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Placing Neuroanatomical Models of Executive Function in a Developmental Context Imaging and Imaging–Genetic Strategies

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Abstract

Children show gradual and protracted improvement in an array of behaviors involved in the conscious control of thought and emotion. Behavioral research has shown that these abilities, collectively referred to as executive functions (EF), can be dissociated into separable processes, such as inhibition and working memory. Furthermore, noninvasive neuroimaging shows that these component processes often rely on separable neural circuits involving areas of the frontal cortex and nuclei of the basal ganglia. As additional noninvasive methodologies become available, it is increasingly possible to continue to dissect and dissociate components of EF and also test predictions made by a number of theoretical neuroanatomical models. One method of late is genetics, which is noninvasive and readily used in concert with neuroimaging. The biological data obtained with neuroimaging and genetics is particularly able to inform neuroanatomical models that link specific brain systems with higher more abstract process models derived from purely behavioral work. As much progress in this area continues to occur, we seek to evaluate the age dependency and manner in which certain aspects of EF and certain anatomical circuits show changes and interactions as children develop. Some examples are taken from research on children with the developmental disability attention deficit hyperactivity disorder. A review of selected developmental research shows that current cognitive and neuroanatomical models of EF offer a great many system- and synaptic-level hypotheses that can be tested using imaging and imaging genetics in longitudinal and cross-sectional study designs. Here, we focus on age-related changes in inhibition and working memory.

Keywords

imaging-genetic strategies; executive function; attention deficit hyperactivity disorder

Executive function (EF) or executive control refers to the higher order cognitive processes involved in the conscious control of behavior, thought, and emotion. Today there is a flurry of empirical activity surrounding executive control processes from a variety of perspectives, including developmental psychology and developmental psychopathology.[1] However, the neurobiological mechanisms underlying developmental changes in executive control are still largely unknown. Motives for the sudden increase in research into EF from a developmental perspective come from evidence that suggests impaired EF to play a key role in several childhood disorders. In particular, robust evidence suggests dysfunctional EF to be one important neuropsychological component involved in the multifactorial etiology of attention deficit hyperactivity disorder (ADHD).[2,3] Yet, developmental change in EF deficits, such as inhibitory control and working memory in children with ADHD, remains in question. As

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Nigg[2] so aptly puts it, "Nearly all research treats ADHD in a static fashion, rather than as an unfolding developmental pathway" (p. 25). In this review, we emphasize the importance of understanding the intrinsic link between cognitive and neural processes in typical and atypical development. We use EF deficits in ADHD as a primary illustrative example here because it is one of the most well-researched areas in developmental psychopathology[3] and arguably ready to be approached from a developmental interdisciplinary perspective. In the first section of this review, we give a short overview of the typical EF development, we then argue for viewing ADHD as a developmental rather than as a static disorder and present preliminary evidence indicating developmental change in executive dysfunction in relation to ADHD symptoms. The developmental findings presented here are in line with current theoretical developmental models of EF and dysfunction.[4] In the second part of this review, we then propose several tools that are appropriate to begin to link theoretical models of the developmental organization of EF to extant models of the basic neurobiological processes that underlie observed behavioral change in typical and atypical populations, such as ADHD. Finally, we cover a few examples of recent progress in neuroimaging and imaging genetics where these tools have been used to test neurobiological models of EF in children, albeit in a static fashion. We propose that neuroimaging and genetic research, when combined with age-appropriate cognitive assessments, may be a useful strategy to begin to relate cognitive development to corresponding neural and synaptic changes in the brain. To this end, we begin with a review of selective evidence that demonstrates the need for a dynamic age-sensitive research model in ADHD. Such a model is readily tested using the current neuroimaging and imaging–genetic methods.

