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PROGRESS IN BRAIN RESEARCH

Gene Expression to Neurobiology and Behavior

Human Brain Development and Developmental Disorders

EDITED BY

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Preface

The developing brain: From developmental biology to behavioral disorders and their remediation

Background

The human brain presents the greatest challenge to developmental biology. Its 10^{11} neurons are organized at different scales into large-scale structures, highly specialized nuclei and cortical areas, columns and layers, and microcircuits whose delicate dynamics determine the difference between complex cognitive functions and catastrophic oscillation. Each of these neurons establishes as many as 1000 synaptic connections, some with neighboring neurons but some across the brain over a range of many centimeters. The correct development of this system is required to determine not just a very complex structure but, more importantly, rich, well-integrated, and adaptive behavioral functions. These are as diverse as manipulating the spatial layout of the environment, generating precisely timed sequences of speech, and predicting and managing social interactions.

The development of these systems must depend on the large fraction of the human genome that is expressed in the brain. However, the specification that is required to organize and connect them correctly seems to go way beyond the informational capacity of the genes. The epigenetic processes guided by the external and internal environment must therefore be critical in allowing the developing brain to function. These are central and intrinsically interdisciplinary problems of human development, which can only be understood by a concerted effort of neurobiologists, geneticists, cognitive neuroscientists, neuropsychologists, and pediatric neurologists, with insights from computational modeling of complex, self-organizing systems.

These are not simply questions of profound scientific importance. The complexity of the structures and systems involved means that they are vulnerable to errors in development, caused either by genetic anomalies or by the impact of external conditions such as prenatal anoxia or postnatal stress. The unfolding system of development is dynamic throughout life so that the endpoint in terms of behavior is the result of many interactions along the way. Developmental disorders, such as cerebral palsy, Williams syndrome, Down's syndrome (DS), or Fragile-X syndrome (FXS), autism, or specific language impairment (SLI), prevent a large number of people from participating fully in the demanding economic, social, and personal life of modern communities. They have a heavy lifelong practical, emotional, and economic impact on individuals and their families, not to mention the burden they place on health-care, educational, and social welfare systems.

Key information on the constraints on brain development will come from these conditions that lead to anomalies of brain and cognitive development. In turn, insights on broader questions of brain development will be needed to achieve progress in the identification, treatment, and remediation of these disorders.

This challenge is fundamentally interdisciplinary. Advances in molecular genetics have made it possible to work with animal models of normal and anomalous brain development at every level from gene

expression through brain anatomy to behavior. Neurobiologists have exploited these tools to advance classic questions of the determinants and plasticity of developing brain structure. However, these models will only provide insights into human development if we can adequately characterize human developmental phenotypes at anatomical, functional, and behavioral/cognitive levels throughout development and over time from birth to adulthood. Cognitive and developmental psychologists have applied increasingly sophisticated approaches to these problems. The past decade has seen great advances in integrating behavioral and cognitive analyses with new neuroimaging techniques (such as magnetic resonance imaging (MRI), high-density electroencephalography (EEG), magnetoencephalography (MEG)) that make possible noninvasive measurements of the human brain in unprecedented detail, and these methods are starting to be applied to developing children. We are also at the beginning of using these methods of developmental cognitive neuroscience to define phenotypes at various levels, which can be linked to genetic variation.

Neurobiologists and geneticists working in these areas will need to understand theories, methods, and insights in human cognitive development. Conversely, cognitive and developmental psychologists and neuroscientists will need to appreciate the possibilities, limitations, and issues of interpretation in the new biological technologies. But ultimately, the opportunities to exploit scientific advances in understanding developmental disorders can only be realized through intellectual and practical interchange with the medical specialists in neuropsychiatry and pediatric neurology who are responsible for the care of the children and families concerned.

The European Research Conference

With the opportunities and challenges of this multifaceted problem in mind, we convened a research conference under the auspices of the European Science Foundation in Sant Feliu de Guixols, Catalonia, Spain, in September 2009. Leading scientists were invited to present state-of-the-art work and reviews from across this range of relevant disciplines. The aim was to allow the cross-disciplinary links to develop both among the invited speakers and in the minds of the younger scientists who participated in the audience and presented posters of their current research. In this emerging linkage, the typical course of development should be used to help characterize and understand neurodevelopmental disorders, and conversely, disorders should throw light on how the process of typical development operates. We hope that the present volume will bring this perspective to a wider audience.

We are particularly grateful that some authors, who did not participate in the original meeting, were nonetheless willing to make contributions to this volume and thereby enhance its scope and comprehensiveness. Among these, Antonello Mallamaci has provided a strong background in the detailed cellular and molecular events that guide the development of the large-scale structure of the brain. Rhonda Booth, Gregory Wallace, and Francesca Happé fill an important niche in considering the relationship between the symptomatology of autism spectrum disorder (ASD) and anomalies of cerebral connectivity in this condition.

Introductory chapters

We open this volume with some chapters that explain the broad theoretical issues linking the elements of our title—gene expression, neurobiology, and behavior. Joan Stiles gives us a brief overview of the

neurobiology of brain development, introducing concepts and processes which are developed in more detail in some of the later chapters such as those by Mallamaci and Giorgio Innocenti. She reviews ways in which this developmental process is modulated and can be redirected by the pattern of sensory input to the brain. The chapter emphasizes the importance of understanding brain development as a process over time, in which the effect of influences (genetic or environmental) at time T_3 depends on what has been laid down in the sequence of events from time T_1 to time T_2. This sequential process of interaction supersedes the naïve dichotomy between "nature" and "nurture," which dominated much psychological debate in the past 100 years.

Tessa Dekker and Annette Karmiloff-Smith develop this approach in the context of the widespread "modular" view of brain and cognition. They critique the idea that specialized modules in the brain are the starting point of cognitive development and argue for a "neuroconstructivist" approach in which initial functional biases are the starting point for an increasingly domain-specific specialization of brain structures in the course of development. On this basis, they critically examine some of the assumptions that may lead to developmental disorders being considered as the impairment of specific modules and the potential analytical pitfalls in comparing patterns of activity in the brain at different stages of development. The ideas of the related "interactive specialization" approach are relevant to a number of the chapters in this volume (e.g., those by Peter Klaver, Valentine Marcar, and Ernst Martin; Oliver Braddick, Janette Atkinson, and John Wattam-Bell; Gaia Scerif and Ann Steele; and Francesca Simion, Elisa Di Giorgio, Irene Leo, and Lara Bardi).

As we focus on the more specific content of subsequent chapters, it is important to see these as a matrix of several intersecting factors: our authors use particular methodologies, they are concerned with particular developmental disorders, and they focus on particular aspects of cognitive ability and disability.

Techniques

The chapters in this volume illustrate much of the wide-ranging armory of techniques which has become available to neuroscience in recent decades and which is being increasingly applied to development. A number of chapters benefit from the powerful tools of molecular genetics; in particular, their application in animal models of anatomical development is at the core of the work described by Antonello Mallamaci. The chapters by Terry Jernigan, William Baaré, Joan Stiles and Kathrine Skak Madsen, and Kate Watkins illustrate the potential scope for relating individuals' genetic characterization to variations in their brain structure, and those by Watkins and by Mayada Elsabbagh, Karla Holmboe, Teodora Gliga, Evelyne Mercure, Kristelle Hudry, Tony Charman, Simon Baron-Cohen, Patrick Bolton, Mark Johnson, and the BASIS Team in relating genetic to cognitive or behavioral variations. It should be noted that genetically based disorders, and polymorphisms found in the typically developing population, have both proved informative in analyzing these gene–brain-behavior relationships.

