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The Cerebellum, Sensitive Periods, and Autism

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Abstract:	Cerebellar research has focused on adult motor function. However, the cerebellum also maintains abundant connections with nonmotor brain regions throughout human postnatal life. Here we review evidence supporting the view that the cerebellum guides the maturation of distal nonmotor neural circuitry. Early-life cerebellar injury is associated with gradual motor compensation but high rates of autism and language difficulties. Perinatal cerebellar injury increases the risk of autism by more than 40-fold, comparable to twin-level genetic inheritance. These findings are consistent with the sensitive period concept, in which early-life perturbations can have lasting consequences at distant, synaptically connected targets. Cerebellar dysfunction is likely to be associated with misprocessing of sensory information, a common feature in early stages of autism. We suggest that over development, specific cerebellar zones influence neocortical substrates for social interaction. Sensitive-period disruption of internal brain communication, which we term developmental diaschisis, can account for many clinical and experimental observations.
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	Catherine Limperopoulos, Ph.D. Director, Children's National Medical Center climpero@childrensnational.org Expert on early-life cerebellar insults in developmental disorders, especially autism.
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	Eric London, M.D. Head, Institute for Basic Research in Developmental Disabilities (IBR), New York State Office for People With Developmental Disabilities eric.london@opwdd.ny.gov Expert on autism and subcortical mechanisms.

	Ralph Adolphs, Ph.D. Professor, California Institute of Technology radolphs@hss.caltech.edu Knowledgeable about several aspects of autism, including amygdala contributions and long-distance brain interactions.
Opposed Reviewers:	Kamran Khodakhah, Ph.D. Professor, Albert Einstein College of Medicine k.khodakhah@einstein.yu.edu Has highly idiosyncratic views on cerebellar function, and appears to be opposed to the idea that cerebellum has nonmotor functions. He is unpredictable and articulate, a dangerous combination!
	Jocelyne Bachevalier, Ph.D. Professor, Emory University jbachev@emory.edu The literature on macaque neonatal lesions, especially amygdala, is contentious. We anticipate that she is likely to be hostile to our hypothesis.
	David Amaral, Ph.D. Professor, University of California Davis dgamaral@ucdavis.edu Amaral's research focuses closely on amygdala and hippocampus. It might not be appropriate for him to evaluate a manuscript that focuses on cerebellum. In terms of rank order, Ralph Adolphs (see Suggested Reviewers) might be a better choice than Amaral, and Amaral is a better choice than Bachevalier.

Cover Letter

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Ann Goldstein, Ph.D.
Editor, *Neuron*

December 18, 2013

Dear Ann,

We are pleased to submit for your consideration as a Perspective "The Cerebellum, Sensitive Periods, and Autism," by Alexander D. Kloth, Aleksandra Badura, and myself. Our discussions with you were very helpful, as well as your response to the extended outline we submitted previously.

Our goal in this Perspective was to bring a novel synthesis to three bodies of research in neuroscience on cerebellar research, sensitive periods, and autism. We suggested reviewers in these domains: cerebellum (Hesslow, De Zeeuw, D'Angelo), sensitive periods (Hensch), and autism (Adolphs, London).

Our synthesis accounts for many observations that have escaped easy explanation. We hope it will spur future research efforts in the field, and we hope you enjoy the article.

Yours sincerely,

Samuel S.-H. Wang
Associate Professor
Princeton Neuroscience Institute and Department of Molecular Biology

The Cerebellum, Sensitive Periods, and Autism

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ABSTRACT. Cerebellar research has focused on adult motor function. However, the cerebellum also maintains abundant connections with nonmotor brain regions throughout human postnatal life. Here we review evidence supporting the view that the cerebellum guides the maturation of distal nonmotor neural circuitry. Early-life cerebellar injury is associated with gradual motor compensation but high rates of autism and language difficulties. Perinatal cerebellar injury increases the risk of autism by more than 40-fold, comparable to twin-level genetic inheritance. These findings are consistent with the sensitive period concept, in which early-life perturbations can have lasting consequences at distant, synaptically connected targets. Cerebellar dysfunction is likely to be associated with misprocessing of sensory information, a common feature in early stages of autism. We suggest that over development, specific cerebellar zones influence neocortical substrates for social interaction. Sensitive-period disruption of internal brain communication, which we term developmental diaschisis, can account for many clinical and experimental observations.

In recent decades, much neuroscience research has focused narrowly on the cerebellum's role in balance, posture, and motor control. This framework has been explored in the greatest detail in cases where input pathways convey sensory information to the cerebellum, and outputs influence motor effectors. Emerging from this program is the view that the cerebellum acts as a coprocessor that uses a variety of inputs to guide movement.

Receiving much less emphasis has been the role of the cerebellum in higher function. This idea is not new: cognitive roles for cerebellum have been discussed since the mid-19th century (reviewed in Steinlin, 2013), with a resurgence of interest in recent years (D'Angelo and Casali, 2012). Evidence for cerebellar lesions leading to nonmotor deficits has come from adult cases showing subtle cognitive and affective changes (Stoodley et al., 2012), and congenital cerebellar defects, where deficits are much more pronounced (Basson and Wingate, 2013; Steinlin, 2013).

Two facts have stood in the way of wider recognition of the nonmotor aspects of cerebellar function. First, the most prominent deficits in acute cerebellar injury in adults are of a motor nature. Monitoring the short-term results of injury does not capture long-term

consequences that can accumulate over time. The consequences of cerebellar deficit are highly dependent on when the outcome is assessed. Second, cerebellar connectivity is highly differentiated, and focal injury leads to focal deficits (Romaniella, 2012). While some cerebellar regions project predominantly to sensorimotor cortex, homologous connections project to cognitive and affective regions, and comprise a large fraction of cerebellar connectivity (Strick et al., 2009). Recently, the extension of this parcellated mapping to nonmotor brain structures has become clearer using modern methods (Buckner et al., 2011; Strick et al., 2009). The cerebellar cortex and nuclei have a distinctive circuit structure that is repeated in a modular fashion throughout the cerebellum, and is highly conserved among vertebrates (Apps and Hawkes, 2009). This has led to the proposal that the cerebellum performs a common algorithm upon a variety of inputs, whether sensory, motor, cognitive, or affective.

In this review, we outline a development-based framework for understanding the nonmotor roles of cerebellum. A variety of observations can be explained by the following unified hypothesis: in addition to its role in the mature brain, the cerebellum acts in early life to shape the function of other brain regions, especially those relating to cognition and affect. We propose that the cerebellum, acting as a sensory co-processor, influences neocortical circuit refinement during developmental sensitive periods. We end by describing how new methods for imaging, mapping, and perturbing neural circuits can be used to explore the complex role of the cerebellum in guiding nonmotor function.

To summarize the concept of developmental influence between brain regions, we use the term ***developmental diaschisis***. Diaschisis (\dī-as'-kə-səs\; Gr. *dia*: across, *schisis*: break) is an existing neurological term indicating a sharp inhibition in activity at a site that is distant from a site of injury, but is anatomically connected with it through fiber tracts. For example, prefrontal injury has been shown to lead to abrupt decreases in blood flow to the contralateral cerebellum, and vice versa. In the same way, we define <u>developmental</u> diaschisis as a phenomenon in which disruptions in activity in a particular brain area can affect the organization and function of other, distal brain sites over developmental time. As a central example, we will focus on autism spectrum disorder (ASD), for which the developmental-diaschisis hypothesis can resolve some longstanding puzzles regarding the cerebellum's role.

AUTISM-RELATED GENE CO-EXPRESSION IDENTIFIES CEREBELLAR AND NEOCORTICAL SITES OF DISRUPTION

Autism spectrum disorder (ASD), the most strongly heritable major neurodevelopmental disorder (Abrahams and Geschwind, 2008), has attracted tremendous research interest. Usually diagnosable by the age of 2, ASD encompasses a wide range of deficits including basic social impairment, communication difficulties, and repetitive and stereotyped behaviors. A Web Of Science literature search reveals over 80,000 scientific publications mentioning autism since 1948, more than half of which have been published since 2009. This work has established a conceptual framework in which fetal brain development is robust, most often leading to normal-range function in the presence of any one risk mutation, of which hundreds have been identified (SFARI GENE; https://gene.sfari.org). Thus combinations of genes are likely to work together to trigger ASD. However, despite this booming literature, it is not yet established how these mutations drive specific missteps in the maturation of brain circuitry.