Normal Development of EF

Although empirical evidence suggests that rudiments of EF emerge very early in life (e.g., delayed response performance in humans[5]), it is now clear that these cognitive control functions follow an exceptionally protracted course of development, with variations in maturational timing depending on specific executive component function. With regard to inhibitory control, many different types of inhibitory processes exist representing different levels of cognitive complexity (see Kipp[6] for an excellent review on different types of inhibitory control in children with ADHD), it has been repeatedly reported that, in typically developing children, many types of inhibitory control are fully matured around 10–12 years of age.[7–9] In contrast, executive attention as measured by the child Attention Network Task appear stable after age seven,[10] whereas performance on many traditional EF tasks involving more component functions, such as set shifting and planning (e.g., the Wisconsin card sorting test and the Tower of Hanoi) and working memory, continue to improve in adolescence and into early adulthood.[7,8,11–13] Behavioral evidence of this sort is often supported by findings showing protracted structural maturation of the frontal cortex. For example, myelination of the pre-frontal cortex starts postnatally and has been shown to continue into adulthood.[14] Further, dendritic and synaptic density in the frontal lobes appear to reach a peak in the first few years of life, with selective pruning of excess connections occurring throughout childhood and adolescence.[15] Development of these structural processes is thought to underlie many of the important functional improvements.[16] These long-standing observations of neural changes that occur during brain development can now begin to be related to changes in behavior and brain activity using noninvasive methods, such as structural magnetic resonance imaging (MRI), functional MRI (fMRI), and diffusion tensor imaging. Additional probes of neuromodulatory changes and synaptic processes are also being explored using selected candidate genetic markers in conjunction with imaging measures. By relating developmental changes in behavior with individual variation in brain structure and genetic markers for synaptic processes, a more detailed and mechanistic basis for cognitive development may emerge. As discussed in the latter part of this review, a number of current developmental and neuroanatomical models offer a framework for hypothesis-driven research in this area.

EF in Relation to ADHD—What Is Known and What Is Not?

Indeed, impaired executive functioning is now recognized as one of the primary components in the complex neuropsychology of ADHD.[2,3] Substantial evidence exists for structural, functional, and neurochemical brain differences in ADHD in regions that are considered key for EF.[17] An association between ADHD and deficits in prepotent motor inhibition constitutes the most robust findings.[18,19] Importantly, however, mean effect sizes for EF measures seem to be only moderate,[18] a result that has contributed to the notion that only a subset of children with ADHD have impaired executive control, whereas others may have dysfunction in other neuropsychological domains (see Refs. 20–22, for alternative neuropsychological models of ADHD). Although we agree with the notion that ADHD may have "etiological types" characterized by deficits in different neuropsychological domains,[2] at least one other potential explanation should be highlighted in relation to the seemingly moderate effect sizes with regard to executive deficits in ADHD. As mentioned earlier in this review, previous studies have treated ADHD as a static rather than as a developmental disorder. In other words, the likelihood that children with ADHD may show variations in executive deficits at different developmental stages has not yet been fully taken into account. Instead, conclusions with regard to the strength of executive dysfunction in relation to ADHD have been based on the mean age of groups of children often spanning a wide range of ages. Thus, it may well be that effect sizes for specific executive component functions have been decreased by large developmental variations in performance within the ADHD group under study. Kipp[6] puts emphasis on this critical issue when stating "it is important to compare performance across small age ranges, so that developmental differences are not missed by great variations in performance when performances of the younger and older children are combined" (p.1258).

Barkley's EF Model of ADHD

Perhaps the most influential and comprehensive account of the neuropsychological deficits underlying ADHD is Barkley's[4] developmental model on the hierarchical organization of EF. Barkley suggests that the primary neuropsychological deficit in ADHD is in inhibitory control (i.e., prepotent inhibition, interruption of an ongoing response, and interference control). This primary deficit in inhibition, in turn, impairs the four other EFs necessary for self-regulation of behavior, cognition, and emotions—that is working memory, internalization of speech/verbal working memory, and reconstitution. Barkley's model has been criticized as one of the theories attempting to explain a common core neuropsychological deficit that should be necessary and sufficient to cause all cases of ADHD, at least with regard to the combined subtype.[23,24] As mentioned earlier, this is most likely not the case as can be partly reflected in moderate-effect sizes for EF tasks and discrepancies in EF performance across studies. Nevertheless, Barkley's model, until proven otherwise, has explanatory power for understanding the neuropsychology underpinning the ADHD subgroup characterized by EF deficits. In addition, Barkley's theory also has important theoretical advantages relating to how ADHD should be conceptualized in terms of development (i.e., a static versus a developmental disorder) and whether ADHD is best viewed as a categorical or a dimensional disorder. These issues have important implications for future ADHD research and theory and therefore deserve further attention.