The range of techniques for probing the brain using MRI is well represented here, making clear that these are increasingly available for use with developing children, although their application to infants is still challenging. The classical use of MRI to visualize brain structure has been applied to neonates, allowing perinatal brain injury to be related to functional measures (see examples in chapters by Braddick et al. and Giovanni Cioni, Giulia D'Acunto, and Andrea Guzzetta). Structural studies of development have become increasingly quantitative, with the use of voxel-based morphometry to characterize the distribution of white and gray matter in the brain (see the chapters by Jernigan et al. and Watkins),

measurements of cortical thickness in the course of development (Jernigan et al. and Klaver et al.), and diffusion tensor imaging (DTI) to assess the organization of white matter tracts and to track these to discover the interconnections of cortical areas (chapters by Klaver et al., Jernigan et al., and Watkins).

Much of the excitement in adult MRI studies has come from functional MRI (fMRI) studies using the BOLD (blood oxygen level-dependent) response to reveal patterns of local brain activation in individuals when they carry out cognitive operations. This approach is reviewed here with examples in the chapter by Klaver et al. and alluded to in many other chapters; published experiments on face processing, visuomotor function, and language processing show that the problems of fMRI with young children are gradually yielding to patient and persistent experimenters. We may hope that technical advances in MRI scanning and analysis will make this powerful method more accessible as a developmental tool in the years ahead. One specific application of fMRI is to use patterns of temporal correlation in activity to infer patterns of connectivity, particularly the "resting state" or "default mode" of brain activity in the absence of a specific task. Such inferences of connectivity in development appear in the chapters by Booth et al. and by Klaver et al.

A more practical route to probe brain activity in the youngest children is to record event-related potentials (ERPs) from sensors on the scalp. This method has yielded much of our information about brain function in the first years of life, as exemplified here by the chapters by Braddick et al., Cioni et al., and Elsabbagh et al. With the use of high-density sensor arrays, it can provide a form of functional brain imaging, carrying a wealth of information about the time course of processing.

The use of new technologies to study the development of cognitive brain function should not be allowed to overshadow the fact that such work and behavioral studies depend totally on the creative and careful application of cognitive task design to ask specific questions about children's capabilities, in a well-controlled, age-appropriate way, and the rigorous application of methods of data analysis. Cognitive and developmental psychologists have been refining these approaches for many years: examples of such creative experimentation and analysis appear in almost every chapter in this volume.

Brain development

The admirable work of anatomists at the end of the nineteenth century, particularly Brodmann (published in 1909) and Campbell (in 1905) demonstrated differences in the cytoarchitecture and myeloarchitecture of cerebral cortical sectors, leading to the identification of cortical areas. Subsequent work, continuing to this date, has established strong correlations between structural and functional properties of cortical areas using a variety of techniques in animal models and in humans. The question tormenting the curious biologist was "what causes the formation of cortical areas in development?" Mallamaci's chapter provides a summary of a recent debate on this issue. More important, it discloses the up-to-date landscape of the fantastically complex (and we are only at the beginning) network of causal-molecular/genetic interactions which lead to the emergence of what can be considered the basis of cortical organization.

Mallamaci presents basic research from animal models, in which genetic manipulations have allowed researchers to unpick the molecular mechanisms guiding these developmental pathways. However, it does not require much imagination to see the longer-term possibilities for understanding human developmental disorders in which genetic anomalies (whether point mutations, deletions, number of repeats, or other rearrangements of the genome) may divert or distort these pathways, leading to a change in the balance or organization of cortical development.

"Environment" in the examples expounded by Mallamaci consists primarily of the internal environment of the developing brain—where the topography of proteins laid out at one stage of the process triggers and modulates the expression of genes defining cortical specialization at a later stage, and patterns of afferent activity guide the differentiation of cortical structure. However, this internal environment is coupled to the pre- and postnatal *external* environment of the developing organism. Such coupling occurs (a) because the chemical environment is determined by events such as anoxia, (b) because internal hormonal effects are coupled to external stressors and to emotionally significant stimuli such as parental grooming, and (c) connectivity is organized by the structure of sensory inputs which in turn is partly determined by feedback loops from the activity of the developing individual. Thus, accounts such as Mallamaci's will in due course become integrated into an account of the recurrent linkages between the molecular architectures produced by gene expression; the pattern of cerebral connectivity; the external chemical, sensory, and social environment; and the internal chemical environment which bathes the nervous system. To quote Joan Stiles' chapter, "the boundaries between what is internal to the organism and what is external are fluid."

The development of long-range connections in the brain has most often been discussed, as in the chapters by Stiles and Mallamaci, in terms of their finding appropriate targets. However, the properties of the connecting axons are also important, especially since they determine the time pattern in which neural information arrives at its destination, a pattern which is critical for some processes such as motion perception (see the chapter by Braddick et al.) and is also important for development, given the role of coincident timing in mechanisms such as the Hebb synapse. The chapter by Giorgio Innocenti focuses on the differentiation of axon types, particularly in their thickness which determines the speed of long-range neural information transmission. Innocenti's chapter is distinctive in taking an evolutionary perspective, using the distribution of axon diameters in different cortical areas and in different primates, macaque, chimpanzee, and human. It points out that the environment exerts selective pressure both in development and in evolution. The fact that both processes seem to act to increase the diversity of axon diameters (and hence the variance of transmission times) raises the question of how and why such variance is adaptive, a challenge for the modeling of cortical circuits but a feature which Innocenti suggests may expand the dynamic range of oscillatory neural interactions and improve the stability of brain activity. Conversely, disruption of this diversity in developmental disorders might conceivably lead to decreased stability, with knock-on effects on functional development.

Jernigan et al. turn to direct neuroimaging evidence of how the human brain changes during childhood. It is now clear that this is a protracted process, lasting through adolescence into young adulthood. It is reflected, counterintuitively, in the progressive thinning of the cortex, which may reflect the increasing myelination and organization of white matter fiber tracts revealed by DTI. The studies reviewed by Jernigan et al. have now gone beyond overall description of population trends in anatomical development, to show the association of local white and gray matter changes with individual measures of intelligence and memory, with task-specific training in reading and sensory-motor skills, and with the independent actions of specific genetic variants. Hormonal levels around puberty also have an important impact in specific structural measures. Overall, this kind of work promises to reveal the neurobiological pathways through which specific genes underlie psychometric variability and the ways in which environmental stimulation intervenes to modulate these pathways.

Specific, distinct pathways from genes through brain systems to behavioral variation are presented in the chapter by Adele Diamond. She explains how the specific neurochemistry of prefrontal cortex determines how that brain area responds to genetic polymorphisms and mutations that impact on the dopamine (DA) system. In turn, these variations affect the development of executive function, critical in the "inattentive"

form of attention-deficit disorder. A different genetic–neurochemical pathway, through the DA system in the striatum, is responsible for the "hyperactive" form. Thus neurobiology can help us to understand how developmental disorders should be properly categorized and, critically, guide therapy.

Environmental impact and plasticity

The chapters by Cioni et al. and by Jörg Bock, Gerd Poeggel, and Katharina Braun provide evidence on how external stimulation can affect the direction of brain development in the neonatal period. Cioni et al. first discuss the plasticity shown in the infant brain in functional recovery from perinatal brain injury, in particular, the transfer of language and sensory-motor functions between hemispheres. Interhemispheric and intrahemispheric transfer of function appear to show different potential in different systems—while the sources of this difference are not fully understood, they have strong implications for choosing the most effective early therapeutic interventions and their timing. More global interventions may also be important as neuroprotective strategies in the developing brain. Animal models have shown that enriching impoverished environments through social housing and providing opportunities for physical manipulation and exploration enhances brain growth and connectivity and that intensive maternal care of rat pups elicits neurotrophic factors that enhance cortical development and reduce cell death. These models have promoted the use of massage for at-risk preterm babies in neonatal intensive care units, which has been shown to have analogous effects on neurochemistry and on the development of the EEG.

