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Childhood obsessive-compulsive disorder, epigenetics, and heterochrony: An evolutionary and developmental approach

Matteo Tonna[1,2], Davide Fausto Borrelli[1,3], Carlo Marchesi[1,2], Maria Carla Gerra[4,*] and Cristina Dallabona[4,*]

[1]Department of Medicine and Surgery, Psychiatric Unit, University of Parma, Parma, Italy, [2]Department of Mental Health, Local Health Service, Parma, Italy, [3]Department of Mental Health, Local Health Service, Piacenza, Italy and [4]Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma, PR, Italy

Abstract

Childhood obsessive-compulsive disorder (OCD) stems from a bunch of restricted and repetitive behaviors, which are part of normal behavioral repertoire up to the age of 7. The persistence of compulsive-like behaviors after that age is often associated with unique comorbidity patterns, which are age-at-onset dependent and reflect different developmental stages. In particular, OCD synchronically co-occurs with a broad constellation of neurodevelopmental disorders, whereas diachronically it is related to an increased risk of major adult psychoses. Moreover, OCD is associated with trait-like sensory phenomena, suggesting a common disrupted sensorimotor grounding.

The present study is aimed at exploring the hypothesis that this specific temporal and comorbidity OCD profile may be due to a developmental heterochronic mechanism of delay in attenuation of ontogenetically early behavioral patterns. The developmental shift of highly evolutionarily conserved behavioral phenotypes might be regulated by epigenetic changes induced by different conditions of sensory unbalance. This evolutionary and developmental model allows capturing childhood OCD in light of the ultimate causes of ritual behavior throughout phylogeny, namely its "homeostatic" function over conditions of unpredictability. Moreover, it may have important clinical implications, as OCD symptoms could represent putative biomarkers of early divergent developmental trajectories, with a pathoplastic effect on course and outcome.

Keywords: autism; neurodevelopment; ritual behavior; schizophrenia; sensorimotor

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Introduction

Obsessive-compulsive disorder (OCD) is a disabling and chronic condition characterized by persistent and unwanted intrusive thoughts, images and urges (obsessions) and repetitive behaviors or mental acts (compulsions) (American Psychiatrc Association, 2013). Even though OCD has been historically considered rare in youth (Geller, 2006), more recent evidence suggests that OCD is actually one of the most common psychiatric disorders in childhood, with an estimated prevalence of 0.25% – 4% among children and adolescents (Krebs & Heyman, 2015). In this regard, OCD characteristically presents two peaks of incidence: an early peak with a mean age of 9 to 10 years (with an SD of± 2.5 years) and a later peak in the early 20s (Geller et al., 2000).

Childhood OCD is physio-pathologically related to a broader constellation of restricted and repetitive behaviors (RRBs), characterized by repetition and invariance (e.g., motor stereotypies, ritualistic behaviors, rigid and inflexible routines, circumscribed and intense interests or activities), which represents a normal behavioral repertoire in early childhood (De Caluwé et al., 2020). During development, obsessive-compulsive symptoms (OCS) are a core behavioral phenotype of many etiologically defined or idiopathic neurodevelopmental disorders (Wolff et al., 2016), whereas longitudinally they are associated with an increased risk of severe psychiatric conditions in adulthood (Micali et al., 2010), including both major endogenous psychoses (Cederlöf et al., 2015).

Therefore, despite the robust epidemiological evidence, three major challenges concern the theoretical conceptualization and clinical identification of childhood OCD. 1) Its relationship (continuity/discontinuity) with normal patterns of ritualistic/routinized behaviors in typically developing children. 2) The synchronic association with different neurodevelopmental disorders. 3) The diachronic association with both affective and non-affective psychoses in late adolescence/early adulthood.

From a developmental perspective, childhood OCD appears in continuity with normative RRBs, from which OCS would stem following an altered trajectory relative to the expected pattern, particularly for those children with or at risk of various neurodevelopmental perturbations (Wolff et al., 2016), with a profound impact on the maturation of sensorimotor connectivity (Cascio, 2010). The study hypothesis is that childhood OCD may at least in part reflect a developmental heterochronic shift of behavioral phenotypes characteristic of all children during specific brain maturation stages, triggered by different sources of sensory

Corresponding author: Matteo tonna; Email: matteo.tonna@unipr.it
*These authors equally contributed to this work

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unbalance. In this regard, epigenetic regulation might mediate the relationship between the lack of attenuation of compulsive-like behaviors and sensorimotor dysconnectivity. During development, in fact, behavioral outputs are strongly shaped by epigenetic changes (Zhu et al., 2022). In particular, during brain maturation stages, which extend from about three weeks after conception throughout childhood and adolescence, sensorimotor connectivity patterns are characterized by rapidly forming, plastic circuits, which heavily depend on epigenetic modifications (Murgatroyd & Spengler, 2012). In turn, epigenetic regulation is highly susceptible to influences from prenatal or postnatal experiences and may be transient or persist throughout a lifetime (Weaver et al., 2004).

The present study aims to offer a working hypothesis on the epigenetic and developmental mechanisms beneath OCD in youth within an evolutionary framework, to grasp the clinical significance and ultimate causes of compulsive-like rituals in childhood and, in particular, to investigate a putative role of OCS as early and reliable biomarkers of different neurodevelopmental conditions. Improved characterization of developmental trajectories of childhood OCD might in fact contribute to better identify at-risk children and delineate clinically meaningful subgroups based on shared and specific phenotypes.

Methods

Given the specific clinically-tailored scope, a narrative review on the different and articulated aspects of the hypothesis proposed was considered more suited than a systematic review. The Web of Science and PubMed databases were searched for articles that met these issues, using a range of related search terms and cited papers within salient articles. Searches were performed in titles and abstracts, using keywords grouped under two blocks separated by 'AND'. In particular, articles were searched with the following keywords: ("restricted and repetitive behaviors" or "rituals" or "obsessive-compulsive disorder") AND ("children" or "adolescents"); ("obsessive-compulsive disorder") AND ("epigenetics" or "sensory phenomena" or "neurocognition"). The search was conducted in February 2023 and updated in September 2024.