Three recent studies have used aggregated gene expression patterns to ask when and where ASD genes are expressed (**Figure 1**; Menashe et al., 2013; Parikshak et al., 2013; Willsey et al., 2013). ASD susceptibility genes show a high degree of co-expression with one another in mouse and human brain, allowing the identification of specific gene networks or "cliques" (Menashe et al., 2013). Based on gene ontology classification, many ASD susceptibility genes are involved in synaptic plasticity, development, and neuronal differentiation (Parikshak et al., 2013).

ASD-related co-expression networks were found during two distinct periods of development. First, during human gestational weeks 10-24 and mouse P0-10, expression was found in a broadly defined somato-motor-frontal region (Willsey et al., 2013) especially in layer 5/6 cortical projection neurons (Parikshak et al., 2013; Willsey et al., 2013) and other layers (Parikshak et al., 2013). Second, in humans from neonatal to age 6, cerebellar network expression is strong (Willsey et al., 2013), particularly in the cerebellar granule cell layer (Menashe et al., 2013). Unfortunately, the other study examining aggregated gene expression patterns did not examine cerebellum (Parikshak et al., 2013). Taken together, these patterns identify two regions where genetically driven developmental programs can go off track: the second-trimester frontal/somatomotor neocortex and the perinatal/postnatal cerebellar cortex.

PERINATAL RISKS FOR AUTISM HIGHLIGHT A ROLE FOR THE CEREBELLUM

The diverse body of autism research provides an opportunity to quantify the contribution of a wide range of risks, with the goal of identifying putative neural substrates and mechanisms. Just as there are two major periods of ASD gene co-expression, epidemiological and clinical literature reveal two major time windows for environmental risk.

To illustrate both genetic and environmental risk factors for autism in quantitative perspective, their associated risk ratios are shown in **Figure 2**. The highest risk ratio is found for identical twins with a substantially lower risk for fraternal twins, a finding that formed the original basis for the idea of genetic causation. Yet ASD is also affected by environmental factors occurring before birth, demonstrating the potential of environmental insults to impede the maturation of social function.

Most known environmental risks for autism occur during late pregnancy and birth, times of vulnerability to stressors. Maternal infection during pregnancy, especially the second and third trimester, is an ASD risk factor (Atladottir et al., 2010), suggesting as a cause the maternal stress response, which includes glucocorticoid signaling and the immune response. Lesser-known ASD risks are consistent with the stress hypothesis: premature birth (Moster et al., 2008), elective cesarean section (Glasson et al., 2004), and even being born to mothers caught in a hurricane strike zone (Kinney et al., 2008) or a severe ice storm (Laplante et al., 2008) during late pregnancy. Maternal emigration has been shown to be positively correlated with risk for autism in the offspring (Magnusson et al., 2012). All of these autism risks are larger than the risk associated with advanced maternal or paternal age.

The second and third trimester in human gestation correspond approximately to the first three postnatal weeks of life in rodents (Workman et al., 2013). Brain development in rodent pups is influenced by stresses such as variation in maternal care, leading to epigenetic variation (Gudsnuk and Champagne, 2011) and long-term changes in behavior (Moriceau et al., 2010). Stress in rodent pups also alters the excitable properties of CNS neurons (Schneider et al., 2013) and impairs classical eyeblink conditioning, a form of cerebellar learning, in adulthood (Wilber et al., 2011).

All of the ASD prenatal/perinatal factors shown are associated with risk ratios between 2 and 7, with one notable exception: injury to the cerebellum. Damage to the cerebellum at birth (Limperopoulos et al., 2007) leads to a risk ratio for autism of greater than 40. This risk factor is quantitatively comparable to that of genome-wide twin risk and to the highest-risk single mutations for autism. These findings suggest that after birth, the cerebellum plays an essential role in the development of basic social capabilities. This idea is consistent with the fact that the cerebellum is among the most frequently disrupted brain regions in autistic patients, at both microscopic and gross levels. The cerebellum in ASD shows gray and white matter abnormalities from early childhood (Courchesne et al., 2005). Adult ASD cerebella show Purkinje cell, olivary, and deep nuclear cellular alterations at frequencies that rival the amygdala (60-70% of patients for both structures) and exceed the neocortex (Palmen et al., 2004). In summary, cerebellar defects in ASD are seen throughout life, and if they arise by birth are often sufficient to cause the disorder.

A second time window of vulnerability to ASD occurs in the postnatal years and suggests a role for experience. Autism becomes apparent during early childhood, usually in what developmental psychologists define as the sensorimotor stage of development (Piaget, 1983). Social and/or sensory deprivation during early childhood can also lead to autism-like social deficits in adulthood. In a study of children adopted from abusive Romanian orphanages into UK families, a high fraction of children who underwent long-term deprivation developed social deficits that closely resembled autism, which could be reversed by placement in a normal adoptive home (Rutter et al., 1999; Smyke et al., 2009). The longer and later the children stayed in deprived conditions, the more severe and difficult the behavioral changes were to reverse. Thus experience-dependent mechanisms are likely to guide the formation of social capacities during the critical first years of life.

These identified risks are likely to share at least some common mechanisms. Genetic risks and epidemiologically-identified environmental stresses most likely act by influencing the developmental program of the nervous system. These risk factors are triggers that act upon as-yet-unidentified neural substrates. In this context, is the cerebellum a special point of vulnerability, or do a wide variety of early-life brain injuries also lead to ASD risk?

ARE AUTISM-LIKE OUTCOMES FROM EARLY INJURY SPECIFIC TO THE CEREBELLUM?

Because ASD arises early in development and eventually involves multiple brain structures, focal brain injury studies in early life can provide valuable information about how ASD unfolds. Although focal brain injury is not thought to be a principal cause of developmental disorders, it provides an approach to systems-level perturbation that deepens the significance of gene expression studies. Here we present focal perturbation data to identify candidate subsystems that may drive the maturation of brain capacities.

Of particular interest for ASD are sites at which early-life injury, but not adult injury, leads to a long-term deficit; we call these *upstream* drivers. This contrast allows regions to be putatively classified as developmentally upstream or downstream (**Figure 3**). A classical example of an upstream driver is the role of retina and thalamus in shaping the circuitry of a *downstream* target, the primary visual cortex. In this example and others, early-life deprivation during a sensitive period can lead to commitments that are difficult to reverse at later ages. More complex functions tend to have sensitive periods that come even later during development (Knudsen, 2004), so the primary visual cortex is itself an upstream driver in the later maturation of yet more complex functions.

In this classification scheme, many brain regions would be expected fall into the downstream category, since cognitive and social functions engage neural substrates throughout the brain. Other regions might fall into a third category, *compensatable*, in which an acute injury's effects diminish over time due to plasticity mechanisms for recovering function.

We will now apply this downstream/upstream/compensatable framework to ASD-like social outcomes. We focus on severe deficits that overlap with autism: inability to develop peer relationships, lack of emotional empathy or enthusiasm for others, inability to use or interpret nonverbal social cues, and perseverative action or thinking. We will focus on a number of brain areas that have a direct role in sustaining specific cognitive and affective capacities (**Figure 4**). The general principle emerging from these studies is that with the exception of the cerebellum, ASD-like deficits arising from early-life lesions are to a large degree recoverable over time.

Amygdala, hippocampus, and the medial temporal lobe. The importance of the amygdala in emotional response led to considerable initial interest in investigations of ASD (Baron-Cohen et al., 2000). As a test of the amygdala's involvement as an upstream cause of

ASD dysfunctions, ibotenic acid injections have been done in macaque monkeys to specifically lesion cells while sparing fibers of passage (reviewed by (Bliss-Moreau et al., 2011). Using this method, early damage to the amygdala does not alter fundamental features of social development, including the development of mother-infant interactions and the ability to interact with peers. Selective deficits eventually appear, including stereotypies, blunted processing (with recognition intact) of emotionally evocative video stimuli, and reduced social fear. In humans, complete congenital absence of the amygdala on both sides leads to relatively mild social deficits and low scores on standardized ASD inventories (Paul et al., 2010). Adult amygdala lesion in macaques also leads to decreased anxiety and social fear and increased social confidence. In short, although the amygdala is important in affective processing, it is not needed for the capacity to identify socially meaningful contexts. Nonetheless, both anatomical and functional abnormalities in the amygdaloid complex are observed in a variety of neuropsychiatric disorders (Schumann et al., 2011), including ASD. This pattern of evidence suggests that a dysfunctional amygdala may be a downstream target in the etiology of ASD.