The purpose of research on developmental disorders and their basis in the brain must be to enable children to reverse or minimize the impact of these disorders on their lives. The approaches discussed by Cioni et al. and Bock et al. help toward this end by interventions in early infancy. However, functions of behavioral and cognitive self-regulation are key for effective social living and achieving life goals. These key functions develop at a later stage and are exemplified in tasks when children work together on tasks which require sustained focus and planning to achieve a goal. Cognitive, affective, and social aspects of behavior are integrated in such tasks. The chapter by Diamond describes a new approach of providing kindergarten children, working and playing together, with "tools for the mind," aiming to give them the means to overcome attentional disorders and become fulfilled members of a purposeful society.

The work reported by Bock et al. illustrates the converse effect, that separation of neonatal animals from parental care and litter mates acts as a stressor which downregulates brain activity in many areas, and if repeated leads to chronic metabolic hypofunction of the brain and atypical behavioral patterns. Both stress and environmental enhancement effects show that external stimulation can radically modify the way in which genetic programs are expressed in brain development. These effects imply that there are profound therapeutic possibilities of stimulation for infants whose neural and behavioral development is at risk through the challenges of premature birth and hypoxia, or through the stressors of neglect and deprivation. The work of Bock et al. also indicates that pharmacological interventions may be able to correct the downregulation and ameliorate its behavioral consequences.

Disorders

Research attention has focused on particular developmental disorders in part because of their impact on the lives and families of those affected, and partly for their scientific potential in revealing processes of development.

WS has attracted much attention; it results from a well-defined and intensively explored genetic deletion and has a highly uneven and characteristic profile of cognitive impairment, notably in the visuospatial domain. This has raised the hope that WS will be revealing about how features of the genotype are translated into specific aspects of cognitive processing. The chapter by Janette Atkinson and Oliver Braddick discusses the pattern of WS performance in terms of the brain mechanisms for vision, action, and attention, considering the hypothesis that the dorsal stream of visuospatial processing is especially vulnerable. This vulnerability, it turns out, is revealed in many different developmental disorders. Accounts of the genetic effects in WS must therefore recognize that while the overall profile of this disorder is unique, it reflects effects on pathways of brain development that are involved in a much wider range of disorders. Processes of attention are closely associated with the dorsal stream and also with frontal executive function. Atkinson and Braddick introduce a new testing battery designed to partition attentional subsystems in children of a young mental age, which reveals that WS and DS have their own characteristic profiles of attentional strengths and weaknesses, over and above the effects of their overall cognitive delay.

FXS is another disorder with a well-specified genetic origin (excessive repeats of a specific three-nucleotide sequence, causing failure to express the FMR1 protein) and a characteristic cognitive/behavioral profile. The chapter by Gaia Scerif and Ann Steele uses the component structure of attention (in a similar approach to Atkinson and Braddick) to compare the developmental trajectories in FX, WS, and DS. They find not only that these conditions differ in their pattern of abilities but also how these patterns change in development. These attentional skills clearly have an impact on the developmental course of other abilities requiring learning and memory; but the syndromes also diverge in how far deficits seen in childhood have their adult counterparts, suggesting that the availability or otherwise of compensatory strategies may be a key characteristic of anomalous developmental trajectories.

Autism, and the broader category of *autistic spectrum disorder*, is one of the most intensively investigated disorders, because of its relatively high incidence, the severity of its impact in some cases, and again its specific profile which may in some cases allow high intellectual capacities to coexist with crippling failures of normal social interaction. The chapter by Rhonda Booth, Gregory Wallace, and Francesca Happé provides an overview of ASD, considering whether the classic diagnostic triad (social withdrawal, communicative impairment, and rigid/repetitive behavior) is in fact unitary. They present evidence that while there are associations between these elements, each of them can be present without the other two. Thus the search for neurodevelopmental pathways should consider the elements of the triad separately as well as together. Booth et al. pursue the hypothesis that ASD is associated with increased early brain growth but impaired cerebral connectivity, especially between the hemispheres. They test whether a distinct neurodevelopmental disorder, agenesis of the corpus callosum, may be a model for some aspects of the ASD triad; they find some commonalities in social and communicative problems, but no evidence for the cognitive rigidity and "detail-focused processing bias." A parallel analysis of other aspects of the triad will be required to understand how these components interact in the developmental trajectory of ASD.

Autism is typically diagnosed in the second or third year of life, but there is a general belief that it has congenital roots. Elsabbagh et al. studied 9 month olds who, as siblings of diagnosed cases, were at risk for ASD and found that they differed from controls in their ERP responses to eye contact and in a proposed measure of attentional flexibility, the "freeze-frame" task. This, and other studies reviewed by Elsabbagh et al., suggests that infants may show perceptual and cognitive biases which reflect the developmental seeds of autism. However, the critical data for tracking this developmental trajectory are to compare the results in infancy with the later emergence of definitive ASD characteristics. As the authors

point out, diagnostic information from larger groups followed up over a longer period will be required to validate the predictive value of infant indicators and to determine whether an ASD outcome depends on the convergence of multiple developmental risk factors.

The idea that an aversion to eye contact is an early stage and perhaps a key mediator of the development of ASD has been an influential one. The chapter by Terje Falck-Ytter and Claes von Hofsten discusses and reevaluates this idea. They review in detail evidence that ASD individuals, compared to controls, when confronted with a face image, look less at the eye area and more at the mouth. While this result seems to have widespread support in adult ASD individuals, the evidence for such a pattern of bias in children under 12 years was found to be weak and fragmentary. The results they review show more reliable excess looking to the mouth, but not reduced looking to the eyes, and that the balance of mouth:eye fixations reduces in typical development but not in ASD. They suggest that this pattern reflects a more prolonged use of visual mouth information for language acquisition in ASD. These results mean that while poor eye contact and deficits in the use of social information are both features of adult ASD, the direction of causality between them in the developmental pathway for the disorder must be questioned.

Perinatal brain injury

Recent decades have seen enormous improvements in obstetrics and the care of the newborn, leading to increased survival, particularly of infants born very prematurely. However, this means that brain damage, resulting from hypoxia and ischemia in the newborn, remains among the developmental problems with the greatest individual and societal impact. Cioni et al.'s chapter provides an overview of the risks and mechanisms of perinatal brain damage, and the plasticity of the developing brain which means that the functional impact of these injuries may fortunately be much less than the equivalent lesion in adulthood. Braddick et al. report work with this group, showing that visual brain responses can be an early and sensitive indicator of the overall effect of perinatal brain damage, and reveal the differential vulnerability of different brain systems, notably the dorsal stream involved in visual motion processing. Laura Bosch describes the impact of preterm birth on some aspects of language acquisition.

Specific cognitive impairments

"Specific learning disabilities" (SLDs), where one cognitive domain is impaired in individuals whose development and abilities are otherwise typical, are the subject of intense scientific and public interest. Proper coverage of SLDs such as dyslexia and dyscalculia would have made the ESF Research Conference, and this volume, impossibly large. However, these disabilities must surely be ultimately understood in terms of genetic dispositions interacting with environmental influences and demands, acting through pathways in the developing structure and organization of the brain, and many researchers are pursuing this route. One example which may serve as a model is the investigation of developmental impairments of language, described in the chapter by Kate Watkins. The discovery of a family with a pedigree of SLI has enabled the links to be established between mutation of a specific gene, atypical brain structure, and the pattern of behavioral impairment. It is instructive that the fundamental impairment appears to be in the organization and control of programs for delicately timed face and mouth movements. Disorganization of the basic motor machinery required for speech production must lead to a cascade of

developmental effects, some of which, for example, in the mastery of grammatical morphology, may seem to be much more linguistically abstract. This is a lesson for all who are trying to understand specific learning difficulties and other syndromes: the developmental roots of a problem may lie in much lower-level mechanisms than the difficulties which are most evident at a later stage. This is also related to a theme of the chapter by Atkinson and Braddick, in their suggestion that early attentional deficits, viewed as difficulties in shifting focus in WS, coupled with motion processing deficits, may be the developmental starting point of many of the later spatial difficulties.