The first author screened all articles based on title (and abstract). Irrelevant articles were excluded, i.e., if they: 1) did not focus on normative rituals/routines or OCD/OCS; 2) did not address younger age groups; 3) were not peer-reviewed articles or did not have a full-text version (e.g., meeting abstracts or expert opinions); 3) were not conducted in humans; 4) had no English full text. To test objectivity and inter-rater agreement, the second author independently screened 10% of the articles based on title (and abstract).

Findings are organized in the following sections related to childhood OCD: relationship with normative rituals, specific comorbidity profile, sensory phenomena, neurocognitive profile, epigenetic mechanisms. In the final section, clinical, psychopathological, neurophysiological and epigenetic data are integrated and discussed together to propose a coherent evolutionary and developmental hypothesis of childhood OCD.

Normative rituals and childhood OCD

From the age of two, RRBs are included in the normal behavioral pattern of young children: complex rituals, particularly at times of transitions (e.g., mealtime, bedtime, bath), are reported in around 80% of toddlers and preschool children (Evans et al., 1997; Leonard et al., 1990). Rigid adherence to "just right" or sameness in daily routines, as well as hyper-attention to minute details such as imperfections or peculiarities in clothes and toys are common features of these compulsive-like behaviors (Evans & Maliken, 2011). Interestingly, there seems to be a specific temporal window for normative rituals during development, with a peak between the ages of 2–6, followed by a linear decline around the age of 7 (Glenn et al., 2012). It has been argued that RRBs have an adaptive significance in early childhood, as they give order and predictability over daily life contingencies (Evans & Maliken, 2011). This is in accordance with the common evidence that rituals in youth are preferentially triggered by abrupt changes in the physical environment or in the daily routine, that are experienced by young children as essentially chaotic or uncontrollable (Zohar & Felz, 2001). Following the development of executive function skills along with the maturation of the prefrontal cortex, children gradually abandon RRBs, which no longer constitute an age-appropriate response, to rely on more flexible and contextual coping mechanisms (Zohar & Dahan, 2016).

Ultimately, RRBs appear to constitute a developmentally normative and roughly normally distributed behavioral trait in earlier years (Bolton et al., 2009). Therefore, the question arises as to whether RRBs are qualitatively different phenotypic expressions from childhood OCD or, rather, whether RRBs and OCD lie on a continuum, with shared pathophysiological underpinnings. In this regard, a recent systematic review (De Caluwé et al., 2020) supports a continuity model from RRBs to OCS in pediatric age. Normative and OCD rituals present in fact common phenotypic features, with a fixed package of themes, which reflect an underlying dimensional architecture (Barahona-Corrêa et al., 2015). Interestingly, in normative rituals, this set of contents or dimensions is age-dependent, as it changes over time as a function of varying developmental salience (Laing et al., 2009), whereas in OCD, it becomes increasingly less developmentally appropriate when children get older (Evans et al., 1999). The specific temporal pattern in which RRBs and OCD follow one another (a decline of RRBs around the age of 7 with a subsequent onset of OCD-like behavior, the contents of which become increasingly more decontextualized with age) hints at a continuity between the two (De Caluwé et al., 2020). This would be further corroborated by the evidence that high levels of normative rituals constitute a risk factor for developing OCD (Zohar and Felz, 2001). In this vein, Zohar and Dahan (2016) found that in 1345 community children (2–6 years old), more pronounced RRBs were related to typical maladaptive OCD characteristics, such as fears, negative-emotional temperament and emotional dysregulation. Remarkably, similar behavioral and emotional profiles run parallel with similar neurocognitive patterns. Evidence in fact indicates a shared neurocognitive background for RRBs and OCD in terms of impaired motor-suppression, motor inhibition and set-shifting deficits (Evans et al., 2004; Pietrefesa & Evans, 2007; Zohar and Dahan, 2016). Finally, only one study (Bolton et al., 2009) investigated whether the relationship between RRBs and OCD may be genetically mediated. The authors found in 4662 twin-pairs of 6 years old a significant correlation between RRBs and OCD symptoms, of which half of the variance (55%) was attributable to genetic effects. In sum, shared phenotypic, neurocognitive and genetic data suggest a continuity between adaptive RRBs and maladaptive OCD (De Caluwé et al., 2020).

Coherently, neurophysiological and neurobiological evidence would confirm a continuity in neural processing beneath the normative and pathological aspects of ritual behavior, mediated by connectivity refinement of cortico-striatal pathways during development (Evans & Maliken, 2011; Graybiel, 2008). In particular, discrete and parallel neural systems within the cortico-striato-thalamocortical circuitry (CSTC) would represent

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the neural scaffolding for the distinct dimensions of ritual contents (Mataix-Cols et al., 2004). Across vertebrate phylogeny, different inborn or learned habitual and routinized motor patterns are encoded and packaged as units ready for expression in basal ganglia loops (Graybiel, 2008). Therefore, CSTC networks represent a repository for 'species-typical' daily master routines, habits and rituals (Ploog, 2003). These cyclic, species-specific, action strategies are expressed depending on age in normative rituals (Pietrefesa & Evans, 2007), whereas they appear excessive and/or temporally mismatched in OCD (Thorn et al., 2010).

Altogether, compulsive-like rituals represent a genetically preprogramed behavioral response, with an important adaptive value in early childhood, but also with an adverse functional impact if they inappropriately persist over time and/or are excessively released (Rapoport et al., 1994). Of course, compulsive rituals far from representing purely behavioral expressions, also involve specific emotional and cognitive domains, which are inextricably intertwined. In fact, the highly conserved CSTC loops participate in complex mutual interactions with other functional networks (Stein et al., 2019). Indeed, the dense connections and functional organizations of the basal ganglia place them in a privileged position to exert a broad coordinating influence on cognitive and emotion processing as well (Pierce & Péron, 2020). In this regard, Shephard and colleagues (Shephard et al., 2021) distinguish the following main neurocircuits in OCD: 1) Fronto-limbic circuit, with a pivotal role in emotional processing; 2) Sensorimotor circuit, involved in the generation and control of motor behavior and integration of sensory information; 3) Ventral cognitive circuit, responsible for self-regulatory behaviors; 4) Ventral affective circuit, involved in reward-related processing; 5) Dorsal cognitive circuit, underpinning executive functions for goal-directed behaviors. Abnormalities in these neurocircuits, deeply interconnected with basal ganglia loops, underlie the complex phenotypic expression of OCD.