Broader lesions reveal that when damage encompasses neighbors of the amygdala, more profound symptoms emerge (Bliss-Moreau et al., 2011; Machado and Bachevalier, 2006). Adult and neonatal lesions to the hippocampus, which has close connections to other parts of the MTL, lead to only limited social defects (Bliss-Moreau et al., 2011). However, combined lesion in 2-week-old macaques of amygdala, hippocampus, and the overlying medial temporal cortex, a structure implicated in Klüver-Bucy syndrome, leads to severe social symptoms, and by 6 months of age and persisting into adulthood, these monkeys fail to initiate social contacts, accept social approaches by peers, or make eye contact. Neonatal lesions to MTL produce more severe core social deficits than adult lesions, indicating that MTL structures as a whole act in a developmentally upstream fashion in the emergence of social capacities. Also, these findings do not rule out an upstream role for the medial temporal cortex acting by itself.

Inferior temporal cortex. One structure related to the medial temporal structures is the inferior temporal cortex, which is involved in face recognition. Adult lesion of this structure leads to face blindness and behavioral abnormalities such as hyperorality and decreased aggression, but if the lesion is done neonatally, these signs fade considerably over time (Málková et al., 2010). Thus inferior temporal cortex, which is well studied in ASD patients, might be regarded as a structure whose contributions to core social capacity are compensatable.

Frontal neocortical regions, including the anterior cingulate cortex. Disruptions to the structure of frontal neocortex have been reported in ASD (Courchesne et al., 2011; Girgis et al., 2007). Perturbation of prefrontal and orbitofrontal cortex do not lead to ASD-like symptoms. In the orbitofrontal cortex (OFC), which is heavily connected to the amygdala, both neonatal and adult damage in humans and in animals impairs the regulation of emotions in social situations and emotion-based decision-making, and responsiveness to changing social and behavioral environments, but no disability in basic social interactions (Bachevalier and Loveland, 2006; Bachevalier et al., 2011; Machado and Bachevalier, 2006). Although neonatal damage results in fewer initiated social interactions in nonhuman primates, it remains unknown whether this deficit persists into adulthood; other studies of OFC damage suggest that adult damage leads to more severe cognitive consequences than neonatal damage (Bachevalier and Loveland, 2006). A similar case may occur with the prefrontal cortex, in which perinatal damage leads to persistent increased irritability, difficulties maintaining friendships, and lack of empathy and fear, but ASD-like social dysfunction is absent (Eslinger et al., 2004).

One region linked to more serious deficits in basic affective interaction is the anterior cingulate cortex (ACC), which is strongly connected with amygdala and OFC. Adult lesion to the ACC in non-human primates produces lack of interest in social situations, loss of emotional regulation, and inability to recognize social and emotional cues (Devinsky et al., 1995; Hadland et al., 2003). Because neonatal lesions of ACC have not been reported, at the time of this writing it is unresolved whether its contribution is downstream or compensatable by other brain regions.

Cerebellum. In adults, cerebellar lesions are unlikely to result in profound social deficits. However, damage can produce cerebellar cognitive-affective syndrome, which is characterized by "dysmetria of thought" (Schmahmann, 2004) involving disturbances of planning, decision-making and working memory, deficits in visuo-spatial reasoning, and verbal reasoning defects, and personality changes, anxiety, and blunted or inappropriate behavior (Wolf et al., 2009). This syndrome is predominantly reported after injury to the posterior cerebellum, with cognitive symptoms associated with the cerebellar hemispheres and affective symptoms with the vermis (Stoodley et al., 2012).

Lesions at earlier ages lead to more conspicuous cognitive and affective changes. and the nature of the developmental delay depends on the area that is injured. Damage to the

hemispheres results in language delay and visual and verbal reasoning deficits, and damage to the vermis results in withdrawn social behavior, impaired gaze, anxiety, and stereotyped behavior (Wells et al., 2008). In children ages 6 to 13, posterior fossa damage, particularly to the posterior vermis, has been known to produce cerebellar mutism, a syndrome in which language capacities regress by years, sometimes leading to total loss of the power of speech (Riva and Giorgi, 2000). Language deficits appear to be more than purely problems of phonological speech production, as they involve specific loss of grammar and/or vocabulary. Mutism is often not permanent, indicating the existence of compensatory mechanisms elsewhere in the brain.

This trend toward cognitive and affective deficits is particularly striking when cerebellar damage occurs near the time of birth. Perinatal damage to the cerebellum due to premature birth or as a secondary consequence of surgery produced social deficits and high scores on ASD inventories, at a rate of 59% (Bolduc et al., 2012). In this study, hypoplasia of the posterior cerebellar vermis strongly predicted autism evaluation scores. Perinatal cerebellar damage leads to a relative reduction in volume of the contralateral prefrontal cortex at age two (Bolduc et al., 2012; Limperopoulos et al., 2012). In addition, a number of cerebellar malformation syndromes have ASD-like signs, including Joubert syndrome, Dandy–Walker malformation, and pontocerebellar hypoplasia, all of which often include substantial delays in intellectual, cognitive, and social function in cases where the vermis is malformed (Boltshauser, 2004). In Joubert syndrome, 25% of cases are diagnosed with ASD (Geschwind and Levitt, 2007). These findings indicate that neonatal damage to the cerebellum can have persistent structural and functional consequences.

At a gross structural level, ASD is often accompanied by cerebellar undergrowth and deviant patterns in white/gray matter growth (Abell et al., 1999; Wegiel et al., 2010). Cellular abnormalities are found in Purkinje cells and neurons of major input and output structures of the cerebellum, the inferior olive and the deep nuclei (Palmen et al., 2004). The pons and thalamus, which provide connections between the cerebellum and the cerebral cortex, have smaller volumes in ASD patients (Hashimoto et al., 1995). A subregion of vermis shows hypoplasia in adults who are diagnosed with infantile autism (Courchesne et al., 1988; Kaufmann et al., 2003; Scott et al., 2009). In summary, early developmental deviations may be a general feature of the cerebellum in ASD.

Cognitive and affective consequences of early-life cerebellar damage have been echoed in animal studies. In rats, midline (i.e. vermis) cerebellar lesions at postnatal day 10 result in perseveration and social disruption in the adult (Bobee et al., 2000). One recent example comes from a mouse model of tuberous sclerosis, which in humans shows cerebellar pathology and a 25% rate of autism diagnosis (Smalley, 1998). Purkinje cell-specific knockout of the tuberous sclerosis gene TSC1 leads to autism-like deficits, including deficient social interaction with other mice, increased repetitive self-grooming, diminished mother-pup interaction, and perseveration when the rule is switched on a T-maze (Tsai et al., 2012). These deficits were rescued by the administration of rapamycin (a drug that epistatically rescues the TSC1 deletion) at postnatal day 7. This study is an example of experimentally induced developmental diaschisis, and provides an important demonstration that early-life cerebellar development can play a necessary role in acquiring core social capacities.

THE CEREBELLUM CAN INFLUENCE COGNITIVE AND AFFECTIVE-RELATED FOREBRAIN STRUCTURES VIA LONG-DISTANCE LOOPS

The cerebellum occupies a relatively constant fraction of the mammalian brain, independent of the proportions of other components (Clark et al., 2001). Since the cerebellum is connected with many brain regions, its role in integrative brain function is likely to be general and similar across species. The cerebellum's circuit architecture repeats nearly identically throughout its extent. Thus it may execute a single canonical circuit computation – but with functional consequences that will vary, depending on where it sends its output, and on the stage of development.

In the case of neocortex, a general organizational principle is that of *cerebello-thalamo-cortical* loops (**Figure 5**). Cerebello-thalamo-cortical loops (Figure 5a,b) have long been appreciated for motor functions (Strick et al., 2009; Prevosto et al., 2010; Voogd et al., 2012). This loop organization also encompasses brain regions known to contribute to cognitive and affective processing (Strick et al., 2009). For example, transsynaptic viral tracing in monkeys and electrical stimulation in rats (Watson et al., 2009) reveals a bidirectional loop joining the dorsolateral prefrontal cortex with lateral crus II and vermal lobules VII on the contralateral side. An even broader picture of the map between neocortex and cerebellum comes from human

default-mode imaging measurements of covariation between neocortex and cerebellum (Figure 5c). These measurements reveal that nearly every part of neocortex has a cognate region in the cerebellum (Buckner et al., 2011; Krienen and Buckner, 2009). The representations are approximately proportional, so that larger functional areas in the neocortical sheet have larger partners in cerebellum (Figure 5c). Notably, cerebellar regions associated with autism communicate with frontal regions of neocortex. Prefrontal cortex is associated with the posterior cerebellar hemispheres (Krienen and Buckner, 2009), and regions comprising lobules VI and VII are associated with contralateral mid-frontal regions that appear to encompass ACC in humans (Buckner et al., 2011) and homologous regions in rats (Suzuki et al., 2012).