Visual processing

Two of our chapters focus on visual processing, an area where animal and human neuroscience have given us a uniquely detailed understanding of the functional networks involved. Both Braddick et al. and Klaver et al. give particular attention to the network of areas involved in global motion processing. Work described by Braddick et al. show that this network undergoes substantial reorganization between infancy and adulthood, and the MRI studies reviewed by Klaver et al. find developmental changes between 5 and 7 year olds and adults in the balance of lower- and higher-level structures activated by displays such as structure from motion. Overall, these studies make clear that an apparently similar ability to detect global motion may be subserved at different ages by differently organized networks. Both chapters also make it clear that the relative rates of development of dorsal and ventral streams have a complex history; any statements about one maturing faster than the other must be qualified according to what stage of development, at what level of the system, is being described. These issues may serve as sources of caution for the study of the developmental trajectory in systems whose organization is less well understood.

Social perception

A specialized aspect of visual processing is our ability to register information about other members of our species—individual identity, emotional state, communicative intent—from their faces. This has been of great interest to developmental neuroscientists for several reasons. First, there is much evidence for the role of a specialized neural system, including the "fusiform face area," in processing visual face information. Second, as discussed above, anomalies in attending to and registering facial information are a characteristic of ASD, and possibly one with an important role in the development of the disorder. Third, sensitivity to faces is apparent at or soon after birth and presents a challenge to neurobiological theories on the emergence of specialized cortical properties. This last question is the focus of the chapter by Simion et al. They show how the newborn's attention to faces can be accounted for by initial biases to some simple geometrical image properties, such as relative contrast density in the upper and lower parts of the image. On this view, relatively coarse-tuned biases in attention can determine the early input to the system, and so provide stimulation which refines the tuning and ultimately leads to a highly specific neural system. They present evidence that the neural systems that make us exquisitely sensitive to biological patterns of motion may be refined by a similar process. Such processes by which broad biases guide the acquisition of information, and so provide the basis for high selectivity in a self-organizing system, may prove to be fruitful models in many domains of cognitive development and lead to understanding of how patterns of developmental disorder emerge.

Language

The organization of a specialized perceptual system deriving from broad biases may have its counterpart in the development of the language system. Language is complicated by the way it combines receptive and productive aspects; as the discussion of Watkins' chapter above makes clear, a disruption on one side of this reception–production cycle may have far-reaching knock-on effects on the other. However, in all aspects of language development, reception precedes production. The chapter by Bosch illustrates that there are many levels at which learning processes have to extract information from speech input: the detection of individual phonetic features characteristic of the particular native language environment is acquired early and robustly, but the partition of the speech stream into distinct words, based on statistical and temporal properties, is more demanding and more subject to impairment by the problems associated with preterm birth. As with vision, the detail with which we can characterize language structure at several different levels may make this area one which suggests models and provides sensitive tests for broader questions about cumulative developmental processes.

Concluding remarks

Inevitably, the constraints of time and commitments mean that not all the invited speakers were available to contribute chapters to this volume. The meeting in Sant Feliu benefited greatly from contributions from Lucy Osborne from Toronto and Tassabehji from Manchester discussing gene expression in developmental brain disorders (see *Am J Med Genet C Semin Med Genet*, 2010, and *Eur J Hum Genet*, 2006) and Ghislaine Dehaene-Lambertz from Paris presenting research on the neural basis of infants' language abilities (see *Trends in Neuroscience,* 2006).

Feedback about the meeting was very positive from both junior and senior researchers alike across all the represented disciplines. We hope that readers of this volume will be inspired by perspectives presented in these chapters and that through their efforts we might gain better understanding and funding for this interdisciplinary approach in the future.

Acknowledgments

In addition to the vital support from the European Science Foundation's Research Conferences Scheme, the meeting from which this volume has developed was aided by generous support from the Guarantors of Brain, and the *Comissionat per a Universitats i Recerca* of the Generalitat de Catalunya. Individual contributors were also aided by their own research grant support as cited in the acknowledgments of their contributions.

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CHAPTER 18

Biological and social influences on cognitive control processes dependent on prefrontal cortex

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Abstract: Cognitive control functions ("executive functions" [EFs] such as attentional control, self-regulation, working memory, and inhibition) that depend on prefrontal cortex (PFC) are critical for success in school and in life. Many children begin school lacking needed EF skills. Disturbances in EFs occur in many mental health disorders, such as ADHD and depression. This chapter addresses modulation of EFs by *biology* (genes and neurochemistry) and the *environment* (including school programs) with implications for clinical disorders and for education. Unusual properties of the prefrontal dopamine system contribute to PFC's vulnerability to environmental and genetic variations that have little effect elsewhere. EFs depend on a late-maturing brain region (PFC), yet they can be improved even in infants and preschoolers, without specialists or fancy equipment. Research shows that activities often squeezed out of school curricula (play, physical education, and the arts) rather than detracting from academic achievement help improve EFs and enhance academic outcomes. Such practices may also head off problems before they lead to diagnoses of EF impairments, including ADHD. Many issues are not simply education issues or health issues; they are both.

Keywords: executive functions; self-regulation; dopamine; COMT; interventions; dopamine transporter; ADHD; gender difference.

Introduction

Executive functions (EFs; also called "cognitive control" functions) are needed for reasoning, problem-solving, and whenever "going on automatic" would be insufficient or worse. They depend on a neural circuit in which prefrontal cortex (PFC) plays a central role and are impaired by damage to, or dysfunction in, PFC. They are critical for mental health, achievement in school, and successful functioning in the world. The three core EFs from which more complex ones (like reasoning) are built are (1) *inhibitory control* (resisting a strong inclination to do one

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thing and instead do what is most needed or appropriate, e.g., focused or selective attention, being disciplined and staying on task, exercising self-control, and not saying or doing something socially inappropriate), (2) *working memory* (holding information in mind and working with it: mentally manipulating ideas, relating what you are learning, hearing, or reading now to what you learned, heard, or read earlier and relating an effect to the cause that preceded it), and (3) *cognitive flexibility* (being able to change perspectives or the focus of attention, thinking outside the box to come up with other ways to solve a problem) (Diamond, 2006; Huizinga et al., 2006; Lehto et al., 2003; Miyake et al., 2000).

Both biology (genes and neurochemistry) and the environment (including school programs) modulate the functioning of PFC and thus affect EFs. Unusual properties of the dopamine system in PFC contribute to PFC's vulnerability to environmental and genetic variations that have little effect elsewhere, and some of those variations appear to differentially affect males and females. The relevance of this to disorders such as ADHD and PKU are discussed in the section below, as well as how genotype and gender can moderate which environment is most beneficial.

What we are learning about the brain is turning some ideas about education on their heads. "Brain-based" does not mean immutable or unchangeable. EFs depend on the brain, yet they can be improved by the proper activities. PFC is not fully mature until early adulthood (Gogtay et al., 2004), yet EFs can be improved even during the first year of life and certainly by 4–5 years of age. Neuroplasticity is not just a characteristic of the immature brain. PFC remains plastic even into old age, and EFs remain open to improvement. Many children today, regardless of their backgrounds, are behind on crucial EF skills compared to past generations (Smirnova, 1998; Smirnova and Gudareva, 2004), yet these skills can be improved without specialists and without great expense. Research shows that activities often squeezed out of school curricula (play, physical education, and the arts), rather than detracting from academic achievement, help improve EFs and enhance academic achievement. Such practices may also help to head off problems before they lead to diagnoses of EF impairments, such as ADHD, and may have dramatic effects on children's life trajectories. Improving key EF skills early gets children started on a trajectory for success. Conversely, letting children start school when they are behind on these skills may launch them on a negative trajectory that can be extremely difficult and expensive to reverse.

