptoms at least in the short term [56,57].

However, the available literature also presents several limitations and open issues. First of all, most of the studies did not control for comorbidities such as mood and anxiety disorders which are linked to diabetes. For instance, one large epidemiological study still found significant increased od ratios of diabetic risk even after removing most other disorders (including mood disorders) but not when removing anxiety disorders (that are highly comorbid with OCD) [28]. Also, data on the prevalence of food addiction (as a proposed behavioral addiction) in OCD are largely lacking in the current literature and none of the presented studies assessed behavioral addictions as moderator factors.

Moreover, except for one study showing a correlation between the absence of physical activity and the presence of medical conditions, no studies analyzed the impact of lifestyle habits such as the level of daily of physical activity, sleep patterns and diet on metabolic profiles of patients with OCD. Another issue regards the temporal relationship between OCD and diabetes, as two studies showed higher OCD symptoms in uncontrolled respect to controlled diabetes but no prospective study investigated a potential correlation between improved diabetic control and improved OCD symptoms over time [37,38]. Finally, little is known about how other clinical characteristics (e.g. age at onset, illness duration, duration of untreated illness, symptom dimensions) could

moderate the link with diabetes and how the presence of diabetes could affect OCD contents (e.g. inducing compulsive checking of glycemic parameters etc.) [37].

Future research based on prospective designs with long-term follow-up assessments are necessary to better clarify the role of comorbidities, lifestyle habits, biological and genetic factors (e.g. inflammatory status and familial risk factors) and medications (especially antidopaminergic agents) in the emergence of insulin-signaling dysregulation in OCD patients.

7. Conclusion

A converging literature seems to supports a bi-directional link between diabetes and OCD. Some studies suggest that diabetes might be more prevalent in OCD, and OCD more prevalent in diabetes, relative to what is expected in the general population. To better clarify a potential role of OCD as risk factor for the development of diabetes or vice versa, further large-sample, long-term longitudinal studies are warranted. Impaired insulin-signaling plays a potential role in the pathophysiology of OCD symptoms via abnormal dopaminergic transmission in the striatum. While vALIC-DBS may improve insulin sensitivity and lower the risk of metabolic disorders and diabetes, a potential protective role of SSRIs should be better investigated by future randomized placebo-controlled trials. The role of comorbidities, lifestyle habits and other factors related to OCD and diabetes, such as inflammation, HPA-axis regulation and gut microbiota, remains to be elucidated.

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