Comorbidity pattern of childhood OCD

Compulsive-like behaviors not only occur during normative childhood development but also are comorbid with a widespread spectrum of etiologically different neuropsychiatric conditions, including neurodevelopmental disorders, neurocognitive impairments and neurogenetic syndromes (De Caluwé et al., 2020). Moreover, compulsive-like rituals have been described in both internalizing and externalizing psychiatric disorders in infancy (Evans et al., 2017; Peris et al., 2017).

It is often difficult to disentangle "true" compulsive rituals from a broader bunch of restricted and repetitive behaviors, which co-occur in comorbid neurodevelopmental conditions. For example, RRBs are also a core diagnostic feature of autism spectrum disorders (ASD) (Comparan-Meza et al., 2021) and may phenotypically result in compulsive-like behavioral outcomes. Moreover, in both OCD and ASD repetitive behaviors seem to be specifically triggered by distressing sensory experiences as a way to restore a sensory balance (Jiujias et al., 2017). Consistently, prevalence rates of OCD are significantly elevated among individuals with ASD and further complicate efforts to distinguish between disorder-specific symptoms (Simonoff et al., 2008). Other highly prevalent comorbidities are tic disorders and Attention-Deficit/Hyperactivity Disorder (ADHD). Up to 59% of children and adolescents with OCD meet the criteria for a diagnosis of a tic disorder at some point during their lifetime (Leonard et al., 1992), whereas co-morbid ADHD occurs with a prevalence estimate of 25.5% (Masi et al., 2010). Regardless of the underlying comorbid condition, the developmental trajectories of this group of behaviors follow a relatively predictable course: their presentation tends to become more cognitively articulate over time, with compulsive symptoms more pronounced in pediatric age and obsessive symptoms more severe in adults (Farrell et al., 2006; Selles et al., 2014).

An exhaustive examination of the different kinds of comorbidity goes beyond the aim of the present study. It should be noted however that RRBs, normative in early childhood, seem to persist and/or to exacerbate, instead of decreasing over time, whenever an underlying neurodevelopmental perturbation occurs, regardless of a specific etiology (De Caluwé et al., 2020). In this connection, also childhood adversities, such as trauma exposure (be it physical, sexual or emotional; abuse or neglect) might play a moderating role, with a triggering and/or cumulative effect over the neurodevelopmental background (Park et al., 2014). Indeed, 50–70% of OCD patients report childhood traumatic experiences prior to the onset of OCD symptoms (Dykshoorn, 2014). Noteworthy, childhood trauma seems to be more related to compulsive behaviors than "pure" obsessions, suggesting that traumatic experiences may preferentially trigger a motor/behavioral response, innate in origin, to avoid intrusive trauma-related emotions and thoughts (Miller & Brock, 2017).

Childhood OCD and vulnerability to adult psychoses

If we turn the attention to diachronic comorbidities of childhood OCD, a primary diagnosis of OCD is associated with an increased risk of receiving a later diagnosis of one of the two major endogenous psychoses: schizophrenia and bipolar disorder (Cederlöf et al., 2015). As to the former, in an 11-year follow-up study on 35,255 adolescents and adults with OCD (Chen et al., 2023), the progression rate from OCD to schizophrenia totaled 7.80%. In this respect, the childhood onset of OCD appears as a specific indicator of schizophrenia vulnerability (Cheng et al., 2019; Meier et al., 2014; Van Dael et al., 2011). Accordingly, Borrelli and colleagues (Borrelli et al., 2024a) showed that the likelihood of developing schizophrenia in outpatients with a primary diagnosis of OCD gradually increased in parallel to the lowering in the age of OCD onset, with very-early onset OCD (< 10 years) presenting the highest rates of pre-psychotic symptoms. In particular, children and adolescents with a primary diagnosis of OCD and at risk for psychosis present with a specific OCD profile: 1) earlier age of OCD onset; 2) more severe OCS; 3) prominent compulsions (mainly washing compulsions); 4) poorer global functioning (Borrelli et al., 2023). Overall, these findings would support the hypothesis that in children with OCD, a specific OCD phenotype may actually cover an underlying vulnerability for the schizophrenia spectrum. In this regard, childhood trauma experiences might play a crucial role in the transition toward full-blown psychosis, as they appear to predict either more severe OCD or pre-psychotic symptoms in the OCD pediatric population (Borrelli et al., 2024b).

Less studied, on the contrary, is the relationship between childhood OCD and bipolar vulnerability. However, there is evidence that OCD in childhood and adolescence increases the risk of a later diagnosis of bipolar disorder (BD) (Cederlöf et al., 2015; D'Ambrosio et al., 2010). In this respect, in more than 60% of OCD-BD patients, OCS precede the onset of BD (Tonna et al.,

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2016a). After BD onset, OCS would initially coexist with BD symptoms and then gradually decrease in adulthood (Amerio et al., 2016).

Therefore, childhood OCD not only frequently co-occurs with various neurodevelopmental disorders but may also cover the developmental trajectories of severe psychiatric conditions (both affective and non-affective psychoses), which will arise later, in late adolescence or early adulthood (Tonna et al., 2015).

Sensory phenomena in childhood OCD

Since childhood, OCD patients typically perceive a broad range of mental and bodily experiences, often referred to as "sensory phenomena" (Cervin, 2023; Moreno-Amador et al., 2023; Poletti et al., 2023; Schreck et al., 2021). Mental sensory phenomena (e.g., "just-right perceptions," "feelings of incompleteness," and "not just-right experience") generally involve feelings of discomfort that something is not right. Remarkably, such experiences normally precede, trigger or accompany repetitive behaviors, thus representing the subjective scaffolding for compulsions, which are performed to regain a feeling of control and order (Ferrão et al., 2012; Prado et al., 2008). Bodily sensory phenomena refer to a variety of physical sensitivities (e.g., intolerance of innocuous sounds such as breathing, rubbing, or sniffing; extreme sensitivity to loud auditory stimuli), underlying a sensory over-responsivity to external stimuli (Ben-Sasson & Podoly, 2017). Moreover, according to the "Seeking Proxies for Internal States" model (Dar et al., 2021), OCD patients also present impaired access to their somatosensory states (including emotions, bodily states and sensations), with the tendency to rely on external "proxies" (i.e., verifiable indices of internal state), which then take the form of rigid rules, rituals or routines.