Special properties of the dopamine system serving Prefrontal Cortex

The dopamine system in PFC is unusual. First, compared with the dopamine systems in most other brain regions, PFC has a relative dearth of dopamine transporter (DAT) protein. This means that while variations in the DAT1 gene that codes for DAT have important consequences elsewhere in the brain, such polymorphisms have little or no direct consequence for PFC.

This also means that unlike other brain regions that have a plentiful supply of DAT, PFC has to rely on mechanisms other than DAT to clear released dopamine. DAT provides the best way to clear released dopamine; those brain regions rich in DAT have little need for secondary mechanisms for clearing dopamine. PFC, because it has little DAT and the DAT it has is not ideally situated (being some distance from synaptic sites), is unusually dependent on the catechol-*O*-methyltransferase (COMT) enzyme for dopamine clearance. Thus variations in the COMT gene that codes for the COMT enzyme have important, direct consequences for PFC, but not for most other brain regions. As estrogen downregulates COMT transcription, there are gender (and menstrual phase) differences in the effects of variations in the COMT gene.

The dopamine system in PFC is also unusual in that, the dopamine neurons projecting to PFC have

a higher baseline rate of firing and a higher rate of dopamine turnover. This makes the PFC dopamine system highly sensitive to small changes in the availability of the precursor, tyrosine (Tyr). Other brain regions, such as in the striatum, are unaffected by small changes in the amount of available Tyr.

Consequence of the relative dearth of DAT in PFC for understanding differences among subtypes of attention deficit hyperactivity disorder (ADHD)

Current diagnostic guidelines list three subtypes of ADHD: primarily inattentive, primarily hyperactive/impulsive, and a combination of the two (DSM-IV; American Psychiatric Association, 1994). Most studies have focused on the combined type. There is much evidence that when ADHD involves hyperactivity (the combined and hyperactive types), the primary disorder is in the striatum and involves a striatal-frontal loop (Casey et al., 1997; Filipek et al., 1997; Hynd et al., 1993; Schrimsher et al., 2002; Soliva et al., 2010; Teicher et al., 1996; Vaidya et al., 1998). As DAT plays an important role in dopamine clearance in the striatum, it follows that polymorphisms of the DAT1 gene should have important consequences for these subtypes of ADHD. That is, in fact, the case (Barr et al., 2001; Bedard et al., 2010; Cook, 2000; Cook et al., 1995; Daly et al., 1999; Gill et al., 1997; Schrimsher et al., 2002; Shook et al., 2011; Swanson et al., 2000; Waldman et al., 1998; Yang et al., 2007).

The primary cause of the cognitive deficits in ADHD (such as inattention and poor working memory) lies in PFC, not the striatum. DAT is sparse in PFC and plays only a minor role there (Durston et al., 2005; Lewis et al., 2001; Sesack et al., 1998). It follows that polymorphisms in DAT1 should have little effect on the cognitive problems that can plague persons with ADHD and little effect on ADHD of the inattentive type. Indeed, that is the case. For example, levels of hyperactive–impulsive symptoms are correlated with the number of DAT1 high-risk alleles but levels of inattentive symptoms are not (Waldman et al., 1998) and DAT binding is related to motor hyperactivity but not to inattentive symptoms (Jucaite et al., 2005).

A role for polymorphisms of the DAT1 gene in the forms of ADHD where hyperactivity is present is consistent with the efficacy of methylphenidate in treating those forms of ADHD, as methylphenidate acts directly on DAT function (Dresel et al., 2000; Seeman and Madras, 1998; Shenker, 1992; Volkow et al., 2002, 2005, 2007). DAT clears released dopamine through reuptake of released dopamine back into presynaptic neurons. Methylphenidate attaches to DAT protein, blocking it from being able to take up dopamine (see Fig. 1). Most children with the combined or hyperactive subtypes of ADHD (as high as 90%) respond positively to methylphenidate; over 67% respond positively to methylphenidate in moderate to high doses (Barkley, 2001; Barkley et al., 1991; Milich et al., 2001; Weiss et al., 2003). That is consistent with methylphenidate acting directly on DAT, DAT being particularly important in the striatum, and the striatum being the site of the primary disturbance in forms of ADHD where hyperactivity is present.

However, a significant proportion of children with the inattentive subtype of ADHD are not helped by methylphenidate or are helped at low doses (Barkley, 2001; Barkley et al., 1991; Milich et al., 2001; Weiss et al., 2003). This is consistent with the different actions of methylphenidate at low doses. At low doses, methylphenidate preferentially increases dopamine neurotransmission in PFC (Berridge et al., 2006).

In humans the dopamine receptor type 4 (DRD4) is present in PFC but not in the striatum (Meador-Woodruff et al., 1996). It follows that polymorphisms in the DRD4 gene should then affect prefrontal function and be related to the inattentive subtype of ADHD, but should not directly affect striatal function. There is evidence to support this. Single-nucleotide polymorphisms (SNPs) in the promoter region of DRD4 have been found to be strongly and primarily

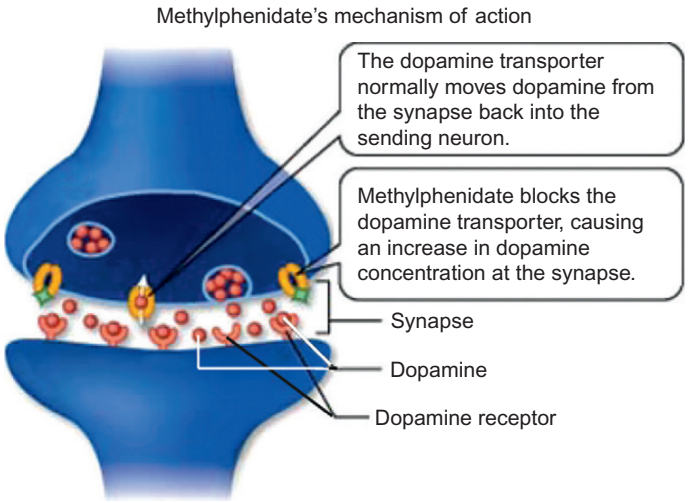


Fig. 1. Mechanism of action of methylphenidate.

associated with inattentive symptoms in ADHD (Lasky-Su et al., 2008), the inattentive subtype of ADHD seems to be the subtype most strongly correlated with the DRD4 7-repeat allele (Rowe et al., 1998), and attentional and working memory deficits have been reported in children with a 7-repeat allele of DRD4 (Auerbach et al., 2001). Moreover, evidence shows a lack of relation between the presence of the 7-repeat allele variant of DRD4 and hyperactivity or impulsivity, deficits which reflect a striatal abnormality (Bellgrove et al., 2005; Johnson et al., 2008; Kramer et al., 2009).

Where hyperactivity is prominent, children with ADHD tend to be frenetic. Children with the inattentive subtype of ADHD, however, are often the opposite; they can be hypoactive, sluggish, and slow to respond (Carlson and Mann, 2002; Carlson et al., 1986; Milich et al., 2001). Where hyperactivity is prominent, children with ADHD tend to be insufficiently self-conscious. Children with the inattentive subtype of ADHD can be overly self-conscious.

Both groups have social problems, but for different reasons. Where the ADHD includes hyperactivity or impulsivity, the child can alienate others by failing to wait his or her turn, butting in line, and acting without first considering others' feelings. Where the ADHD includes no hint of hyperactivity, the child is more likely to have social problems because of being too passive or shy. Such children are not so much easily distracted as easily bored. Their problem is more in motivation (underarousal) than in inhibitory control. Rather than distraction derailing them, they go looking for distraction because their interest in what they had started has dwindled. Having lost interest in their current project, their attention drifts as they look for something to engage their interest. Challenge or risk, something to literally get their adrenaline pumping, can be key to keeping their attention and optimum performance.

It is no coincidence that methylphenidate in low doses (the dosage most efficacious for such children), not only inhibits dopamine reuptake (as it does at high doses) but also preferentially stimulates release of dopamine and norepinephrine (Ishimatsu et al., 2002). Children with ADHD are often given untimed exams to help them, but children with the inattentive subtype often perform better when challenged by presenting test items at a quick rate.