ADHD—A Developmental and Dimensional Disorder

Barkley[4,25] advocates a move away from current diagnostic criteria of ADHD (i.e., Diagnostic and Statistical Manual of Mental Disorders [DSM IV-TR-2000]) that characterize ADHD as a categorical and static disorder, with symptoms remaining essentially the same regardless of age. Instead, Barkley along with other researchers, such as Edmund Sonuga-Barke, propose ADHD as a dimensional and developmental disorder.[4,25,26] To be more specific, viewing

ADHD as a dimensional disorder means that clinical features of ADHD are taken to represent the extreme end of normal traits rather than as a distinct category. Further, viewing ADHD as a developmental disorder means understanding it as a delay in the rate which a normal trait is developing. Therefore, quantitative rather than qualitative deviations in EF should be predicted in children with ADHD compared to normal controls. Further, Barkley's model is, to our knowledge, the only one that allows for specific developmental predictions with regard to executive control in relation to ADHD.

EF as a Potential Developmental Pathway in ADHD

Most previous research on EF deficits in children with ADHD have focused on school-aged children and have not included longitudinal data. Studying neuropsychological deficits in children in the preschool age is important given the theoretical importance of this period in contemporary neuropsychological accounts of ADHD. For example, according to Barkley's[4] framework model, one would primarily predict inhibitory dysfunction to be associated with ADHD during the preschool years. Inhibitory deficits are therefore seen as the developmental precursor to more general and later developing EF problems. Further, the need for longitudinal studies has been pronounced along with the up and coming perspective of ADHD as possibly developing along distinct and multiple neuropsychological pathways, of which impairments in EF most likely is one. In order to determine such pathways, longitudinal studies tracking the unfolding of key domains, such as EF, reward response, or regulation of arousal/activation, using age-appropriate tasks are necessary. Better understanding of the roots of executive control has potential implications for early detection and intervention of this disorder. Further, the need for longitudinal studies has been emphasized so that pathways between potential risk factors and later manifestation of the disorder can be distinguished from transient behavioral disturbances.

Following the developmental perspective of ADHD, robust age-related changes in executive control in typically developing children should be taken to indicate that development is an important factor that should be emphasized in research on the neuropsychological manifestation of ADHD. However, age-dependent changes in the relation between neuropsychological deficits and ADHD behavioral symptoms have hitherto been largely ignored in extant ADHD research. Therefore, the very few studies showing preliminary evidence of developmental change in EF deficits in relation to ADHD symptoms should be brought to the fore. Brocki and Bohlin[27] investigated age-related effects in the relation between EFs and ADHD symptoms. The results from this study, based on a normal sample ranging in age from 6 to 13 years, suggest that poor inhibition is most clearly associated with ADHD symptoms (both hyperactivity and inattention) for younger children, whereas poor functioning with regard to later developing and more complex EFs, such as working memory, is associated with inattention symptoms for older children. In line with these findings are also recent data from several other cross-sectional and longitudinal studies showing contrasting results with regard to executive dysfunction in preschool versus school-aged children. For example, in a recent longitudinal study,[28] it was found that different types of inhibitory control were good independent predictors of ADHD symptoms in a preschool sample including children at risk for ADHD and/or oppositional defiant disorder (ODD). In contrast, no relations were obtained between working memory and symptoms of ADHD or ODD, neither concurrently nor longitudinally. Indeed, this result is in line with previous studies linking ADHD symptoms to poor inhibitory control in the preschool age.[26,29–31] However, the longitudinal study[28] also makes an important new contribution to the ADHD research field by providing 2-year longitudinal findings showing that distinct types of inhibitory control may represent separate developmental roots or pathways giving rise to later ADHD symptoms. This is particularly important in relation to the possibility of children with ADHD showing different patterns of competence and deficit in each inhibitory process depending on age, an issue that awaits