Few studies to date have attempted to investigate the neuroanatomical substrate of sensory phenomena in people with OCD (Cervin & Borrelli, 2025). Sensory phenomena have been found associated with gray matter volume increases within the sensorimotor cortex (Subirà et al., 2015). In particular, mental sensory phenomena appear related to increased activation in the left mid-posterior insula as well as somatosensory, mid-orbitofrontal, and lateral prefrontal cortical activity (Brown et al., 2019). OCD sensory over-responsivity would be specifically linked to orbitofrontal pathways, which play a key role in processing the value and consequences of sensory stimulation (Cervin, 2023; Collins et al., 2024). Altogether, sensory phenomena in people with OCD are related to brain circuits involved in sensorimotor processing and in the integration of sensory information (Van Hulle et al., 2019). This is consistent with the hypothesis that OCD, and particularly compulsive behavior, may be associated with hypo-functioning of sensory gating (Rossi et al., 2005) and/or a dysfunction of sensorimotor integration (Russo et al., 2014).

Sensory phenomena have been repeatedly found in youth with OCD dispositions, thus appearing as a trait-like condition (Cervin, 2023; Van Hulle et al., 2019). For example, there is evidence for a strong relationship between oral and tactile hypersensitivity and the severity of compulsive-like behaviors in pediatric age as well as with OCD severity later in life (Bart et al., 2017; Dar et al., 2012). In other words, at least a subgroup of pediatric OCD patients presents with symptoms that are primarily triggered by sensorimotor stimuli, where perceptions, sensations and urges actually precede repetitive behaviors (Tal et al., 2023). Therefore, it is possible to speculate a link between multisensory disruption and compulsive-like behavior in developmental years. It has been hypothesized that imparting a sense of control via rituals helps to overcome sensory-related issues (Dar et al., 2012; Lidstone et al., 2014). In this connection, compulsive behavior would represent a coping mechanism to regain a sensory balance over a condition of sensorial unpredictability (Bart et al., 2017; Jiujias et al., 2017). Both motor and cognitive pathways may be involved: on the one hand, repetitive and rigid physical actions per se reduce physiological arousal due to anxiety-related unpredictability (Anderson & Shivakumar, 2013; Karl & Fischer, 2018; Lang et al., 2015). On the other, hyperattention to the reordering sequence of ritual acts (repetition, specific number of procedural steps, and time specificity) leads to the subjective perception of a "reordered" world (Legare & Souza, 2012). Therefore, the sensorimotor experience of engaging in sequenced actions that are rigid, formal, and repetitive, coupled with the motor control required to enact these actions, allows regaining a feeling of stability and predictability in the perceptual experience (Tonna et al., 2022). From this perspective, it is possible to assume that childhood compulsions may represent a developmental adaptive response to sensory phenomena stemming from primary difficulty in modulating sensory input.

Neurocognitive endophenotypes of childhood OCD

An early perturbation of multisensory integration has also a relevant impact on neurocognitive development (Dionne-Dostie et al., 2015). Unfortunately, to date research on a specific neurocognitive profile in childhood OCD is limited and has yielded variable results (Abramovitch et al., 2015).

In childhood, more promising seems to be the search for candidate neurocognitive endophenotypes (Chamberlain and Menzies, 2009). An endophenotype is a heritable quantitative trait that correlates with an increased genetic susceptibility to a disorder; it is co-inherited with the disease and can be detected in unaffected first-degree relatives. As such, endophenotypic traits may manifest long before the onset of the disorder (Gottesman and Gould, 2003). In this regard, Chamberlain and Menzies (2009) identified several potential cognitive endophenotypes in OCD, including motor inhibition, cognitive flexibility, decision-making, action monitoring, reversal learning and memory. In this vein, a recent systematic review by Marzuki et al. (2020) confirmed in youth OCD patients robust increases in brain error related negativity associated with abnormal action monitoring, impaired decision-making under uncertainty, planning, and visual working memory. A recent study (Uhre et al., 2024) found in children with OCD specific impairments in cognitive flexibility, decision-making, working memory, and processing speed.

However, only few studies have examined cognitive function in pediatric OCD patients and their unaffected relatives. Negreiros et al. (2020) found that youth with OCD and unaffected siblings performed significantly worse in planning ability compared to healthy controls. In a large, rigorously screened cohort of pediatric OCD probands, their unaffected siblings, and parents, Abramovitch et al. (2021) identified deficits in the specific subdomains of cognitive flexibility and inhibitory control (i.e., proactive control and initial concept formation) across all three groups, proposing them as valid endophenotypes in pediatric OCD. The next step should be to investigate whether these traits are associated with specific candidate genes, so to unravel the developmental interplay between endophenotypes, genetic factors and environmental influences, in the progression towards OCD (Marzuki et al., 2020).

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Epigenetic mechanisms of OCD

Data from twin, family and segregation studies strongly support a genetic component of OCD (for a comprehensive summary, see Blanco-Vieira et al., 2023). The genetic influence on OCD is polygenic, with many genes involved (in particular, within the serotonergic, dopaminergic and glutamatergic systems), which individually exert a relatively small effect on the phenotype (Krebs & Heyman, 2015). Although existing literature has yielded important insight into the genetic basis of OCD (Mahjani et al., 2021), the investigation of epigenetic changes might be a crucial point to understand the developmental trajectories of OCD psychopathology. On the one hand, there is increasing evidence that environmental factors have a prominent role in OCD onset (Grünblatt et al., 2018; Mataix-Cols et al., 2013; Pauls et al., 2014); on the other, different environmental factors have been found to play a role in epigenetic modification (Essex et al., 2013; Parade et al., 2021). In this direction, epigenetics may represent the interface between environmental events resulting in alterations in gene expressions (Mohammadi et al., 2023).