In 2005, colleagues and I laid out the evidence that ADHD that includes hyperactivity and ADHD that is exclusively inattentive are fundamentally different disorders, with different genetic and neural bases, cognitive profiles, responses to medication, and patterns of comorbidity (Diamond, 2005). It resonated deeply with clinicians and patients. Almost overnight, the number of Web sites devoted to ADHD inattentive (ADD) rose from four to thousands. The Founder and Head of the Dutch ADD Assoc. (Stichting ADD Nederland), Karin Windt, wrote, "Many people with attention deficits have great talents, often a high IQ, and are innovative and creative. However, they are seen as daydreamers who cannot concentrate well. In the old days, we would be called stupid or lazy .... Through [Diamond's] work we are now able to explain to others why ADD is so different from ADHD. This question remained unanswered until her article appeared in 2005." Although DSM-V has not yet been released, it appears that the upcoming edition of the diagnostic manual will list ADD and the forms of ADHD that include hyperactivity in separate categories, as fundamentally different disorders.

Consequence of the higher rate of dopamine turnover in PFC for understanding why dietary treatment for phenylketonuria (PKU), if insufficiently rigorous, results in deficits limited to the cognitive abilities (the "executive functions") that depend on PFC

PKU is an inborn (i.e., genetic) error of metabolism usually caused by any of a family of point mutations or microdeletions of the phenylalanine hydroxylase gene, which codes for the enzyme, phenylalanine hydroxylase (DiLella et al., 1986; Lidsky et al., 1985; Woo et al., 1983). Phenylalanine hydroxylase is essential for hydroxylating the amino acid, phenylalanine (Phe), into the amino acid, Tyr. In persons with PKU, phenylalanine hydroxylase activity is either absent or markedly reduced.

As little, if any, Phe is metabolized, Phe levels in the bloodstream skyrocket. If this drastic increase in blood levels of Phe is not corrected early, it causes widespread brain damage and severe mental retardation (Cowie, 1971; Hsia, 1967; Koch et al., 1982; Krause et al., 1985; Tourian and Sidbury, 1978). It would be ideal if the intake of Phe could be reduced to almost trace levels, but the only way to reduce Phe intake is to reduce protein intake, so dietary treatment for PKU must necessarily be a compromise between the need to minimize Phe intake and the need for protein. For this reason, the low-Phe diet rarely results in fully normal blood levels of Phe; Phe levels are reduced but remain moderately elevated. Further, blood levels of Tyr are moderately reduced, as little or no Tyr is produced from Phe, and oral supplements of Tyr only slightly increase blood Tyr levels. The upshot is that dietary treatment for PKU results in a mild imbalance in the ratio of Phe to Tyr in the bloodstream (without dietary treatment, the ratio of Phe to Tyr would be grossly elevated).

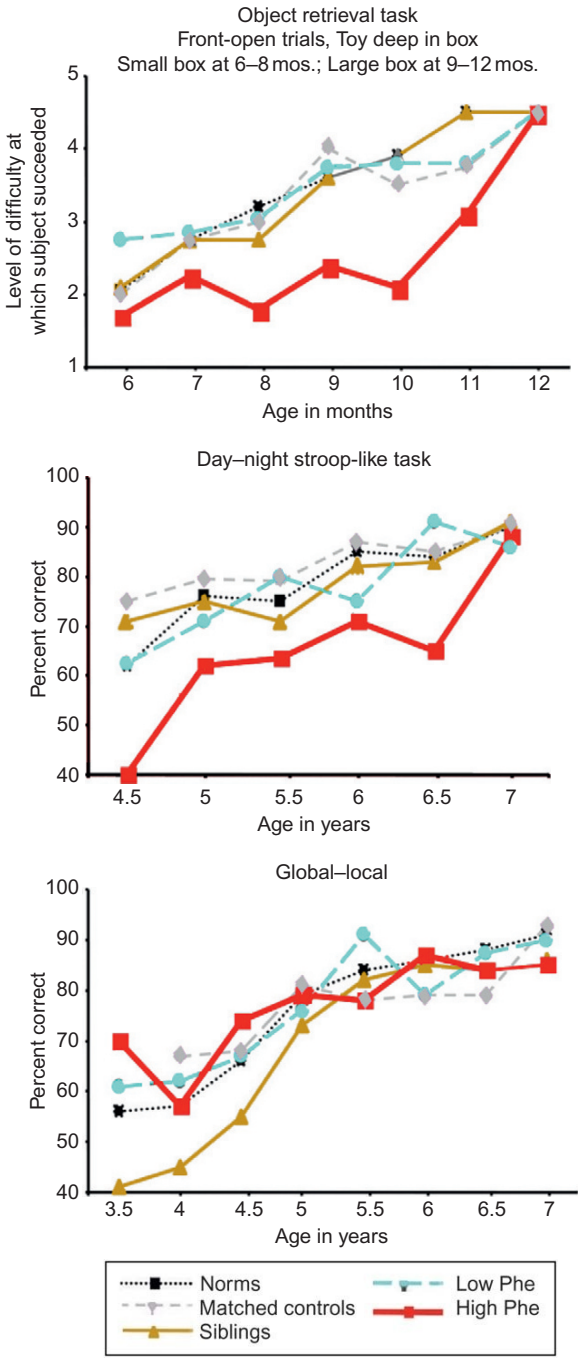
When PKU is treated early and continuously by a diet low in Phe, gross brain damage and severe mental retardation are averted (Bickel et al., 1971; Holtzman et al., 1986). However, young children on such treatment still show deficits if their blood levels of Phe are only brought down to 6–10 mg/dL (360–600 mmol/L)—roughly three to five times normal—levels considered safe worldwide until the late 1990s. Those deficits are specific to and limited to the functioning of PFC and the cognitive abilities dependent on PFC (DeRoche and Welsh, 2008; Diamond, 2001; Diamond et al., 1994, 1997; Smith et al., 2000; Welsh et al., 1990). The reason is as follows:

Phe and Tyr compete for the same limited supply of transporter proteins to cross the blood–brain barrier. Indeed, those protein carriers have a higher affinity for Phe than for Tyr (Miller et al., 1985; Oldendorf, 1973; Pardridge, 1977; Pardridge and Oldendorf, 1977). Elevations in blood levels of Phe relative to Tyr thus result in

less Tyr reaching the brain. Because the ratio of Phe to Tyr in the bloodstream is only modestly increased in PKU children on dietary treatment, the decrease in Tyr levels in the brain is only modest. Unlike dopamine systems in most brain regions, which are robust in the face of modest decreases in available Tyr, the dopamine system in PFC is profoundly affected. (Tyr is the precursor of dopamine.) The higher rates of firing and of dopamine turnover of the dopamine neurons that project to PFC result in PFC being acutely sensitive to even a modest decrease in available Tyr. Reductions in Tyr too small to affect dopamine systems in other brain regions, such as the striatum, profoundly reduce prefrontal dopamine levels (Bannon et al., 1981; Bradberry et al., 1989; Tam et al., 1990; Thierry et al., 1977).

Thus, infants and young children treated early and continuously for PKU show deficits in the cognitive abilities dependent on PFC if their phenylalanine levels are not kept at 2–6 mg/dL (120–360 μmol/L; see Fig. 2), and the higher their Phe levels, the worse their performance on EF tasks that require PFC (Diamond et al., 1997). As long as Phe levels in young children do not exceed 10 mg/dL, the deficits appear to be exclusively in those abilities dependent on PFC. What affects how much Tyr reaches the brain is not simply the level of Phe in the bloodstream but also the level of Tyr. It follows that EF deficits in children with PKU are even more closely related to the Phe : Tyr ratio in blood than to either blood Phe or Tyr levels alone (Luciana et al., 2001).

