Can Cerebellar Neurodevelopmental Disorders Affect Behavioral Disorders or Vice Versa?

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Abstract Recent investigations have been focused on understanding the role of the cerebellum in non-motor behaviors and of the cerebellar dysfunction in neurodevelopmental, neurobehavioral, and schizo-affective disorders. Non-motor behaviors, including emotion, cognition, and social behavior, seem to be modified by impairment of the cerebellar structure-function relationship. Clinically, these behavioral defects have been observed in patients with autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), and schizophrenia. These behavioral outcomes have been demonstrated to be associated with prenatal and/or early postnatal damages of cerebro-cerebellar circuits. Concerning to the essential role of the cerebellum in early neurodevelopment, understanding the association between cerebellar injury and long-term alteration in behavior is highly crucial. This chapter's attempts are to summarize the recent evidence of involvement of the cerebellum in neurodevelopment and behavior and that both these views remain to be revised for declaration of the paradoxical relationship between cerebellar function and behavioral despair, as well as neurodevelopmental disorders including ASD and ADHD.

Keywords Cerebellum • Neurodevelopment • Behavioral despair • Schizo-affective disorders

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Introduction

The cerebellum is traditionally considered as the brain region that is involved in the motor and non-motor activities [30, 83]. Regarding to the major role of the cerebellum in the posture and movements, preliminary studies showed that elimination of this area can be resulted in disruption of these activities [40]. These were in line with clinical reports demonstrating that the cerebellum degeneration may impair posture and speech, voluntary movement of extremities, and gait [42]. Several studies have been performed to understand the exact function of the cerebellum [43] and to find the importance of this area in control of motor movements [85] and learning [45]. On the other hand, the evidences have shown that extensive connections of the cerebellum with the other brain regions (e.g., prefrontal and posterior parietal cortex) are associated with non-motor tasks [16, 17]. Lately, imaging techniques have demonstrated an association between function of the cerebellum with cognitive processes such as language [74], attention [2], and affective processes [38]. Therefore, it is believed that alteration of cerebellar structure and function can be concluded to several abnormalities in the emotional, cognitive, and social domains which were observed in patients with such neurodevelopmental disorders as autism spectrum disorders (ASD) and behavioral despair [61, 62, 79]. In accordance to the complex neurobiology of neurodevelopmental disorders and behavioral despair, the role of the cerebellum in the non-motor functions should be well defined [7].

In this chapter, we provide a brief summary of the importance of the cerebellum in pathophysiology of neurodevelopmental and behavioral disorders. Although the cerebellum has been found to be involved in neurodevelopmental disorders, structural and functional differences in different regions of the cerebellum play a role in attention deficit hyperactivity disorder (ADHD), developmental dyslexia, and ASD. This suggests the hypothesis that involvement of different cerebro-cerebellar circuits may result in the differences between the neurodevelopmental disorders [86]. In addition to these disorders, there are such neurodevelopmental disorders as developmental coordination disorder (DCD), which frequently co-occur with the abovementioned neurodevelopmental disorders (e.g., ADHD and dyslexia) hypothesizing a relation to cerebellar dysfunction [10, 109]. This information makes a question in mind how the cerebellar dysfunction affects developmental processes and causes developmental disorders and differences in localization of cerebellar dysfunction may cause different disorders.

The cerebellar growth has been enormously occurred during the first 24–40 weeks of pregnancy, leading to approximately fivefold in volume and over 30-fold in surface area [18, 102]. The cerebellar growth continues throughout the first postnatal year, although the neural differentiation and growth of axonal inputs and outputs occur slower than prenatal stage [18, 102]. The process can interpret this event that premature infants are encountered an increased risk of cerebellar developmental disorder, hemorrhages, and future neurodevelopmental disabilities [18, 102]. As a result, cerebellar injury in childhood may lead to a range of long-term motor, cognitive, and affective disorders with poorer outcomes than cerebellar damage in