The term "epigenetics" refers to heritable modifications that alter gene function without changing the DNA sequence. At the molecular level, these mechanisms, able to affect the phenotype without altering the genotype, include DNA methylation, histone modifications and variants, chromatin remodeling, and non-coding RNA, which work together to control DNA packaging and gene regulation and ensure genomic stability (Feng et al., 2007). In addition to genetic factors (Gerra et al., 2021; Takesian & Hensch, 2013), these epigenetic mechanisms are actively at work in shaping neural connectivity during sensitive periods (Dunn et al., 2019; Nagy & Turecki, 2012; Zhu et al., 2022). In this regard, different developmental factors, including childhood adverse experiences, which occur in sensitive periods as developmental stages, heavily influence synaptic plasticity and thus neurobiological and behavioral outcomes (Krause et al., 2020; Zhu et al., 2022). Similarly, growing evidence is unraveling the association between alterations in epigenetic signatures and neurodevelopmental disorders (Jobe et al., 2012; Murgatroyd & Spengler, 2012). Consistently, the search for possible associations between epigenetic changes and psychopathology, how these alterations may persist during development and potential reversal strategies is increasingly becoming a focal point for different psychiatric conditions, including OCD (Bagot et al., 2014; Dunn et al., 2019; Lewis & Olive, 2014; Zhang et al., 2014). However, the individuation of putative epigenetic risk factors in OCD onset is still at a preliminary stage (for a comprehensive summary, see Mohammadi et al., 2023).

Candidate epigenetic OCD studies have initially focused on the potential contribution of DNA methylation alterations in specific gene regions or CpG dinucleotides. DNA methylation, consisting of the methyl group addition in cytosine nucleotides occurring next to a guanine nucleotide, is involved in gene regulation (Chen et al., 2023; Ma et al., 2009; Martinowich et al., 2003), memory and learning (Day & Sweatt, 2010; Muotri et al., 2010), and transcriptional processes in the central nervous system (CNS) (Muotri et al., 2010; Skene et al., 2010). In particular, two CpGs in the oxytocin receptor gene were found hypomethylated in OCD patients compared to controls (Park et al., 2020). The lack of replication and validation in candidate epigenetic studies has led to conducting epigenome-wide studies without prior hypotheses about which genes might have epigenetic alterations in OCD patients. These studies would confirm that DNA methylation plays an important role in the etiology of OCD. About 2000 genes, previously identified as associated with OCD, were found differentially methylated in peripheral blood samples, including BCYRN1, BCOR, FGF13, ARX, and HLA-DRB1 (Yue et al., 2016). Hypomethylation was also detected in brain tissues of cortical and ventral striatum in post-mortem analysis of individuals with OCD (de Oliveira et al., 2021). The differentially methylated regions belonged to genes involved in G-protein signaling pathways, immune response, apoptosis and synapse biological processes. Another epigenome-wide study on a wide cohort of OCD patients identified 12 differentially methylated CpGs, which are close to or in genes associated with dopaminergic transmission in the striatum and insulin signaling sensitivity (Campos-Martin et al., 2023).

Interestingly, a recent study identified five differentially methylated sites mapping to the region of the microRNA12136 gene (MIR12136) (Schiele et al., 2022), thus indicating a potential role of miRNAs in OCD onset. MicroRNAs (miRNA), small regulatory RNA, participate, through a post-transcriptional control of gene expression, in almost every cellular process (Shyu et al., 2008), including axon outgrowth, embryonic patterning, neural differentiation (Cao et al., 2016), adult synaptic plasticity, and cognition (Rajman & Schratt, 2017). However, only few studies to date have assessed a possible association between alterations in the expression of circulating miRNAs and OCD. One research identified miR22-3p, miR24-3p, miR106b-5p, miR125b-5p, and miR155a-5p expression as significantly increased in the OCD subjects compared to controls, suggesting their involvement with DNA damage, oxidative stress, hypoxia, and inflammation (Kandemir et al., 2015). Another research (Yue et al., 2020) identified two miRNA (miRNA-132 and miRNA-134), previously associated with CNS-related pathologies, with higher expression in the OCD group compared to the control group. In addition to miRNA analyses, Song and colleagues (Song et al., 2018) generated whole-genome gene expression profiles of peripheral blood mononuclear cells from 30 patients with OCD and 30 paired controls using microarrays: 45 mRNA were down-regulated and 6 mRNA up-regulated. Enrichment analysis showed that these genes mainly belonged to the ribosomal pathways. Finally, two studies (Lisboa et al., 2019; Piantadosi et al., 2021) explored differentially expressed genes in human postmortem brain samples of OCD subjects comparing to controls using RNA sequencing.

Finally, very few studies explored the overall changes in epigenetic signatures across the genome over the life course (Simpkin et al., 2017). Nissen and coworkers (Nissen et al., 2016) were the first to longitudinally analyze DNA methylation in blood spots in neonates later diagnosed with OCD and in the same adolescents at the time of OCD diagnosis compared with matched controls. The authors failed to find significant results, probably due to the candidate genes design. Another study (Goodman et al., 2020) investigated DNA methylation differences in the critical period of the first peak of OCD onset (7-13 years old), identifying specific differentially methylated CpG associated with OCD; however, the lack of a longitudinal design prevented hypotheses about the causal role of these identified epigenetic factors on OCD development.

Altogether, the few available studies (Table 1) hint at a key role of epigenetic changes in OCD onset. The next step should be to investigate the relation between different (bio-psycho-social) sources of developmental exposure, epigenetic changes, and childhood-onset OCD, specifically in relation to the various stages of this critical period of development.

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Table 1. Epigenetic studies on obsessive-compulsive disorder