As another example of cognitive/affective related connectivity, the cerebellar nuclei project to parts of the basal ganglia associated with reward. A long line of evidence using both transported tracers (Phillipson, 1979; Geisler and Zahm, 2005) and viruses (Watabe-Uchida et al., 2012) shows that the deep nuclei project monosynaptically to the ventral tegmental area, a structure central to the signaling of reward (Schultz, 2002). The cerebellum also sends indirect connections to basal ganglia (Hoshi et al., 2005). In the converse direction, the basal ganglia also send a pathway from the subthalamic nucleus back to the contralateral cerebellar hemisphere (Bostan and Strick, 2010). Thus long-distance cerebellar loops may participate in shaping dopamine-based reward and other unexpected events that influence reinforcement learning.

Several locations in cerebello-thalamo-cortical loops are potential targets of ASD-related gene expression. As previously stated, the cerebellum is a site of co-expression in early postnatal years, especially in granule cells (Menashe et al., 2013; Willsey et al., 2013). A second site for ASD gene co-expression is deep-layer projection neurons of the neocortex during the second trimester (Willsey et al., 2013). Corticopontine projections originate from layer 5, suggesting that this arm of the cerebello-thalamo-cortical loop may be vulnerable to ASD mutations. Therefore the concept of developmental diaschisis extends beyond focal lesion, and can include the possibility that disrupted molecular signaling pathways can interrupt long-distance guidance of neural circuit refinement.

DO CEREBELLAR BRAIN PATHWAYS DRIVE SENSITIVE-PERIOD MATURATION OF ASSOCIATIVE NEOCORTEX?

The foregoing findings point to a role during early life for the cerebellum to shape the eventual organization of mature brain functions. The consequences of early-life damage to the cerebellum are similar to the effects of social deprivation. Both abnormal processing within the brain and deprivation of external social input could disrupt the maturation of downstream circuits in a similar fashion.

Strikingly, the cognitive and social consequences of cerebellar injury show an opposite age-dependence from the motor consequences. When motor-related cerebellar regions are lesioned, adult injury leads to ataxia, dysarthria, dysphagia, and other problems of muscular coordination and timing (Timmann et al., 2008). These motor dysfunctions attenuate with time. In children, acquired lesions of the cerebellar hemisphere lead to motor development that is normal or only moderately delayed (Tavano et al., 2007). In very preterm children, no correlation has been observed between the volume of the underdeveloped cerebellum and motor function later in childhood (Allin et al., 2001). Long-term compensation is unlikely only in cerebellar agenesis, in which motor function remains underdeveloped throughout life (Timmann et al., 2003). Thus, the cerebellum is compensatable with respect to motor functions, but cognitive and social functions are specifically vulnerable to early-life perturbation of cerebellum – suggesting a sensitive-period mechanism..

Brain development in early life is a robust process, but normal experience is an essential component (**Figure 3**). In the process of experience-expectant plasticity, developing brains go through sensitive periods (Wiesel, 1981; Knudsen, 2004) during which they require a minimum level of normal experience. Activity in one brain area can induce nearly irreversible changes in another brain area through structural and synaptic plasticity mechanisms (Hensch, 2005). For example, in primary visual cortex, mismatch of visual input due to monocular deprivation during the sensitive period for ocular dominance column formation leads to an overrepresentation of the nondeprived eye and a failure to create a binocular map. A sensitive period has been observed for thalamocortical auditory processing (Barkat et al., 2011).

Dendritic and axonal mechanisms for sensitive-period refinement. A characteristic pattern of cellular growth during sensitive periods is initial exuberant growth of dendritic and

axonal arborizations, followed by activity-dependent pruning of unwanted connections (Knudsen, 2004). In activity-dependent plasticity, incoming information is a driver of circuit refinement. The same pattern may apply to developmental disorders. For example, cerebral palsy can be modeled in animals by blocking corticospinal activity on one side in early postnatal life (Friel and Martin, 2007). In this case, descending corticospinal projections normally undergo an initial period of bilateral mapping, after which Hebbian activity-dependent competition leads to the preferential elimination of ipsilateral projections. Blockade of activity prevents this process and the functional separation of the two tracts does not occur.

In infants who later go on to develop autism, differences in brain growth become apparent by age 1, as quantified by increased head circumference (Stigler et al., 2011). Extreme head growth is associated with the most severe clinical signs of autism (Courchesne et al., 2004). In volumetric MRI measurements, ASD brains grow faster on average than neurotypical brains in the first two postnatal years (Redcay and Courchesne, 2005). By age 2.5, brain overgrowth is visible as enlargement of neocortical gray and white matter in frontal, temporal, and cingulate cortex (Schumann et al., 2010). Since this abnormal growth comes after the time of neurogenesis, volume differences are likely to arise either from disruption of progressive (growth) or regressive (pruning) events. Disruption to either of these processes would account for perturbations in the trajectory of gross volume changes. Finally, overgrowth in ASD brains is followed by premature arrest of brain growth after age 4. These abnormalities would be expected from defects in plasticity mechanisms – for example, dendritic growth and pruning, or axonal branching. In the case of early-life cerebellar defects, reduced numbers of Purkinje cells (Palmen et al., 2004) may provide inadequate activity to drive neocortical plasticity mechanisms.

Sensitive periods for cognitive and social function. Higher sensory capabilities may also undergo sensitive periods, once lower sensory structures have matured (Knudsen, 2004). A similar principle is likely to apply to cognitive functions. One candidate example is the ontogeny of reading (Turkeltaub et al., 2003). In early readers, activated brain regions are distributed on both sides of the neocortex and cerebellum. Between childhood and adolescence, these regions come to exclude auditory regions, leaving a more focused, largely left-hemisphere network that includes the visual word form area. Notably, in readers who first learn to read as adults, activity patterns are more bilaterally distributed (Dehaene et al., 2010) and are reminiscent of literate

children starting to read. This observation indicates that adults have considerably less capacity for refinement.

The sensitive-period concept also applies to social development. In social isolation experiments by Harry Harlow and others in the 1960s, infant monkeys were raised under conditions in which the birth mothers were replaced with artificial surrogates for the first six months of their lives. At later ages, these deprived monkeys displayed rocking behavior, perseveration, and inability to communicate or socially bond with other monkeys (Novak, 2008). This work supported a critical period hypothesis for social function, and it was later found that targeted interventions using peer monkeys could partially rescue the effects on previously isolated monkeys.

Like the plight of the Romanian orphanage children, the Harlow experiments are disturbing because the degree of deprivation is extreme. The developmental diaschisis hypothesis raises the possibility that ASD has similarly profound effects on forebrain circuit maturation. The difference is that the flow of information is interrupted not externally, but internally to the brain. In this way, developmental diaschisis of information flow to the neocortex could lead to long-term effects that resemble those of severe early-life deprivation, even under normal environmental conditions.

CONTRIBUTIONS OF THE CEREBELLUM TO LEARNING AND PLASTICITY

The cerebellum is widely believed to be a site for supervised learning (**Figure 6**). Unexpected events are thought to be signaled via the inferior olive's climbing fibers, which strongly innervate Purkinje cells to drive a dendritic calcium-based action potential. This dendrite-specificity allows the instructive signal to be separated from the effects of the mossy fiber pathway, which drives the Purkinje cells' output, somatic and axonal sodium spikes. The climbing fiber signal drives plasticity of a high-dimensional input from the mossy fiber pathway, the feedforward architecture of which is well suited to support the supervised learning of specific mossy fiber/granule cell patterns (Raymond et al., 1996) carrying predictive value on a subsecond time scale. The learned information is then transferred to the deep nuclei. Such architecture is capable of fine discrimination of stimulus features and transforming multisensory information to predictive output.

Examples of multisensory learning tasks requiring the cerebellum are most well studied in the motor domain. Delay eyeblink conditioning (Raymond et al., 1996) is a form of multisensory learning, in which an initially neutral stimulus (*e.g.* a tone or a light flash) becomes associated with a strong teaching stimulus (corneal airpuff or periorbital shock) that, by itself, evokes an unconditioned blink response. The unconditioned stimulus is conveyed to cerebellar cortex and nuclei via the inferior olive and its climbing fibers. Neutral (conditioned) stimuli are conveyed to the cerebellum via the mossy fiber pathway. After hundreds of closely timed pairings of conditioned and unconditioned stimuli, eventually the conditioned stimulus alone evokes a blink at the predicted time of the unconditioned stimulus. In this paradigm, different modalities (e.g. corneal airpuff and tone) are associated with one another. The cerebellum plays a similar role in vestibuloocular reflex gain adaptation (vestibular input and retinal slip signal).