adulthood [82, 103]. The findings put the cerebellum at center point of neurological investigations of neurodevelopmental disorders, such as ASD [18, 31]. The confidential evidences emphasized to an obvious association between the cerebral cortex damage at early life result in an elevated risk of affective and attention deficits, internalizing behavioral disorders, and withdrawal from social contact [64, 103]. Consistent with cerebellar tumor and/or resection of the tumor in children, an abnormally increased risk of cognitive and adaptive impairments [9], as well as the vermis injury, has been shown to be related to long-term affective dysregulation [63]. Also, it is demonstrated that the vermis malformations are involved in higher rates of affective and behavioral disorders, including ASD [18, 92]. Congenital cerebellar malformations, as well as a variety of early cerebellar lesions, have a direct relation to ASD. To conclude these findings, some scientists like Schmahmann et al. included ASD among the category of psychiatric disorders associated with cerebellar damage or disease [81]. The studies have demonstrated that cerebellar injury in infancy is one of the major risk factors, which increases approximately 40-fold in developing ASD [64, 103]. The evaluation of different pathological conditions damaging the cerebellum has verified the relationship between the injuries and ASD. For instance, tuber load in the cerebellum in children with tuberous sclerosis is considered as a specific predictor of ASD [18, 104]. The cerebellar damage may cause some complications, including gaze aversion, stereotyped movements, linguistic impairments, as well as complete avoidance of physical contact, ultimately leading to ASD [78]. In line with the basic and experimental findings, the clinical evidences have been suggested that cerebellar injury at early stages via developmental diaschisis can affect the development of cerebral cortical area to which the cerebellum projects [103]. Therefore, not only cerebellar function but also the structure and function of multiple regions of the cerebral cortex can negatively be influenced by cerebellar developmental differences in patients with ASD.

Several investigations of patients with ASD have indicated to an abnormal modification of size and shape of neurons of the deep cerebellar nuclei, as well as decrement of the number of Purkinje cells (PC) [4, 51, 52, 70, 83]. Postmortem studies have confirmed the experimental results showing a reduction in gyrification, and in size of granular and molecular layers of the vermis, along with loss of PC [7, 67, 91]. These findings may adjust the hypothesis that ASD has a prenatal origin of defects, which continue at early postnatal stage [31]. Neuroimaging techniques, such as structural magnetic resonance imaging (MRI), have presented conflicting information that vermal hypoplasia is observed in the majority of individuals with ASD. To confirm these data, studies using functional MRI have further implied that patients with ASD exhibit abnormal function of the cerebellum ([111, [31, 100]). The neuroimaging studies also have shown an alteration in anatomical and functional connectivity of the cerebellum with other regions of the brain, including the thalamus and cerebral cortex [66, 83, 101].

In addition to the neuroimaging studies, pharmacological investigations have demonstrated that the cerebellar glutaminergic and GABAergic systems are considered as a target of dysfunction in ASD patients [11, 83].

Also, major psychiatric disorders, including major depressive and bipolar disorders and schizophrenia, are hypothesized to be contributed by comprehensive alteration in GABAergic signaling system, such as changed expression of cerebellar GABA receptor [83]. This can be associated with reduction in expression of FMRP and alteration in FMRP-mGluR5 signaling and its downstream targets including RAC1, APP, STEP, and homer 1. On the other hand, expression of GABA receptor is influenced by epigenetics or monoallelic expression. As a result, agonism of GABAergic receptors, modulation of mGluR5 activity, and inhibition of glutamate-induced excitotoxicity that may be potential therapeutic strategies, along with the drugs, affect monoamine systems including dopaminergic or serotonergic pathways [32–34]. Actually, GABAergic system can be an important target for novel medication for the psychiatric disorders [36].

Furthermore, the literature resulted from gene and protein expression analyses have demonstrated the downregulation of synaptophisin, SNAP-25 (synaptosome-associated protein), and complexin, as well as upregulation of semaphorin 3A, an axonal chemorepellant [28, 29, 68, 83]. Interestingly, a dysregulation of activity and levels of D-amino acid oxidase (DAO), the enzyme that metabolizes D-serine, a co-agonist of NMDA (N-methyl-D-aspartate) receptor, was also observed [14]. Therefore, the available evidence seem to indicate to disease-specific, including decreased volume of the vermis, and nonspecific pathological factors, including reduction in the number PC and pharmacological changes of the cerebellum in the neurodevelopmental disorders [83].