empirical testing and should be of interest in future studies examining ADHD from a developmental perspective. Further, in a recent clinical study,[32] marked impaired performance in working memory processes and mild impairment in prepotent motor inhibition in elementary school-aged children with a diagnosis of ADHD-C compared to normal controls were demonstrated. These results are partly inconsistent with the findings obtained in the longitudinal study[28] just cited, in that the extent to which ADHD symptoms could be accounted for by problems in inhibitory control and working memory varied between the two studies. To be more specific, a general weakness in working memory was observed in the ADHD-C group with particularly marked impairments on a verbal working memory task thought to put a heavy load on the central executive of the working memory system.[32] In contrast, the results from the longitudinal study[28] showed an important role for inhibitory control rather than working memory in explaining preschool ADHD symptoms. The discrepancy in findings between these studies may represent relative immaturity versus maturity in working memory and inhibitory processes in preschool children compared to school-aged children. Further, in a longitudinal study by Berlin *et al.*,[33] inhibition in the preschool age (5 years) not only predicted symptoms of hyper-activity and inattention in school age (8½ years) but also functioning in more complex EF, such as working memory. Together, these results indicate that inhibitory control deficits may be most pronounced in relation to ADHD symptoms in the preschool age and early elementary school age, whereas more complex cognitive functions, such as working memory, come into play in later elementary school age. Thus, these findings are in line with Barkley's[4] developmental prediction suggesting deficits in inhibitory control to be an early developmental precursor to, or which "sets the stage" for, more complex EF, such as working memory. The results from the Berlin *et al.* study[33] also indicate that changes in earlier phases of EF development may impact later stages. It should be mentioned, however, that some studies do report associations between impaired working memory and ADHD behavioral symptoms already in the preschool age.[31,34,35] Contrasting results for working memory and ADHD in preschool children are not easily explained, but may be due to variations in samples and types of measures used. For example, it is currently unclear both empirically and theoretically whether short-term memory measures actually do tax working memory processes in preschool children.[36] The preliminary findings just presented should motivate future research to examine developmental change in neuropsychological deficits not only in ADHD but also in other developmental disorders. A cohesive understanding of these developmental trajectories may, possibly, be resolved from research on basic mechanisms of working memory, inhibition, attention, and the common and unique neural networks that carry out these functions.

Anatomical and Mechanistic Framework Models of Catecholamine Regulation of Executive Function

To begin to further understand how a wide range of neuropsychological endophenotypes may interrelate at various developmental timepoints, we rely on existing—albeit rather static—neuroanatomical framework models. Using these models, we propose to draw out specific predictions that can be adequately tested using imaging and imaging–genetic tools. Neuroimaging and human genetics both have been used in this way to illuminate important issues of typical and atypical development during the last decade. For example, neuroimaging has revealed separate neural networks related to several aspects of human attention[37] and, further, has made it possible to work out the time course and connectivity of these networks.[38] Genetic research, when employed with behavioral data and/or imaging data, can document the correlation of individual differences in performance or brain function with specific chromosomal locations. Recent technological advances in genome sequencing and genome manipulation serve as potent drivers of experimentation aimed at linking gene function to brain development.[39] To begin to relate developmental changes in EF to corresponding changes in neural circuitry (via imaging) and synaptic processes (via imaging genetics), we review

selected neuroanatomical models of attention and EF that will serve as our framework for hypothesis construction and future testing.

Imaging findings in adults support the presence of three networks related to different aspects of attention. These networks carry out the functions of alerting, orienting, and executive control.[40–42] Alerting is defined as achieving and maintaining a state of high sensitivity to incoming stimuli; orienting is the selection of information from sensory input; and executive control is defined as involving the mechanisms for resolving conflict among thoughts, feelings, and responses. The alerting system has been associated with frontal, parietal, and thalamic regions and can be assayed by the use of warning signals prior to targets in an fMRI setting.[37] The influence of warning signals on the level of alertness is thought to be from the modulation of neural activity by the norepinephrine system.[42] Orienting can be manipulated by presenting a cue indicating where in space a person should attend, thereby directing attention to the cued location.[43] Event-related fMRI studies have suggested that the superior parietal lobe is associated with orienting following the presentation of a cue.[37,44] The superior parietal lobe in humans is closely related to the lateral intraparietal area in monkeys, which is known to produce eye movements.[45] When a target occurs at an uncued location and attention has to be disengaged and moved to a new location, there is activity in the temporal parietal junction.[44] Lesions of the parietal lobe and superior temporal lobe have been consistently related to difficulties in orienting.[46]