In the case of social learning, making sensory discriminations and predictions is important because most sensory information has little intrinsic social valence (Cohn and Tronick, 1987). A mother's smile is unlikely to be intrinsically rewarding to a baby, but instead must be paired with other information such as food or touch (Stack and Muir, 1992). It has been postulated that in autism, difficulties attending to socially salient stimuli may arise from an impairment of assigning reward to the stimuli (Dawson et al., 2002). Broadly, the cerebellum's potential role in acquiring the ability to associate a sensory pattern with an innately rewarding or aversive event, can contribute to information processing – and even drive learning – in the neocortex. Such a role is potentially supported by the monosynaptic projections that lead from the cerebellar nuclei to VTA.

For associating an innately rewarding stimulus with other sensory events, a principal computational function of the cerebellum might be that of detecting closely-timed associations. Eyeblink conditioning and vestibulo-ocular reflex gain control have specific timing requirements for the instructive (climbing fiber) stimulus to come within a few tenths of a second after the learned (mossy fiber) stimulus. This timing relationship is reflected in the temporal order requirements for parallel fiber-Purkinje cell long-term depression (LTD; Wang et al., 2000). Thus a major computational function of the cerebellum in social learning might be the ability to associate a fast social cue (sensory feedback) with a reward-outcome. In this way, the role of cerebellum in processing timing information across sensory modalities (D'Angelo and De Zeeuw, 2009) might be of specific relevance for social learning.

Cerebellar supervised learning has also been proposed as a means of acquiring internal models (both forward and inverse) about the environment (Wolpert et al., 1998). The cerebral cortex can also learn predictive models of the environment, but it does so using a very different circuit architecture, one that is rich in loops and recurrent excitation. Due to these markedly contrasting architectures, it has been proposed that the cerebellar and cerebral cortex differ in their learning algorithm, with the cerebellum performing supervised learning, while the cerebral cortex performs unsupervised learning (Doya, 1999). The cerebellum thus may play a complementary functional role to neocortex, regardless of modality. If the two structures were suited for different types of learning, cerebello-thalamo-cortical loops would provide a substrate for tasks to be processed by two very different architectures working together. Such a hybrid architecture is potentially quite powerful, as it could combine the strengths of the two respective learning approaches.

Indeed, patterns learned by one structure could be passed to the other structure. Such transfer is an example of memory consolidation. In memory consolidation, the acquisition of a memory requires rapid adaptation in one brain region coupled with gradual plasticity in a second brain region, where the memory is stored (Krakauer and Shadmehr, 2006). This process has been observed between the cerebellar cortex and the deep cerebellar nuclei for cerebellum-dependent behaviors such as eyeblink conditioning, in which the expression of motor memory (but not its timing) comes to require the interposed nucleus but not the cerebellar cortex (Attwell et al., 2002). A similar process has been observed for motor skill learning, in which the motor cortex consolidates input from the cerebellum after many trials of learning (Krakauer and Shadmehr, 2006). Thus, changes in cerebellum may, over time, drive changes in corresponding cortical areas.

For example, regions encompassing lobules VI and VII, where abnormalities have been reported in ASD (Carper and Courchesne, 2000), show strong covariation of default-mode signaling with contralateral mid-frontal regions that appear to encompass ACC (Buckner et al., 2011). ACC roles include motivating and attending responses, detecting errors to those responses, and switching flexibly between cognitive and affective tasks (Devinsky et al., 1995). Autistic persons show deficits in response monitoring, making adjustments to optimize outcome, and the ability to monitor one's self (Mundy, 2003; Thakkar et al., 2008), and ASD patients who score high on repetitive behavior show abnormal signaling in rostral ACC. We suggest that

during development, ACC and lobule VI-VII may pass each other information as part of the acquisition of emotional and social capacities.

The timing of cerebellar maturation is also consistent with the developmental diaschisis hypothesis. The cerebellum reaches its mature volume within months of birth in humans (Rice and Barone, 2000). In humans the cerebellum develops throughout pregnancy with rapid growth in the third trimester and in the first postnatal year (Limperopoulos et al., 2007; ten Donkelaar et al., 2003; Zervas et al., 2005). Cerebellar circuitry is vulnerable in the days and weeks following birth (ten Donkelaar et al., 2003), a period during which the cellular makeup and the quantity of inputs changes quickly (Wang and Zoghbi, 2001) and ASD genes are co-expressed in cerebellum (Willsey et al., 2013). In contrast, cortical areas continue to mature for a longer period of years (Rice and Barone, 2000). Thus, the cerebellum grows during a period of known genetic and environmental vulnerability, and reaches full size in time to potentially guide the refinement of neocortical structures.

A SENSORY HYPOTHESIS OF CEREBELLAR CONTRIBUTIONS TO DEVELOPMENTAL DISORDERS

Just as sensory areas are organized by experience, cognitive and social processing may also be guided by structures that process sensory information to extract useful parameters. In this context, the cerebellum, which is thought to integrate sensory information (Bower, 1997) to modulate movement (Thach et al., 1992), is a candidate to play a similar role in nonmotor function (Ito, 2008). The architecture of the cerebellum appears to be well suited to learn to make fine discriminations, especially in the domain of multisensory learning. Such learning might be of considerable use to the social and cognitive brain – a coprocessor to other brain structures (D'Angelo and Casali, 2012).

The cerebellum integrates many converging multimodal sensory inputs via the mossy fiber pathway, which converge with unexpected events as transmitted by the climbing fiber pathway. Mossy fibers synapse onto cerebellar granule cells, which comprise approximately half the neurons of the human brain. Many different sensory receptive fields are found near one another in the granule cell layer; as granule cell axons give rise to parallel fibers, multisensory information is thoroughly mixed and distributed across many Purkinje cells. Notably, ASD-gene-associated co-expression networks have the strongest expression in the cerebellar granule layer

(Menashe et al., 2013), where information from multiple sensory modalities can be integrated (Huang et al., 2013). Thus, multisensory integrative tasks would be one area where ASD and cerebellar function may meet.

Multisensory defects in ASD suggest cerebellar dysfunction. Atypical sensory responsiveness in ASD children can be detected as early as 4-6 months of age (Zwaigenbaum et al., 2005). Autistic individuals show abnormalities in eyeblink conditioning (Oristaglio et al., 2013; Sears et al., 1994; Tobia and Woodruff-Pak, 2009). Mouse models of ASD also show disrupted eyeblink conditioning, including Fragile X mouse model (Koekkoek et al., 2005), as well as Shank3(+/ΔC), Cntnap2-/-, and MeCP2, and the paternal duplication of the human ortholog of 15q11-13 (Kloth et al., 2013, *Soc Neurosci Abstr*). Thus multisensory learning deficits appear to be widespread features of both human ASD and animal models of ASD.

Consistent with the importance of subcortical sensory processing is the observation that from infancy onward, autistic children (and often their siblings) show atypical sensory responsiveness. Visual orienting latencies to nonsocial stimuli are atypically slow in 7-month-olds who later meet ASD criteria (Elison et al., 2013). At later ages, sensory abnormalities persist (Leekam et al., 2007) and more complex deficits emerge. (Klin et al., 2009) reported that 2-year-old autistic children attended more strongly to multisensory simple synchrony than more complex combinations associated with natural biological motion. ASD patients show unreliable evoked neocortical responses to simple, nonsocial sensory stimuli (Dinstein et al., 2012). These abnormalities are potentially causative, since sensory responsiveness and social symptoms are strongly correlated in high-functioning autism patients (Hilton et al., 2010). Together, this evidence suggests that abnormal sensory preprocessing may arise early in the etiology of ASD, and perhaps play a causative role. This concept would provide a functional interpretation for the developmental diaschisis hypothesis.

Finally, cerebellar learning deficits could also affect not only sensory information arriving in cerebellar cortex, but also nonsensory information. The cerebellar mossy fiber pathway has a considerable corticopontine component, which conveys efference copy for motor – and perhaps nonmotor (Huang et al., 2013) – information. Considering the self-similarity of cerebellar circuitry, any cerebellar deficits would be expected to affect the processing of all information arriving via the mossy fiber pathway.

NEW APPROACHES TO TESTING THE DEVELOPMENTAL DIASCHISIS HYPOTHESIS

Although it seems likely that the cerebellum shapes cognitive and affective domains during development, the evidence to date comes largely from lesion experiments and clinical observations. These results provide a starting point and an opportunity to use newer and more powerful tools to map, image, and manipulate brain circuitry. The development of these tools is likely to accelerate with projects such as the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative in the United States. Technologies drawn from molecular biology, physical sciences and engineering, statistics, and computation (Bargmann, 2013; Sun et al., 2012) will enable probing nonmotor and developmental roles of the cerebellum to new scientific depths.