In addition to ASD, the cerebellum has been suggested to be involved in schizophrenia, demonstrating coordination and postural abnormalities, impaired eyeblink conditioning, and procedural learning deficits [53, 54, 84]. The neurological signs are thought to be related to structural alterations in the cerebellum [7, 106]. Regarding to the extensive connections between the cerebellum and forebrain regions, cognitive dysmetria and poor mental coordination are proposed to be produced by cerebellar abnormalities in schizophrenic patients [5, 6].

Contribution of the Cerebellum in Neurodevelopment

There are increasing evidences emphasizing the major role of the cerebellum in the development of the brain. The studies of fetal, neonatal, and pediatric individuals support the hypothesis that the developing cerebellum clearly participates in motor, cognitive, and socio-behavioral development and exerts the role that is associated with a regional functional topography of the cerebellum. Consistent with these data, investigational studies have indicated to the relationship between early life and older children with cerebellar injury (e.g., pediatric posterior fossa tumors), and infants with cerebellar malformations and neurodevelopmental disorders, clarifying the importance of cerebellar structure-function relationships in the brain development [87].

The developmental process of the cerebellum possesses a highly regulated pattern, as which more rapidly grows during 20–40 weeks of gestation in comparison with other cerebral structure, demonstrating the importance of the critical period for cerebellar development [15, 65]. Thus, the vulnerability of the cerebellum and its developmental repercussions of injury can disrupt this highly orchestrated, programmed developmental process during the important period. On the other hand, disruption of cerebellar growth significantly affects other regions of the brain, for instance, the developing cerebral cortex [103]. This is related to the richly interconnection of the cerebellum with different areas of the cerebral cortex supporting movement, cognition, and affective regulation [89]. In this regard, the cerebellum seems to play a modulatory role in the cerebro-cerebellar circuits, supporting the behavioral optimization, particularly in procedural learning and skill acquisition [87].

Subsequently, it is believed that early disruption of the cerebellum, due to prenatal cerebellar developmental lesions (i.e., malformations), preterm birth, and cerebellar posterior fossa tumors in early childhood, can lead to neurodevelopmental disorders with long-lasting and wide-ranging alterations in the structure and function of cerebro-cerebellar systems that result in long-term behavioral disorders [87].

Role of the Cerebellum in Adaptive Behaviors, Autism Spectrum, and Neuropsychiatric Disorders

It is evident that cerebellar tumor removal in children and cerebellar parenchymal injury in very preterm infants resulted in impairment of adaptive behaviors [9] and a variety of affective disorders [63, 64]. For instance, affective dysregulation is associated with cerebellar dysfunction in children [63], while emotional lability is also observed following posterior fossa syndrome [75].

Regarding to specific structure-function relationship, an association between the posterior vermis injury and vermal lesions with behavioral dysregulation, flattened affect, and disinhibited behavior was observed [1, 21, 63]. Some reports have mentioned that most of the children with midline or vermal tumors are encountered to affect dysregulation [1]. These findings were supported by a study by Richter et al. [77] that both positive (e.g., decreased aggression and thoughtful behavior) and negative (e.g., depression, anxiety, and aggression) behavioral symptoms were seen in children with chronic cerebellar lesions. The association between the vermis and behavioral regulation pays our attention to the important role of the posterior vermis and its defects in neurodevelopmental disorders, including ADHD [48] and autism [8].

In addition, Schmahmann implied that more than half of the surviving preterm infants with damage of parenchymal tissue of the cerebellum show psychiatric disorders [81] and functional limitations in socialization skills. Also, distinct socio-behavioral defects of attention, affective, internalizing, and pervasive subdomains were reported in the children with cerebellar injury [64].

Taken together, the reports have shown that cerebellar injury and lesion at early life in preterm infants are associated with wide-ranging neurodevelopmental disorders [13]. Moreover, a reduction in volume of the posterior vermis is thought to be in line with neurodevelopmental-related behavioral dysregulation, including autism and ADHD. Psychiatric disorders are also reported to be correlated with cerebellar injury during childhood [87].