More specifically, in the area of executive control of attention, tasks that involve such processes as working memory, stimulus-response conflict, and inhibitory control are often employed as a means of dissecting the functional contributions of different areas that underlie executive control. Casey[47] and reviews[48–50] showed that the use of multiple experimental tasks and parametric manipulations within tasks provide a method for specifically relating changes in brain function to component processes of EF. In several cases, the structural and functional imaging data gathered across tasks has been interpreted with reference to specific circuits that are activated in these EF tasks. Neuroanatomical models centered on the role of so-called basal ganglia thalamocortical loops involving the dorsolateral frontal cortex, anterior cingulate gyrus, striatum, and basal ganglia have been a particularly successful framework for modeling and testing neuroimaging results on EF in developing populations.[50–53] Disruptions in these reciprocally connected basal ganglia thalamocortical circuits can alter behaviors ranging from simple motor responses to cognitive and emotional processes,[54] and, furthermore, the basal ganglia thalamocortical loops are heavily innervated and regulated by dopamine and noradrenaline. As described below, selected hypotheses concerning the role of dopamine and noradrenaline on the function of these circuits has been extensively probed using positron emission tomography (PET) and, more recently, using behavioral and imaging genetics.

One of the central features of the basic basal ganglia thalamocortical circuit model it that specialized anatomic structures and functional properties of cells and synaptic connections within these loops are invoked to dissociate cognitive processes associated with different aspects of EF. For example, in working memory tasks, properties of the prefrontal cortex are often ascribed the function of actively maintaining rules and task-relevant experience in a dopamine-dependent fashion.[55] Primate research shows that during working memory tasks representations in the prefrontal cortex are supported by extended firing of cortical cells that are stabilized by frontal dopamine levels.[56] In the basal ganglia thalamocortical network model, frontal striatal connections mediated by dopaminergic input and unique structural properties of striosomes, along with direct and indirect GABA-ergic neural pathways in the basal ganglia, serve to probabilistically filter, integrate, and select actions.[57] Primate research reveals that the direct and indirect pathways are independently regulated by dopamine where dopamine increases the probability of positive Go responses in a D1 receptor-dependent fashion, and dopamine dips favor Nogo responses that are mediated through D2 receptors.

[58,59] D1 and D2 pharmacological agonists/antagonists that differentially modulate activity and gene expression in separate Go and NoGo striatal populations support the filtering and counterbalancing function of the direct and indirect pathways in action selection and inhibitory control processes.[60] In adult human populations, for example, dopamine medications modulate Go and NoGo responses in opposite directions.[60] Thus, the basal ganglia thalamocortical circuit models provide a rich framework to begin to dissociate working memory processes from inhibitory control processes. This framework model—although developmentally static—provides a footing to begin to explore the developmental trajectories in working memory and inhibitory control as described above.

In cases of development change in EF in developmental disorders, such as ADHD described above, the core basal ganglia thalamocortical loop model is also particularly useful in framing a great many pharmacological, imaging, and genetic results. For example, inefficiencies in inhibitory control have been linked by many to diminished dopaminergic tone in the striatum.[61–63] Much genetic evidence supports the dopamine transporter gene (DAT1) as a risk factor for ADHD, and patient populations often show higher than normal densities of striatal dopamine transporters.[64,65] The upregulation of extracellular striatal dopamine[66] and not frontal dopamine by methylphenidate[67,68] further supports that notion that subcortical portions of the basal ganglia corticothalamic circuits develop inefficiently in ADHD. In addition, ADHD subjects often show more within-subject variability in overall reaction times of cognitive tasks.[69,70] The noradrenergic innervation of frontal striatal loops has been used as a framework to account for this aspect of the ADHD phenomenon since reciprocal connections between locus coeruleus and anterior cingulate cortex may account for the link between alerting and phasic release of noradrenergic and response variability.[71] For example, deficits in response inhibition can be ameliorated by noradrenergic transporter blockers,[72–74] and primate studies using sustained-attention tasks have shown that tonically released cortical noradrenergic can affect response variability[71] wherein phasic noradrenergic release leads to more exact reaction times and less response variability.[75] In general then, catecholaminergic hypotheses concerning the etiology of ADHD can also be examined within the context of our general basal ganglia thalamocortical circuit models. It should be noted, however, that there are likely to be many other brain systems involved in the developmental deficits seen in ADHD, such as circuits that carry out verbal and visual–spatial processes. We focus on a particular mechanistic neuroanatomical model insofar as specific, well-substantiated, and testable hypotheses can be drawn. We acknowledge that our model covers only one of many possible systems implicated in developmental impairments of ADHD.