Tests of the developmental diaschisis hypothesis fall into the following three categories. These tests can be conducted to probe a variety of upstream triggers: the cerebellum, other brain structures, and specific molecular defects associated with genetic susceptibility loci.

(1) Does early-life disruption of upstream trigger regions have selective effects on adult cognitive and affective function? Lesion experiments are irreversible and are defined spatially, encompassing all cells within reach of a burn or chemical injection. It is now possible to express inactivating receptors in specific cell populations, which do not act unless exposed to a ligand or light. These tools can target defined nuclei and cell types and are reversible on time scales into the subsecond range. Inactivation can even be performed during specific behaviors. Such tools can be used to test when in development, and under what circumstances, a region shapes cognitive and affective circuitry at distal sites. It should be possible to target specific lobules of cerebellum (for instance lobules VI/VII), as well as smaller structures throughout the brain (for instance the deep nuclear-VTA pathway).

(2) In adult life, do specific cerebellar regions have specific influences on distal counterparts in neocortex, and vice versa? One major technological priority for the BRAIN initiative is monitoring neural activity at multiple regions. Already, neural activity can be optically monitored in behaving mice using two-photon microscopy and whole-cell single cell recording. Social and cognitive interactions can be probed using head-fixed tasks or using miniaturized microscopes in freely-moving animals.

Once specific brain locations and cell types of interest have been identified, it will be useful to map the exact circuitry to which the location connects throughout the brain. A variety of transsynaptic tools have been developed to achieve controlled labeling of circuitry. Reconstruction is somewhat limited by the time required for sectioning and tracing. Tissue-clearing and automated tracing methods should allow viral tracing efforts to be accelerated considerably. As an example, it would be of great interest to know what type of information is passed between lobules VI/VII and ACC. ACC is thought to participate in exploration and exploitation in the environment, and the role of cerebellar learning and discriminative sensory processing remains to be explored.

(3) Is the upstream region a potential target for rescue in mouse models of developmental disorders? The availability of mouse models for developmental disorders opens the possibility that adult dysfunctions in these animals could be rescued by early-life interventions. If dysfunction in an identified circuit drives the maturation of brain circuitry off track, it might be possible to rescue a normal trajectory by boosting or restoring the circuit's function. Conceivably optogenetics, pharmacogenetics, or even flexible electrode technologies could be used to enhance the output or effectiveness of an upstream brain region such as the cerebellar cortex or nuclei.

In addition, until recently it was believed that once a sensitive period closes further modifications to the circuit become extremely difficult if not impossible. Recently, however, it was shown that critical periods can be reopened (Bavelier et al., 2010). It remains to be determined whether this is true for social capacities, which would be expected to have later sensitive periods.

In summary, we propose that the concept of developmental diaschisis may be of general utility in the understanding of pediatric neurology, in which it is commonplace knowledge that early-life damage to a brain region can have very different consequences than adult cases (Stiles et al., 2005; Swaiman, 2012). Bridging this gap requires new experimental tests to fill in a conceptual framework for how the cerebellum may guide other regions in the process of constructing the functions of the brain.

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FIGURE LEGENDS

Figure 1. Co-expression of ASD susceptibility genes in the cerebellum. Patterns of ASD gene co-expression show specific expression in cerebellum during early postnatal years (image adapted from (Menashe et al., 2013); see also (Willsey et al., 2013).

Figure 2. Risk ratios for ASD for a variety of genetic and environmental factors. Risk ratios are expressed relative to the US general-population risk. At 40X, cerebellar injury carries the largest single non-heritable risk. For explanation of other risks see text.

Figure 3. A developmental diaschisis model for neurodevelopmental disorders. (left) A diagram of activity-dependent influences on neural circuit refinement in primary sensory neocortex during sensitive periods of development, as articulated by Hubel and Wiesel. (right) A proposed generalization for the influence of cerebellar processing of multisensory information on neocortical areas essential for social and cognitive processing.

Figure 4. Upstream influences and downstream targets in autism spectrum disorder (ASD). Categorization of regions showing abnormalities in ASD brains according to whether they act early in development (upstream), are necessary for normal function in adult brains (downstream), or can be fully or partially compensated after an injury (compensatable).

Figure 5. The cerebellum and forebrain are bidirectionally linked in an orderly mapping. (a) The general structure of cerebello-thalamo-cortical loops. Each projection indicates a monosynaptic pathway. The pontine-cerebellar and deep nuclear-thalamic projections cross the midline to the contralateral side. (b) Regions are mapped precisely to form closed loops as demonstrated using classical and viral tracing methods in rodents and nonhuman primates. Adapted from (Strick et al., 2009). Regions of the cerebellar cortex are indicated in purple and corresponding regions of neocortex are indicated in green. An additional ascending pathway with cognitive/affective significance passes through the ventral tegmental area (VTA; yellow), and a descending pathway joins the substantia nigra (SN) with cerebellum hemispheric lobule VII and crus II. (c) In human brains, spontaneous waking (a.k.a. default-mode) activity measured using

functional magnetic resonance imaging reveals a parcellated relationship of covarying activity between corresponding zones of cerebellum and neocortex. The colored maps at left indicate 7 zones in which a single color denotes regions of neocortex and cerebellar cortex with strongly covarying activity. The plot at right indicates the fraction of neocortex in each zone of a 17-zone map, plotted against the fraction of cerebellar cortex in the corresponding zone. This plot indicates that representation in the neocortical and cerebellar cortical sheets is approximately proportional (Buckner et al., 2011).

Figure 6. Circuitry for instructed learning in the cerebellar cortex. Purkinje cells (black) receive the two major excitatory streams of input to the cerebellum: the mossy fibers (red), which synapse onto granule cells (green); and climbing fibers (blue). Mossy fibers and climbing fibers also send collaterals to the cerebellar deep nuclei. Cerebellar granule cells represent approximately half the neurons of the rodent or primate brain, and convey sensory, motor efference, and other information to the cerebellar cortex. They give rise to parallel fibers (green) which then converge massively onto Purkinje cells. Climbing fibers act as an instructive signal that can drive plasticity at recently active parallel fiber synapses. In this way, learning in the cerebellar cortex can integrate multiple sensory modalities with precise timing in the subsecond range. The sole output of the cerebellar cortex is Purkinje cell inhibition to the cerebellar deep nuclei, which in turn project to thalamus and many other brain regions.

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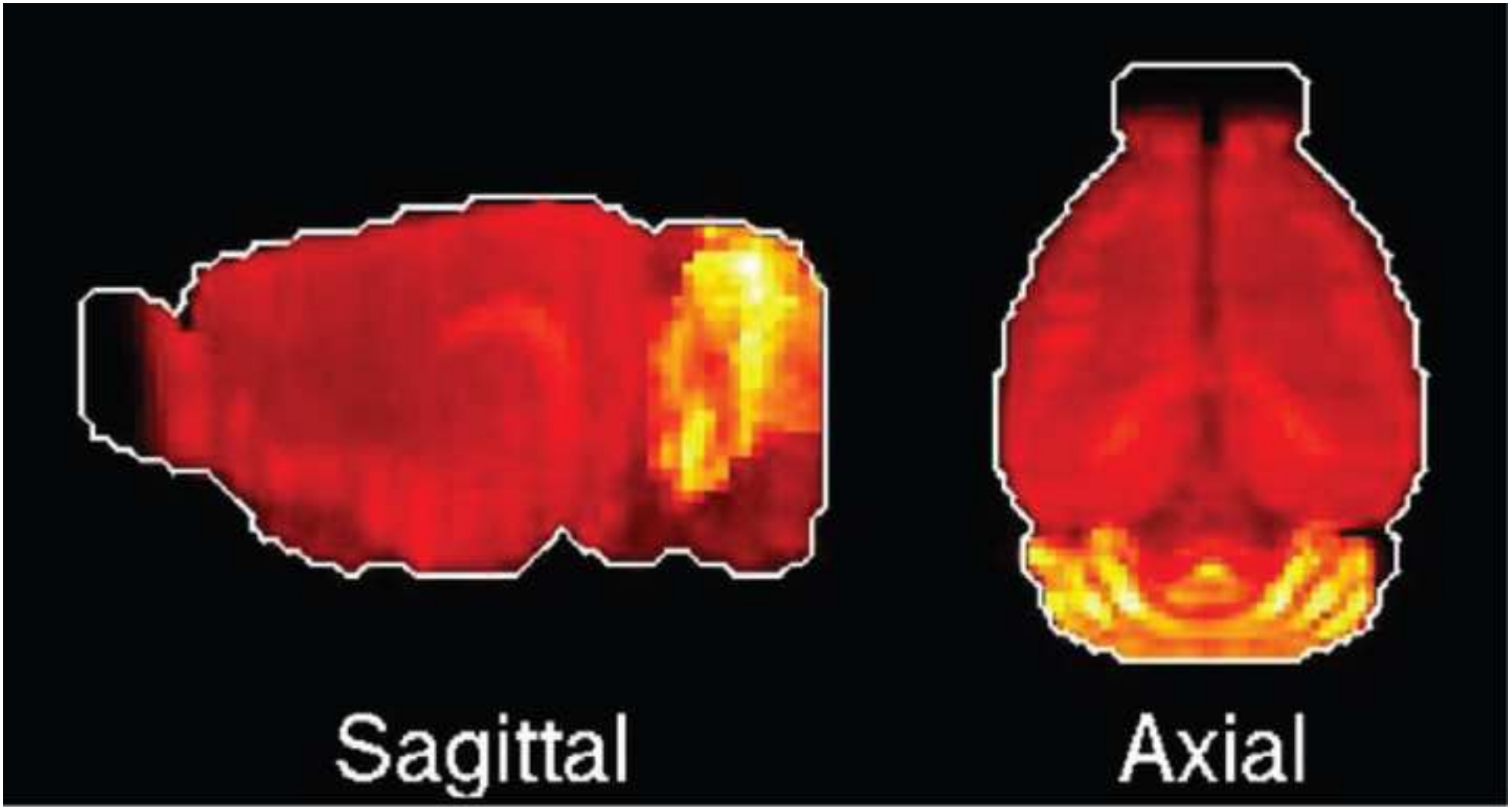