Cerebellum Plays a Role in ASD

Evidences have proposed that dysfunction in specific regions of the cerebellum can result in neurodevelopmental disorders, including ASD, according to the involvement of the cerebellum in the developing brain. Scientists have demonstrated the major role of cerebellar damage in the neuropsychiatric consequences in five main domains: (1) impairment of attention and (2) emotion and (3) disruption of social skill, (4) psychosis, and (5) autism spectrum disorders [81]. In ASD, there are data that strongly support the structural-functional abnormalities in the cerebellum in patients with autism. Although ASD is adjusted to be resulted from cerebellar dysfunction, it is obvious that multiple regions of the brain undergo dysfunction. Thus, the specific contribution of the cerebellum in the pathophysiology of ASD is needed to be clearly understood. The cerebellum has been demonstrated to modulate and automatize the motor movements, in order to optimize performance [46]. Also, it has been observed that the activation patterns in the primary motor cortex are modulated by transcranial magnetic stimulation of the cerebellum [37]. This shows the cerebro-cerebellar relationship and verifies that alteration in cerebellar activity can affect different regions of the cerebral cortex, influencing internal models of behavior, and optimization and prediction of future behavior [47]. Despite these effects, it does not mean that the cerebellar injury leads to complete loss of its function [79]. To this, cerebellar injury may not include paralysis, but classic motor dysfunction, such as poorly calibrated dysmetric movements, can be occurred. The modulatory effect of the cerebellum is not exclusively related to the motor movement but is associated with impairment of cognition and affect [47]. Moreover, there is region-specific motor dysfunction, as the posterior cerebellar injury demonstrates no severely impaired cognition and language but can lead to disrupted modulation and optimization of cognitive performance such as agrammatism or semantic fluency [79, 80]. These findings emphasized the importance of the cerebellum in implicit learning and skill acquisition, which are directly associated with the process of building and optimizing internal models. The cerebellum is believed to be completely associated with initial motor skill learning, while cortico-striatal pathways and primary motor cortex are more involved in the learned motor behaviors, as well as cognition and working memory [23, 37]. A cerebellar role in learning and skill acquisition is compelling in the neurodevelopment and neurodevelopmental disorders. Indeed, impairment of skill acquisition is more correlated to developmental disorders including ASD, dyslexia, and developmental coordination disorder [10, 96]. These differences are assumed to be related to cerebro-cerebellar

circuits [86]. Thus, behavioral defects resulting from neurodevelopmental disorders are linked to differences in structure-function relationship of specific regions of the cerebellum [112]. For instance, damage of the posterior cerebellar area may result in communication impairments in patients with ASD, whereas motor defects of speech, stuttering, are found to be relevant to overactivation of the anterior lobe of the cerebellum [90]. Deficits of the mentioned cerebellar circuits were observed to cause long-term disorders by influencing the acquisition of motor, communication, and social skills during early neurodevelopment in patients with ASD.

Cerebellum Plays a Role in ADHD

Regarding to the present findings, alteration in structure and function of the cerebellum is believed as the common phenomenon in ADHD [20, 25, 97], but the genetic and environment are thought to be predisposing risk factors of the neurodevelopmental disorder. Genetic investigations have shown that a family-based single-nucleotide polymorphism (SNP) in the XKR4-gene (XK-Kell blood group complex subunit-related family, member 4) in the cerebellum is suggested to be related to incidence of ADHD [57, 69]. Despite the unclear function of this gene in the brain, the importance of this gene was understood by finding that it codes for an inferred protein related to the XK-protein, part of the XK-Kell blood group complex [25, 59, 60]. XK-protein is observed to be widespreadly overexpressed in the brain compared to Kell-protein in the Purkinje cells of the cerebellum [113, 114]. As the linkage between XK gene and McLeod syndrome, a syndrome with sex-dependent defects of central nervous, neuromuscular, and hematologic systems in males including impairment of movement and cognition and psychiatric disorders [19], was found, the hypothesized relationship between XKR4-gene and psychiatric phenotypes was potentiated. It is noteworthy that a correlation exists between XKR4-gene and substance abuse [95], while a SNP in the XKR4-gene has been contributed to responsiveness to antipsychotic therapy [35, 58].