Study	Country	Model	Methods	Tissue	Sample size	Findings
DNA methylation						
Campos-Martin et al., 2023	Germany	Human	Epigenome-wide association study, using Illumina MethylationEPIC BeadChip	Peripheral blood	185 OCD patients and 199 HCs	12 epigenome-wide significant CpGs for OCD were identified, which were close to or in genes associated with the *sweet-compulsive brain* hypothesis
Yue et al., 2016	China	Human	Genome-wide DNA methylation study, using the Illumina Infinium Human Methylation450 BeadChip	Peripheral blood	65 OCD patients and 96 HCs	*BROC, BCYRN1, HLA-DRB1, ARX* were found to be differentially methylated between OCD patients and healthy control subjects
microRNA						
Deng et al., 2022	China	Human	Analyses of candidate single nucleotide polymorphism (SNPs) of miRNAs.	Leukocytes	636 OCD patients and 612 HCs	The C allele of the SNP rs2222722 in miR-30a-5p was found to be associated with early-onset OCD
Schiele et al., 2022	Germany	Human	Epigenome-wide association study	Peripheral blood	76 OCD patients and 76 HCs	A particular role was suggested for differential methylation within the greater region of the microRNA hsa-miR-12136 (*MIR12136*) and humanin-like 2, 3, and 8 (*MT-RNRL2, MT-RNRL3*, *MT-RNRL8*) genes
Yue et al., 2020	China	Human	Candidate targets, qPCR	Plasma	30 OCD patients and 32 HCs	The levels of miRNA-132 and miRNA 134 were significantly higher in the OCD group
Kandemir et al., 2015	Turkey	Human	Candidate targets (7 miRNAs)	Peripheral blood	23 OCD patients and 40 HCs	The levels of miR22-3p, miR24-3p, miR106b-5p, miR125b-5p, and miR155a-5p were significantly increased in the OCD group
Gene expression						
Piantadosi et al., 2021	USA	Human	RNA sequencing with lluminaHiSeq 2500, using the gene set enrichment analysis platform	Postmortem tissue from two orbitofrontal (medial, lateral) and two striatum (caudate nucleus and nucleus accumbens) brain regions	7 OCD patients and 8 HCs	Genes involved in synaptic signaling were lower expressed in OCD patients
Lisboa et al., 2019	Brazil	Human	RNA sequencing with lluminaHiSeq 2500, using the Genome Reference Consortium Human build 38	Postmortem tissue from striatum (putamen, caudate nucleus and nucleus accumbens)	6 OCD patients and 6 HCs	Different differentially expressed genes as well as network connectivity deregulation were specific for each *striatum* region by comparing OCD patients and HCs
Song et al., 2018	China	Human	Microarrays genome-wide scan	Peripheral blood	30 OCD patients and 30 HCs	45 mRNAs down-regulated and 6 mRNAs up-regulated between OCD and controls (mainly ribosomal pathway genes)

Note. OCD = Obsessive-Compulsive Disorder; HCs = Healthy Controls.

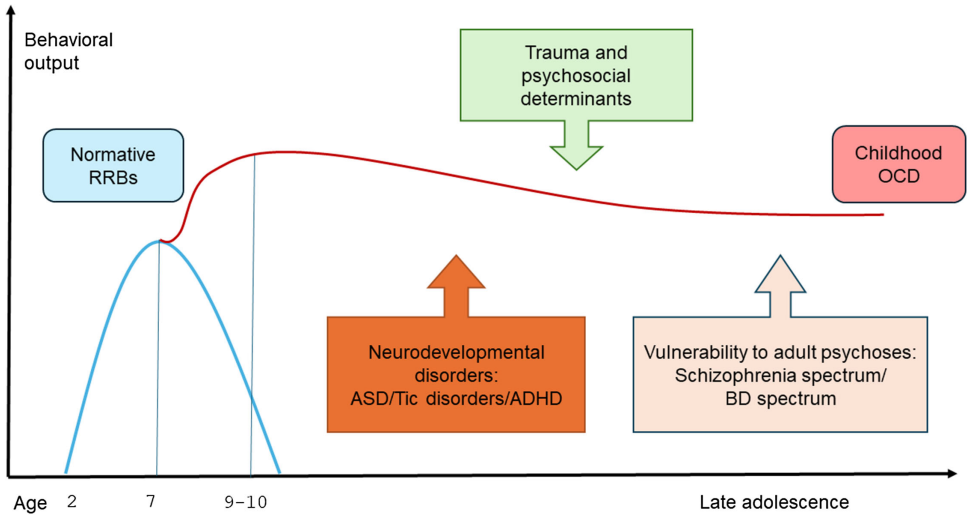


Figure 1. Temporal pattern and comorbidity profile of childhood OCD. Note*: RRBs= restrictive and repetitive behaviors; OCD= obsessive-compulsive disorder; ASD=Autism spectrum disorders; ADHD= attention-deficit/Hyperactivity disorder; BD= bipolar disorder.*

Childhood OCD and heterochrony: an evolutionary and developmental hypothesis

Altogether, childhood-onset OCD shows distinct comorbidity patterns (Geller et al., 2001), which are age-at-onset dependent and reflect different developmental stages (Peris et al., 2017). In fact, OCS chronologically emerge as a continuation of RRBs, which are part of normative behavioral repertoire in typically developing children from 2 to 7 years of age. Their persistence after the age of 7, generally marked by maladaptive features, such as distress and emotional dysregulation, often covers divergent neurodevelopmental trajectories, whose phenotypical expressions extend from birth to late adolescence. Within this complex interplay, early trauma exposure may play a moderating role, interacting with the underlying developmental pathways. As such, OCD represents a crucial node for childhood psychopathology (Figure 1).

We hypothesize that this specific OCD temporal pattern is consistent with a model of developmental heterochronic shift in the timing and rates of evolutionarily conserved behavioral responses. Heterochrony refers to the evolutionary mechanism of genetically controlled diversification of the ontogenetic sequences of a trait, including behavioral traits (Wobber et al., 2010). Indeed, the retention of typical juvenile phenotypes in adults due to evolutionary changes in rates and timing of development (also referred to as "neoteny") represents a core mechanism of recent human evolution (Brüne, 2000). Childhood OCD has been generally conceptualized in terms of dysfunctionality and deficit and, as such, investigated in its proximate (molecular-genetic, neurobiological, cognitive) mechanisms. Instead, under the lens of an evolutionary-developmental framework, OCD can be better explained as the result of developmental delays or non-completion of ontogenetically early behavioral patterns, eventually leading to mismatches with chronological age. In this vein, a heterochronic mechanism has already been advocated for RRBs in ASD (Crespi, 2013). We speculate that this model of developmental heterochrony may also account for the delay in attenuation of compulsive-like behaviors, synchronically or diachronically related to a wide range of neurodevelopmental perturbations, from childhood to adulthood.