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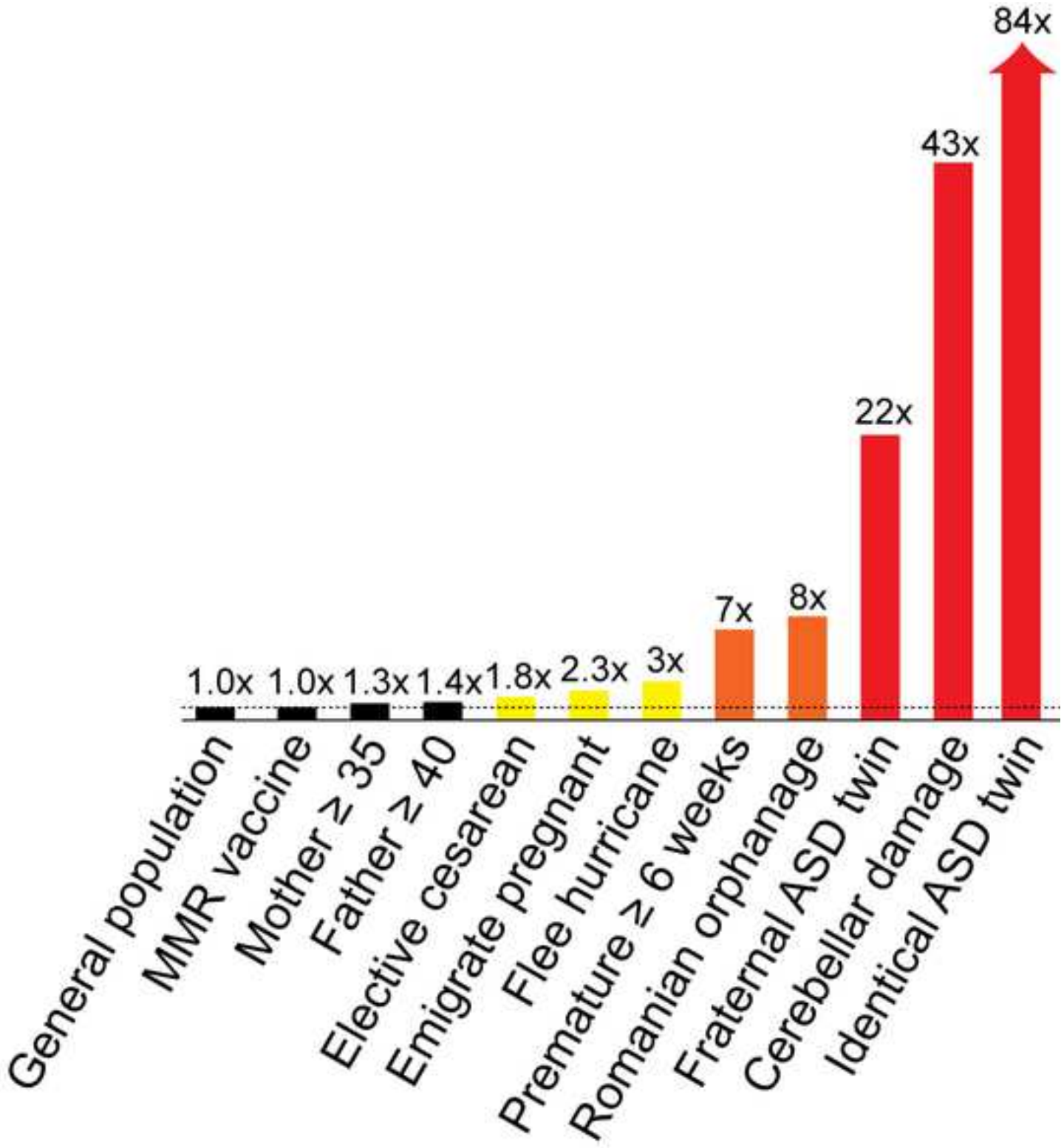

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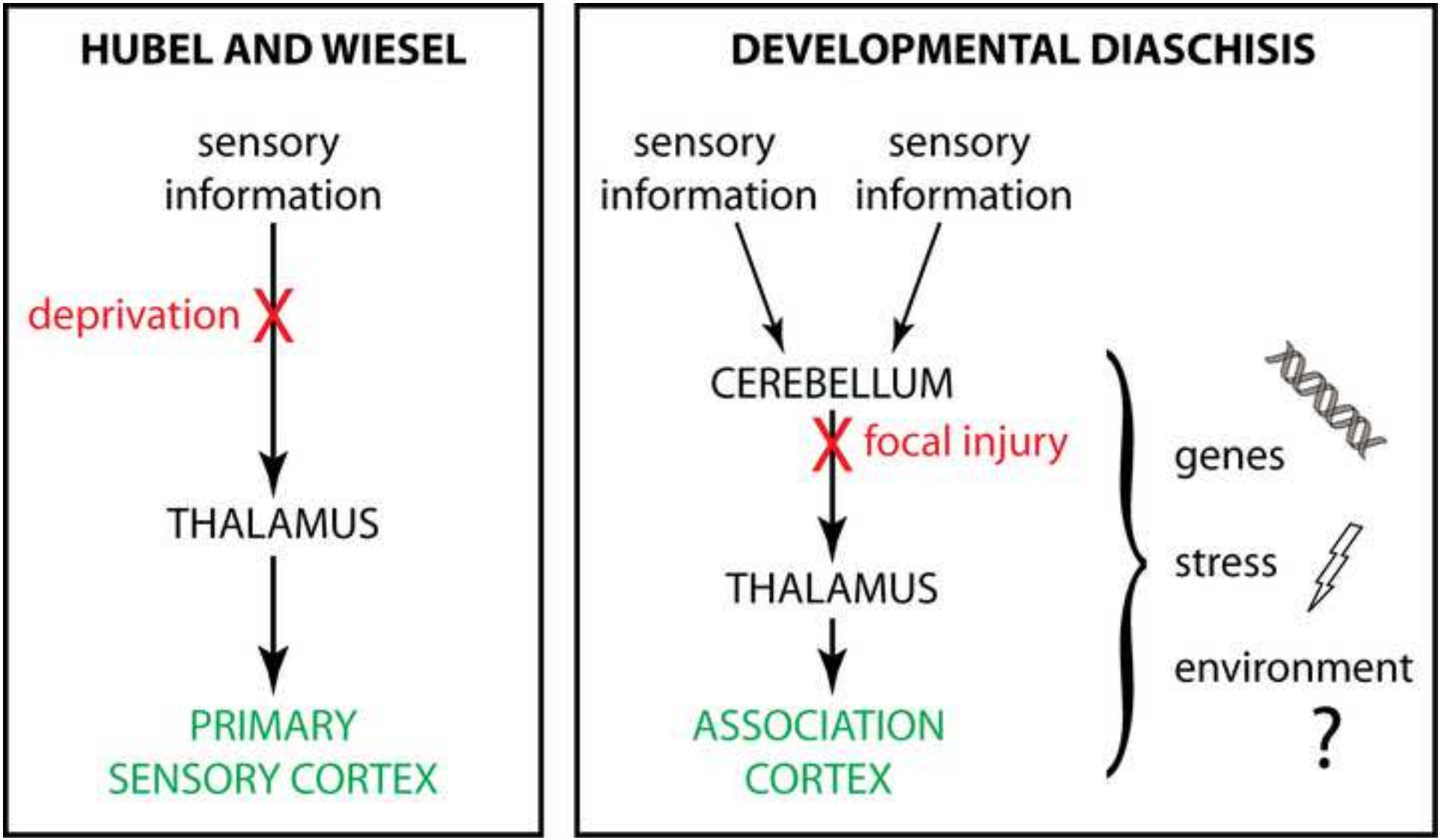