Environmental and epigenetic factors are found to be linked to the cerebellum and its function in prenatal and postnatal stages. Studies of children with ADHD have demonstrated lower pronounced familial effects on the cerebellum volume compared to other regions of the brain [26]. Moreover, in contrast to some reports suggesting that the cerebellum's heritability may be enhanced into adolescence and adulthood [73, 98], the cerebellum is considered as the least heritable brain structures at birth [39] and in childhood [72]. Prenatal adversity may influence the cerebellar development, which begins at early intrauterine life [65, 93, 94]. These show the importance of prenatal and early postnatal period in development of cerebellum to reach a normal structure and function. Unless, negative effects on the cerebellum in patients with ADHD have demonstrated to be relevant to impairment of the cognitive phenotypes, such as temporal processing [27]. However, the role of environmental effects on the cerebellar development and its contribution to the symptoms of the neurodevelopmental disorders are remained to be obviously understood.

Cerebellum Plays a Role in Behavioral Despair and Neuropsychiatric Illnesses

Body of evidences has proposed that there is regionally abnormality in the brain volume in patients with major depressive disorder (MDD). Several meta-analyses have confirmed this hypothesis that a reduction in gray matter volume (GMV) of dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and hippocampus was observed in patients with MDD [12, 22, 24, 55, 108, 110]. The reports have suggested two disorders as the pathophysiological factors of MDD, as below:

- Impairment of structure and function within cortico-limbic circuitry [49]
- Alterations in the functional organization of multiple brain networks implicated in attention regulation, emotional processes, and cognitive control [49]

Although the involvement of the cerebellum in both cognitive and affective processes is now well established, meta-analyses show no significant and obvious contribution of the cerebellum in MDD. The studies indicated that the linkage of the cerebellum with cerebral cortices and paralimbic regions indeed, as cortico-cerebellar circuits, is key point to clarify the role of the cerebellum in MDD [81, 88]. The limited data on the involvement of the cerebellum in MDD may be related to the few investigations of cerebellar structure in MDD. However, the analytical studies were focused on the vermian volume and lack of gray/white matter parcellation [107]. Moreover, clinical evidences reported an abnormal structure of the cerebellum in depressed patients using whole-brain investigations of altered GMV in depression [22, 56, 71, 99, 107].

To better understand the role of the cerebellum in behavior, fMRI data were analyzed in adolescents and young adults to identify the possible association between emotional and behavioral disorders with brain areas [76]. Interestingly, the results emphasized that the cerebellum, as well as cerebral sensorimotor and limbic areas, had the strongest link to behavioral despair.

In addition to MDD, the investigations demonstrated a significant association between obsessive-compulsive disorder (OCD) and abnormalities in the cerebellum. There were found significant, obvious abnormalities in the cerebellum, along with in the temporo-parieto-occipital and fronto-striatal areas in patients with OCD compared to healthy controls [44]. Although we have limited data on the role of the cerebellum in pathogenesis of anxiety disorders, accumulation of evidence of the importance and involvement of the cerebellum in a wide variety of psychiatric and neurodevelopmental disorders are needed to be elucidated [3].

Schizophrenia, as known as neurodevelopmental disorder with uncertain etiology, is thought to be associated with the cerebellum, which has been considered as a proposed target of the neurodevelopmental processes. The schizophrenic phenotype consists of a variety of neuronal and behavioral disorders. Also, it includes the impaired cognition, termed as “cognitive dysmetria” that involves the thought form. The literature proposed that this condition may be relevant to the pathological status of the cerebellum [105]. The brain regional analogy has also demonstrated that

deficits in the cerebellar cognitive or affective circuits may lead to thought disorder and/or tangentiality. The investigations using longitudinal and cross-sectional structural MRI proposed the implication of cerebellar development in schizophrenic patients with childhood onset and compared the resulted data to healthy controls [3, 50]. The results showed a decrease of the volume of the cerebellum and cerebrum in adolescent patients with schizophrenia. Moreover, Greenstein et al. [41] explored abnormal different trajectories of cerebellar development in patients with childhood-onset schizophrenia.