Neuroimaging and Imaging–Genetic Tools for Testing Neuroanatomical Framework Models in Developing Populations

In conjunction with a current neuroanatomical model, there are several technological tools that are suitable for hypothesis testing in developing human populations. Noninvasive imaging and genetic methods are ideal for the study of development in children both in cross-sectional and, more advantageously, in longitudinal study designs. Such imaging and imaging–genetic research is well situated to begin to relate developmental changes in behavioral performance to corresponding changes in brain structure and function as well as specific genetic differences. A general review of the literature shows that comparisons of brain structure and function in healthy and ADHD populations show a great many differences in basal ganglia thalamocortical circuits and, furthermore, that age-dependent improvement in inhibitory control from ages 4 to 12 can be related to changes in specific regions of these circuits.[76–79] Although an in-depth treatment of the imaging literature on development of EF in typical children and in children with ADHD is beyond the scope of this review, there are several exemplars of how specific links have been made between changes in behavioral performance and specific components of the developing basal ganglia thalamocortical circuits.

Initial developmental neuroimaging findings found that whole brain volumes lag by up to 5% in children with ADHD and, more specifically, in structures of basal ganglia thalamocortical loops.[80] Reduction in prefrontal and caudate volumes[81,82] as well as reductions in Globus pallidus have been observed.[83] These neuroimaging results can be used to support a developmental-delay etiology of ADHD whereby widely distributed brain systems are slower in gaining the necessary coordination and coherent communication. Along these lines, brain activity in children with ADHD during the performance of cognitive operations can be more diffuse than in normal children.[53,84] Such diffuse patterns of brain activity have been noted in young children and found to become more focal with development.[85] Children with ADHD can have higher frontal activation and lower striatal activation than control children during response inhibition,[86] as well as reduced activation of frontal areas in adolescents with ADHD.[87] Abnormal networks of regions involving insular, inferior frontal, and striatal regions are also reported.[88] The hypoperfusion of frontal and striatal areas again supports a working framework model that implicates abnormal or delayed development wherein dorsal and ventral aspects of basal ganglia thalamocortical loops are differentially affected.[89]

In addition to standard neuroimaging strategies, it has recently become possible to integrate genetic methods into current studies. The current imaging genetics methods can be used to link individual differences in genotype to changes in brain structure or function. When candidate genes are those known to confer risk of ADHD or other developmental disabilities, it is of interest to ask what types of structures and synaptic connections might be related to genetic risk. For example, in the case of the DAT1 and the dopamine receptor type 4 gene (DRD4), two known risk factors for ADHD, these genes influence the structure and activity of the caudate and frontal cortex in familial and mixed populations, respectively.[90] Family and twin research shows that variation in frontal regions and EF tasks are influenced by heritable factors.[91–93] In the case of ADHD, twin and familial genetic studies show that the disorder tends to cluster in families, with an increased incidence among first- and second-degree relatives of affected individuals and siblings of children with ADHD.[64]

Initial candidate gene investigations were based on two theories of ADHD: (i) the dopamine deficit theory of ADHD[94,95] and (ii) a neuroanatomical network theory of attention,[96] which suggests how dopamine is involved in the component process of executive attention. The candidate gene studies of ADHD have focused on two dopamine genes whose locations were known: the DAT gene on chromosome 5 and the DRD4 gene on chromosome 11. Early studies conducted by Castellanos and colleagues examined brain volumetric measures in two groups of ADHD children, with and without the DRD4 7-repeat VNTR allele.[97] More recently, a longitudinal study of the DRD4 found that the 7-repeat allele of the DRD4 gene was associated with cortical thinning in regions important in attentional control. This regional thinning was most apparent in childhood but this association diminished during development.[79] Such imaging–genetic research provides a synthetic approach capable of tying together basic synaptic processes with more global changes in neural structure and activity.

Concluding Remarks

The availability of noninvasive neuroimaging and imaging–genetic measurement tools are useful tools when used in conjunction with neuroanatomical models of cognition that seek to dissect and dissociate component processes that underlie behavior. The current models are understandably somewhat static with respect to age-dependent changes but nevertheless provide a rich source of testable predictions suitable for populations of different ages. We propose that future developmental models will grow by hypothesis at multiple levels of analysis in longitudinal and cross-sectional populations. In this way, the complex internal structure of childhood disorders can be better understood, resulting in more effective age-related treatments

and eventually modification in current diagnostic procedures so that diagnostic thresholds can be adjusted to the child's age.

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