The wonderful news is that deficits in EFs are preventable and reversible. When average blood Phe levels of children with PKU are kept between 2 and 6 mg/dL, cognitive function seems to be completely normal. EFs deficits can be completely prevented in young children with PKU if their Phe levels are kept between 2 and 6 mg/dL (120–360 μmol/L; Diamond et al., 1997; Stemerdink et al., 1995), and EF deficits in children and adults with PKU can be reversed by a strict dietary regimen that brings Phe levels down



(Schmidt et al., 1994). Also, there are individual differences in the kinetics of the blood–brain barrier that result in variation in the permeability of the blood–brain barrier to different amino acids. Some people have unusual protection against how much Phe reaches the brain and so show little or no deficits from sky-high ratios of Phe to Tyr in their bloodstreams (Koch et al., 2000; Moller et al., 1998, 2000; Weglage et al., 2001).

There were reports in the 1970s and 1980s of cognitive deficits in some PKU children despite treatment and that those deficits appeared to be limited to the cognitive skills requiring PFC. The effect of those reports was muted, however, because no one could imagine a mechanism that would produce such a selective effect. Luckily, unbeknownst to those working on inborn errors of metabolism, a discovery by neuropharmacologists in the 1970s and 1980s—the special sensitivity of prefrontally projecting dopamine neurons to small decreases in Tyr—provided such a mechanism. Neurochemical and behavioral work in an animal model (Diamond et al., 1994) and extensive neurocognitive testing of children (DeRoche and Welsh, 2008; Diamond et al., 1997) confirmed that this mechanism did, indeed, account for PFC cognitive deficits in treated PKU patients. By 2000, the guidelines for the treatment of PKU in young children were changed worldwide, requiring stricter dietary compliance so that average plasma Phe levels remain 2–6 mg/dL, and that has enabled many thousands of children with PKU to lead more productive lives.

Fig. 2. Comparison of the performance of PKU children whose blood Phe levels were 6–10 mg/dL (360–600 mmol/L; labeled the "High Phe" group) with the performance of four comparison groups on tasks that assess executive functioning (the top and middle panels) and a task that does not tax EFs (bottom panel). At each age range investigated (the top panel shows one of the age ranges and the middle panel shows another), and on all EF measures requiring working memory and inhibitory control, the PKU children with relatively high Phe levels (though still within the clinically accepted range at the time) performed significantly worse no matter who they were compared with (other PKU children with lower Phe levels [Phe levels of 2–6 mg/dL, 120–360 mmol/L; labeled the "Low Phe" group], their own siblings, matched controls, or children from the general population). They were not impaired on any of the ten control measures (one shown in bottom panel), most of which required the functions of parietal cortex or the medial temporal lobe. (Modified with permission from Diamond et al., 1997).

Consequences of the relative dearth of DAT, and hence dependence on COMT, for PFC

With less extensive reuptake of dopamine by DAT, PFC is more dependent on secondary mechanisms for terminating the action of released dopamine, such as the COMT enzyme, which deactivates dopamine by adding a methyl group (Napolitano et al., 1995; Weinshilboum et al., 1999). The COMT enzyme accounts for $>60\%$ of dopamine degradation in PFC, but $<15\%$ of dopamine degradation in the striatum (Karoum et al., 1994). Administering an inhibitor of COMT (Tolcapone) to Parkinson patients improves their EFs (Gasparini et al., 1997) because it results in more dopamine in PFC, but it does not improve their motor problems, which are due to striatal dysfunction (Chong et al., 2000).

Variations in the COMT gene disproportionately affect PFC. A common variation in the COMT gene, a guanine to adenine missense mutation (a single base pair substitution [C**G**TG for C**A**TG]), results in a substitution of methionine (Met) for valine (Val; AG**V**KD vs. AG**M**KD) in the coding sequence of the gene (Lachman et al., 1996). Met at codon 158 of the COMT gene codes for a more sluggish COMT enzyme in brain; it methylates dopamine four times more slowly than the COMT enzyme coded from the Val-158 version of the COMT gene (Lotta et al., 1995; Tenhunen et al., 1994). The slower COMT works, the longer the temporal and spatial presence of dopamine at PFC synapses.

The variant of the COMT gene that prolongs the action of dopamine in PFC (Met-158) has been shown in both adults and children to result

in superior performance on cognitive tasks requiring EFs (Diamond et al., 2004; Egan et al., 2001; Malhotra et al., 2002) and to result in more efficient prefrontal functioning holding cognitive performance constant (Egan et al., 2001; Winterer et al., 2006). This effect is specific to PFC function. There is no relation between the Met versus Val COMT genotype and IQ or other cognitive abilities not centrally dependent on PFC, such as recall or recognition memory (Diamond et al., 2004; Egan et al., 2001; see Fig. 3).

Val and Met are equiprobable at codon 158 in COMT alleles of persons of European descent (Palmatier et al., 1999). As COMT Met-158 is associated with better PFC function, you might wonder why it has not been selected for over the course of evolution and become the more common version of the gene. The reason is likely that COMT Val-158 also confers certain advantages. Persons homozygous for the Val variant of the COMT gene tend to be calmer in the face of stress, whereas those homozygous for COMT Met-158 tend to be more sensitive to stress, have higher anxiety, and have higher pain stress responses (Diatchenko et al., 2005; Zubieta et al., 2003).

The reason homozygosity for COMT Met-158 (which results in more dopamine in PFC) is associated with weathering stress less well is probably because even mild stress markedly increases dopamine levels in PFC (though not elsewhere in the brain; Del Acro et al., 2007; Deutch and Roth, 1990; Roth et al., 1988; Reinhard et al., 1982; Thierry et al., 1976). Persons homozygous for

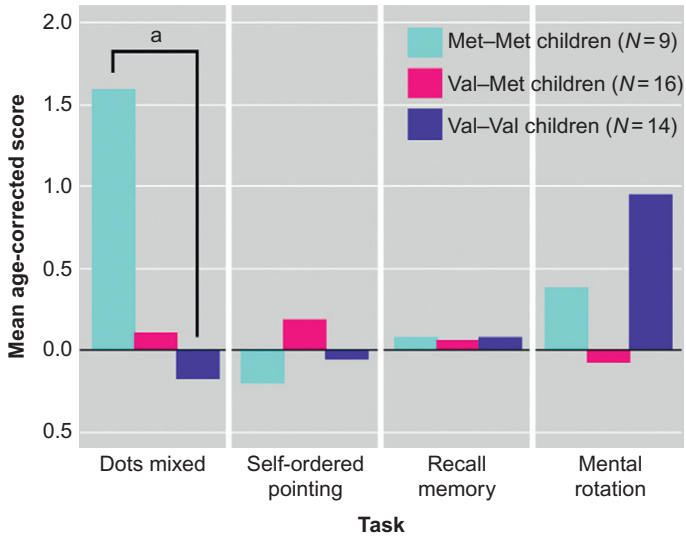


Fig. 3. Performance of children by COMT genotype on four cognitive measures. Children homozygous for COMT Met-158 performed significantly better (Wilcoxon $t = 126.0$, $p < 0.01$) than children homozygous for the COMT Val-158 genotype on the Dots-Mixed task, which requires holding two higher-order rules in mind and switching between inhibiting a prepotent response and making it, and is sensitive to the level of dopamine in PFC. All groups performed comparably on all control tasks (i.e., there was no effect of COMT genotype on any control task): (1) self-ordered pointing, which depends on PFC but is not sensitive to the level of dopamine in PFC; (2) recall memory, which depends on the medial temporal lobe; and (3) mental rotation, which depends on parietal cortex. To control for the effect of age, age mean difference scores were used. For each task, the mean percentage of correct responses for the subject's age in years was subtracted from the subject's percentage of correct responses, yielding an age difference score. This partialled out any effect of age. Gender was not significantly related to performance on any of these three cognitive tasks. (From Diamond et al., 2004, with permission).