Many of these neurodevelopmental disorders, regardless of the huge heterogeneity in symptoms and etiologies, are associated with a diffusely impaired multisensory/sensorimotor connectivity (Cascio, 2010). Indeed, in humans, multisensory integration networks are more vulnerable to early injury due to less constrained neural configurations and extensive neotenic synaptic plasticity, eventually leading to potentially relevant deviations in normative developmental trajectories (Stein & Rowland, 2011). Multisensory processing in fact, while tuned to species-specific spatiotemporal ranges (Borghi et al., 2022; Stevenson et al., 2014), retains highly plastic properties, especially in developmental years (Powers et al., 2009; de Klerk et al., 2021). An early disruption in the maturation and refinement of sensorimotor grounding has an impact on the processing and integration of different sensory modalities into a coherent perceptual whole and on the execution of a contextually appropriate motor action (Carment et al., 2019), with a cascading effect on neurocognitive development (Dionne-Dostie et al., 2015). For example, individuals with ASD show specific sensory features (e.g., hypo/hyperactivity and unusual sensory interest), and a broad range of sensorimotor deficits (in visual-tactile perception, visual-motor skills, praxis and balance) (Schaaf et al., 2023). Similarly, children with ADHD exhibit a unique pattern of trait-like impairments in multisensory integration, motor performance and coordination (McCracken et al., 2022; Panagiotidi et al., 2017). In schizophrenia, there is evidence for a widened temporal window of integration (i.e., reduced ability to segregate stimuli in time) (Di Cosmo et al., 2021), as well as a reduced and less demarcated peripersonal space (i.e., the space surrounding the body for sensorimotor integration) (Ferroni et al., 2020; Ferroni et al., 2022), reflecting in specific motor and postural biomarkers (Carment et al., 2019; Presta et al., 2021; Walther & Strik, 2012). Childhood adversities, including early traumatic experiences, also seem to alter the course of sensorimotor development, with a greater impact if the traumatic event occurs before the age of 7, which is a crucial period for the early maturation of sensory integration networks (Matson et al., 2024).

Remarkably, compulsive-like behavior appears directly linked to multisensory impairment, regardless of the underlying neurodevelopmental disorder. For example, compulsive-like behaviors are strongly associated with distressing sensory experiences, such as sensory over-responsivity, both in children with ASD (Istvan et al., 2020) and in children with OCD (Bart et al., 2017; Dar et al., 2012). Therefore, we speculate that the heterochronic delay in attenuation of compulsive-like behavior would be driven by different sources of sensorial unbalance, due

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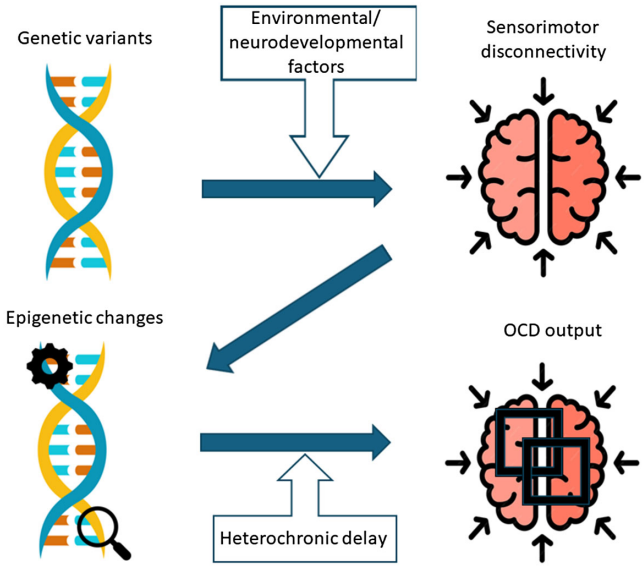


Figure 2. Developmental heterochronic model of childhood obsessive-compulsive disorder.

to heterogeneous (either biological or socio-psychological) developmental conditions. In this regard, the age of 7 would represent an important turning point, at which normative ritual behavior starts to decline in parallel with the maturation of sensorimotor networks or, conversely, pathologically persists as an expression of a failure of sensorimotor development (De Caluwé et al., 2020).

In this respect, epigenetic changes might mediate the heterochronic mechanisms underlying the continuity of OCD phenotypes with typical childhood behavioral rituals (Figure 2). This is in line with the evidence that epigenetics and environmental exposures hugely affect developmental processes, leading to neurobiological dysfunctions with immediate or later consequences in life (Gupta et al., 2010; Weaver et al., 2004). The fact that the brain exhibits high plasticity and undergoes prolonged development over time has both advantages and disadvantages; on the one hand, it allows for a prolonged fine-tuning of sensorimotor grounding for higher cognitive and social functions throughout development. On the other, it exposes the high "flexibility" of synaptic networks to divergent developmental trajectories with consequently different behavioral outputs (Crespi & Dinsdale, 2019; Tonna et al., 2023). Therefore, epigenetic mechanisms might bridge the gap between the disrupted sensorimotor background and childhood OCD, specifically in relation to the various stages of this critical development period. In this respect, different epigenetic mechanisms, which play a key role in neural circuit development, maturation, and function, could be involved, with preliminary evidence for both transcriptional (DNA methylation), and post-transcriptional (miRNA) modifications of gene expression in OCD patients. Other epigenetic mechanisms, such as histone modifications and chromatin remodeling, could also be at work, due to their role in neurogenesis and synaptic plasticity and their association with various neurological and psychiatric disorders (Borrelli et al., 2008; Ma et al., 2010; Nelson & Monteggia, 2011; Telese et al., 2013; Zhang & Meaney, 2010).

The ultimate causes of the delay in developmental attenuation of compulsive-like behavior have yet to be investigated. It is remarkable however, that across vertebrate phylogeny rituals and compulsive-like behaviors invariably conserve the adaptive significance of coping with conditions of environmental unpredictability (Eilam et al., 2006) or "high entropy" states (Hirsh et al., 2012). Across taxa in fact, whatever condition of potential danger or threat (Boyer & Liénard, 2006; Szechtman & Woody, 2004; Woody & Szechtman, 2013), or anxiety-related uncertainty (Krátký et al., 2016; Lang et al., 2015) may trigger behavioral ritualization. Accordingly, the peculiar structural features of ritual behavior, based on acts repetition and intrusion of nonfunctional acts (Eilam, 2017) serve the function to interrupt the automaticity of motor performance as to align behavioral response to changing environments (Blanchard et al., 1991; Schleyer et al., 2013; Stürzl et al., 2016). In this connection, OCD compulsions and ritual behavior share overlapping features in terms of face validity (i.e., homologous motor structure) (Boyer & Liénard, 2006; Lang et al., 2015), construct validity (i.e., homologous neurobiological pathways, centered on basal ganglia structures) (Graybiel, 2008) and predictive validity (as shown by robust animal models of OCD) (Wolmarans et al., 2018). Such evolutionarily conserved proximate and ultimate mechanisms would therefore suggest a homologous continuity between ritual behavior and OCD compulsions (for a review, see: Tonna et al., 2019; Tonna et al., 2020). During development, ritual behavior is gradually abandoned in favor of more adaptive cognitive-behavioral strategies along with sensorimotor maturation and the refinement of executive functions (De Caluwé et al., 2020). We hypothesize however, that in case of impaired sensorimotor maturation, due to early deviations from normal developmental patterns, compulsive-like behavior, instead of being switched off, is maintained or reinforced with the adaptive function of coping with condition of sensory unpredictability.