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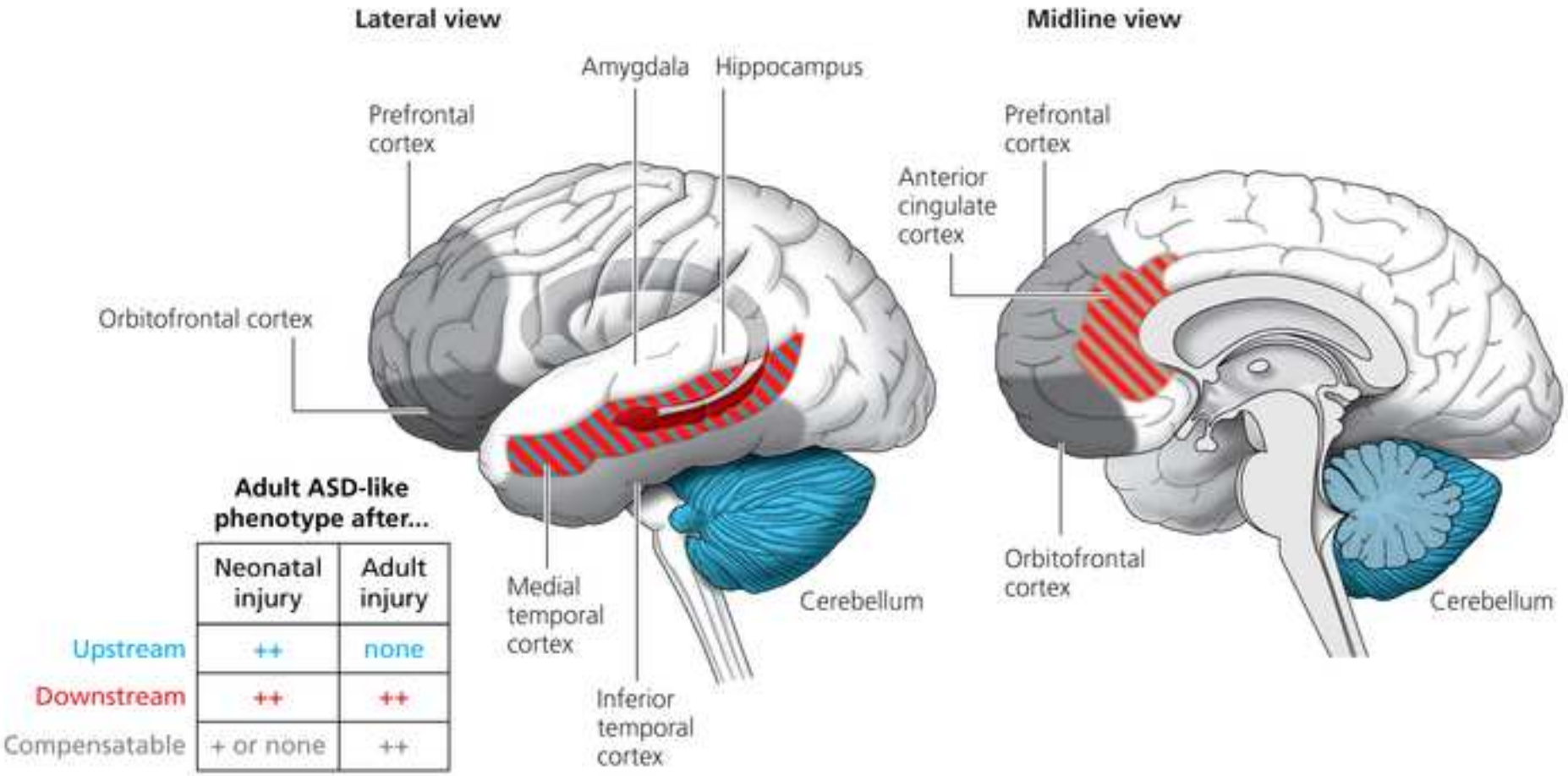

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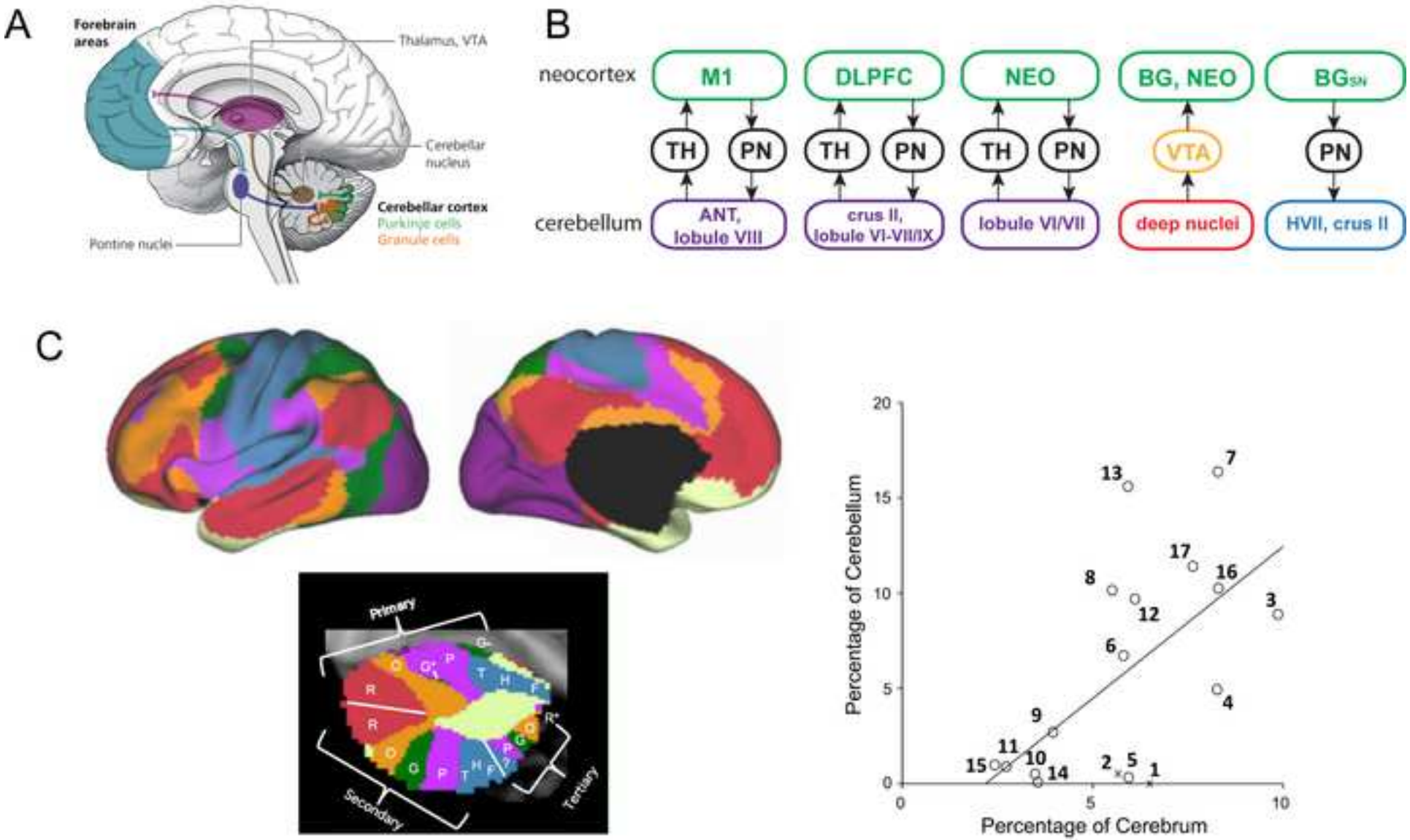

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