Conclusion

Body of evidences has found a critical role of the cerebellum in the development of motor and non-motor (e.g., cognition and behavior) conditions, which was disrupted by cerebellar injury in preterm infants, developmental cerebellar lesions in infants, cerebellar tumor in pediatric patients, and neurodevelopmental defects. As developmental differences occurred in cerebellar malformations and neurodevelopmental disorders, it is thought to be associated with motor, cognitive, and behavioral dysfunction. The cerebellar injury in preterm infants could enhance the rate of cognitive and socio-behavioral dysfunction. Consistent with preterm newborns, cerebellar tumor resulted in similar motor, cognitive, and behavioral defects in pediatric patients. Furthermore, the region-specific lesions may determine the effects of early cerebellar damages on the neurodevelopmental and behavioral disorders. The cerebellar dysfunction at early life can cause distinct, long-term effects on the brain distal areas which are projected by the cerebellum. The developmental diaschisis can influence the structure-function relationship of the regions of cerebral cortex which may be optimized by the cerebellar input. In summary, increasing clinical and neuroimaging evidences in newborns that undergone acquired and developmental cerebellar lesions, along with older children with cerebellar damage, presented novel approach to the role of the cerebellar lesions at early life on cerebral development. On the other hand, determination of the age of cerebellar injury to the developing brain may help us to predict the possible long-term outcomes (Fig. 1).

However, the effects of cerebellar lesions at prenatal and postnatal periods on cerebral development should be clarified. Further studies are needed to better understand the structure-function relationship in the developing cerebellum to improve clinical prognosis, early intervention services, and educational planning. The findings can open a new avenue to explore novel treatment of the cerebella injury-induced neurodevelopmental and behavioral disorders by cerebellar neuromodulation. It is also possible that therapeutic interventions, such as cerebellar neuromodulation, could provide alternate treatment options in these populations. Growing of our knowledge of the association between cerebellar circuits and specific behaviors can facilitate to reach to point of optimization of timing and localization of the therapeutic strategies. These essential findings will guide us to improve the life of millions of children impacted by cerebellar injury and the subsequent developmental disorders.

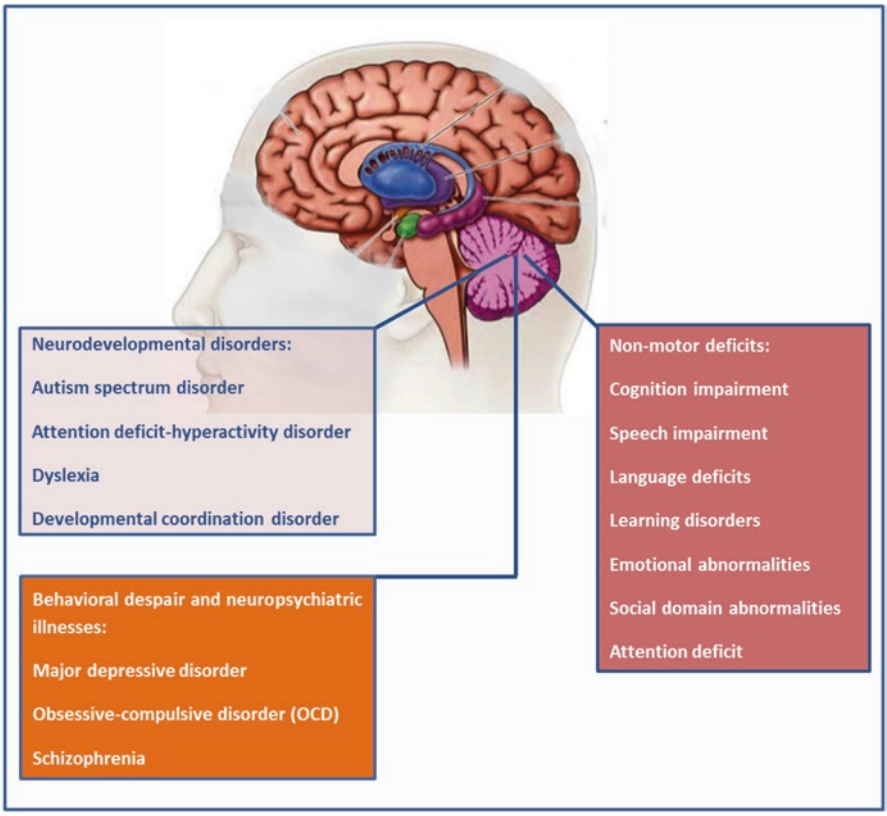

Fig. 1 Schematic of the cerebellum and its associated non-motor, neurobehavioral, and behavioral disorders. The cerebellar damages and dysfunction may lead to a variety of non-motor deficits and behavioral outcomes in patients with neurodevelopmental disorders

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