This evolutionary perspective fits well with the evidence of the homeostatic function of children's normative RRBs to cope with sensory and environmental unpredictability due to daily life contingencies (Evans & Maliken, 2011). RRBs in children with ASD have the same compensatory function of decreasing sensory arousal, simplifying complex situations and fostering a sense of control (Glenn et al., 2012). Interestingly, in both ASD and typically-developing children, compulsive-like behaviors are directly associated with conditions of sensory unbalance (Schulz & Stevenson, 2019). In individuals with OCD, the very motor structure of their compulsions is directly related to the underlying developmental perturbation, as it raises in complexity (in terms of acts repetition and ritual duration) in relation to increasing severity of both pre-psychotic symptoms (Tonna et al., 2022) and childhood trauma experiences (Tonna et al., 2023). Therefore, we assume that fixed, evolutionarily conserved behavioral patterns may give order and control over different "high-entropy" or chaotic sensory states, due to sensorimotor networks, which in humans, because of their high plasticity, are also inherently vulnerable.

The effect of sensory balancing due to OCS would eventually lead to more stable syndromic configurations, allowing the individual to preserve specific functional domains in the real-life. Unfortunately, longitudinal studies on the effect of childhood OCD over the psychopathological course and the individual's functioning in the real-life are lacking. However, a sort of OCD counterbalancing mechanism appears to be actively at work in comorbid OCD-schizophrenia adults. In those patients in fact, mild-moderate OCS are associated with more preserved levels of functioning (Tonna et al., 2016b; Tonna et al., 2016c), particularly in those functional areas (vocational and everyday activities), which are more sensitive to the superimposed "ordering" effect of ritual behavior (Tonna et al., 2024).

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Ultimately, we suggest some possible clinical and therapeutic implications of the evolutionary-developmental hypothesis of OCD compulsions proposed here, based on the heterochronic shift in the timing and rates of conserved behavioral responses.

1) Childhood OCD might represent a putative biomarker of underlying neurodevelopmental perturbation, due to both biological and psychosocial determinants.

2) Prominent compulsive-like symptoms may have a pathoplastic effect, as they can mask symptoms pertaining to other diagnostic entities, particularly if their clinical presentation is prodromal, sub-threshold or non-prototypical.

3) Childhood OCD might influence the course and outcome of underlying psychopathological trajectories, as its homeostatic role in regaining a sensory balance might sustain levels of functioning and perhaps prevent or at least mitigate the onset of full-blown symptoms.

Of course, this is not to say that childhood OCD necessarily stems from neurodevelopmental conditions or vulnerabilities. Early-onset OCD may be in fact direct expression of "pure" OCD dispositions and/or be released by any pathogenic mechanisms or injuries which eventually lead to fronto-striatal dysconnectivity (Graybiel, 2008; Mataix-Cols et al., 2004). Therefore, compulsive symptoms in childhood may actually identify subgroups of patients with different etiopathogenetic pathways.

The present contribution should be considered with the caveat of the following limitations. First, as a main limitation, this work is not a comprehensive review of all available evidence for an evolutionary and developmental approach to childhood OCD, but it cites selected papers that the authors considered as conducive to address the main hypothesis presented. Second, the hypothesis proposed does not fully capture the complexity of the intertwined neurodevelopmental pathways to childhood OCD; for example, it does not take into account other pathophysiological trajectories, such as intellectual disabilities, autoimmune conditions (e.g., Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections-PANDAS-) or other organic forms of OCD (including rare genetic syndromes) (Runge et al., 2023). Third, for the reason of brevity, an exhaustive description of OCD psychopathological profile was limited. This has left out important clinical facets of OCD, such as levels of insight and specific symptom dimensions, to name but a few, which might vary in accordance with the underlying neurodevelopmental background. Fourth, response to treatment has not been investigated. Future research should be addressed to identify specific treatment targets based on different phenotypic subtypes, underlying comorbidities and developmental stages.

In conclusion, the approach of this study is speculative but provides hypotheses to be tested in future research. In particular, our hypothesis of developmental heterochrony allows to grasp the continuity of OCD phenotypes with typical childhood behavioral repertoire and thus to highlight the adaptive significance of ritual behavior across phylogeny. This continuity is rooted in development trajectories, which are highly inherently malleable (Hauser et al., 2019). We suggest that the chronological shift of compulsive-like behaviors, which are normative preprogramed behaviors at specific temporal stages, may be driven by any condition of multisensory unbalance due to neurodevelopmental factors in association with child's environment (e.g., early life stress and childhood adverse experiences) through epigenetic mechanisms, with a profound impact on connectivity organization and brain maturation.

Analyzing the timing and type of childhood adversities and/or neurodevelopmental perturbations in association with OCD onset and epigenetic changes could reveal new findings. In this regard, cohort studies based on exhaustive biopsychosocial data would be needed to test the main hypothesis of the study. Furthermore, subgrouping youth OCD population based on their comorbidities and comparing them on the phenotypic expressions of OCS might provide a deeper insight into the clinical heterogeneity of the disorder and refine diagnostic tools. Since OCD is a multifactorial condition, it should be further explored how gene-environment interactions influence epigenetic processes. In particular, longitudinal studies based on high-throughput sequencing technologies would allow understand how epigenetic factors can mediate lived experiences and thus contribute to the persistence of OCS after childhood. This might form the basis for new guidelines aimed at prompt therapeutic interventions, including epi-drugs or epigenetic editing.

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Authors' contribution. MT designed the study, which was critically revised by all the authors.

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