COMT Val-158 have a bit more room for stress to increase PFC dopamine levels before detrimental effects are seen because their fast-acting COMT enzyme is quickly clearing away released dopamine. Persons homozygous for COMT Met-158 have relatively high PFC dopamine levels even when calm because of their sluggish COMT enzyme; stress can easily push their PFC dopamine levels well past optimal.

It has long been known that some of the brightest people also have the most fragile personalities and are highly reactive to stress. Here is a possible mechanism for why the two might go together. A person homozygous for COMT Met-158 might have outstanding executive functioning but might be highly vulnerable to stress and anxiety. Boyce (2007; Boyce and Ellis, 2005) has talked about "orchid" and "dandelion" children. "Dandelions" are children who do okay wherever they are planted. They are often identified as models of resilience. Yet research shows that some of the children who look the worst when they are in an unsupportive, stressful environment are exactly those who blossom the most when in a good environment (e.g., Belsky and Beaver, 2011). Perhaps children homozygous for COMT Val-158 are the dandelions; they are more robust in the face of stress but do not have the fine-tuning of PFC to achieve the brilliance of which a COMT Met-158 child might be capable. Perhaps some children homozygous for COMT Met-158 are among the orchids—they might look like a disaster when in a stressful environment, but might blossom brilliantly in the right environment.

Most studies of the effect of COMT genotype have included all males, mostly males, or have not investigated possible gender differences. Yet estrogen downregulates human COMT transcription in a dose- and time-dependent manner (Ho et al., 2008; Jiang et al*.,* 2003; Xie et al., 1999) and results in COMT enzymatic activity being 30% lower in women than men (Boudikova et al., 1990; Chen et al., 2004; Cohn and Axelrod, 1971). The story that being homozygous for Met at codon 158 of COMT confers a cognitive advantage is not true for women during the portion of their menstrual cycle when their estrogen levels are high. COMT activity varies inversely with estrogen levels. With estrogen reducing COMT activity, when estrogen levels are high, being homozygous for the Met variant of the COMT gene (and so having a more sluggish COMT enzyme) confers no cognitive advantage for women, indeed, just the opposite. During the midluteal phase of the menstrual cycle (when estrogen levels are high), young women (ages 19–35) show better executive functioning if they are homozygous for Val at codon 158 than if they are homozygous for COMT Met-158 (Evans et al., 2009). During the follicular phase of the menstrual cycle (when estrogen levels are low), women show the male pattern of better EFs by those homozygous for Met at codon 158 (Evans et al., 2009).

Increasing the level of dopamine in PFC is beneficial only up to a point. The optimal level of dopamine in PFC is an intermediate level; too much dopamine is as bad as too little (Mattay et al., 2003; Zahrt et al., 1997). This inverted-U dopamine dose–response curve has been observed in mice, rats, monkeys, and humans (Arnsten et al., 1994; Cai and Arnsten, 1997; Gibbs and D'esposito, 2005; Lidow et al., 2003; Vijayraghavan et al., 2007). Thus, a double boost to PFC dopamine levels—high estrogen levels reducing COMT activity and COMT Met-158 homozygosity reducing COMT activity—evidently increases PFC dopamine levels too much, past the optimal level for PFC functioning.

Elderly women homozygous for COMT Val-158 perform better on the Wisconsin Card Sort (a measure of executive functioning) than do elderly women homozygous for Met-158, while elderly men tend to show the pattern so often reported in the literature, with those homozygous for COMT Met-158 performing better than elderly Val-158 men (Diamond, 2007). Elderly, postmenopausal women do not have menstrual-cycle mediated estrogen surges in their body.

The gender difference here is probably due to setting effects of the sex hormones very early in development (Shansky et al., 2004; Shors and Miesegaes, 2002).

Male animals perform better on tasks dependent on PFC when they are mildly stressed than when they are calm, but female animals do not; they perform worse when even slightly stressed than when calm (Arnsten and Goldman-Rakic, 1998; Shansky et al., 2004; Shors, 2001; Shors and Leuner, 2003; Wood and Shors, 1998; Wood et al., 2001). This gender difference appears to be estrogen-mediated. Female animals show the male pattern in response to mild stress when their estrogen levels are low, but mild stress impairs cognitive functions dependent on PFC in female animals during the point in the estrus cycle when estrogen levels are high (Shansky et al., 2004).

Perhaps there is a gender difference, not hereto considered or reported before, in the baseline levels of dopamine in PFC. Females may have higher baseline levels of dopamine in PFC (an optimum level) and males may have slightly too little dopamine in PFC at baseline. That would be consistent with slight stress bringing males' PFC dopamine levels up to optimal but raising females' PFC dopamine levels past optimum (see Fig. 4).

If so, this would have important practical implications for gender differences in the effective dosages of medications that affect PFC dopamine levels. Women may need lower dosages than men, at least when their estrogen levels are high. Certainly, there already appears to be evidence of menstrual-phase differences in the optimal dosage levels of drugs that affect PFC dopamine; when a woman's estrogen levels are high, she has more dopamine in PFC than when her estrogen levels are low; hence, the same dosage of medication affecting PFC dopamine levels that is beneficial during certain times of the month might be detrimental during other times of the month.

It is also important to remember the general principle that a genotype that is beneficial in one environment may not be beneficial in another. The COMT Met-158 genotype is probably not beneficial in a highly stressful environment. Yet this same genotype that confers risk on individuals when they are in adverse, stressful circumstances holds out promise of extraordinary potential if only the right fit of circumstances can be found for the individual. When working with children living in disadvantaged, at-risk conditions, it is important to bear this in mind.

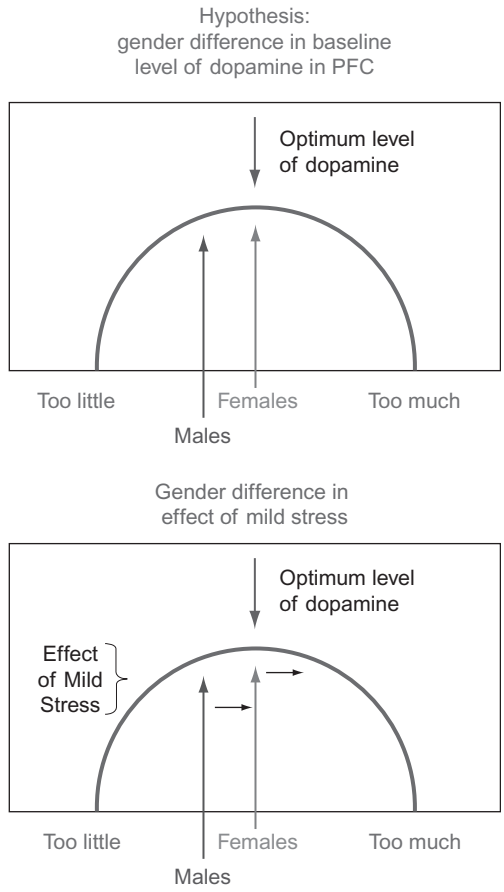


Fig. 4. Illustration of how, if males and females have different baseline levels of dopamine in PFC, that would account for the differential effects of slight stress on males and females (with slight stress being beneficial for males' EFs but detrimental for females' EFs).

Environmental conditions and interventions that enhance the development of the cognitive control processes dependent on PFC

Just as we can improve our physical fitness through exercise, through challenging ourselves to push our limits, and through a regular practice regimen, so too, our EFs can be improved through exercising them, challenging them, and using them throughout the day, every day. Research shows this is true throughout life, from infancy to old age, and that it does not require anything expensive, highly technical, or complicated.

Bilingualism places heavy demands on inhibitory control and cognitive flexibility (two core components of EFs). A bilingual speaker needs to inhibit using a language the listener would not understand (even if only that language has the perfect word for what the speaker wants to express), one needs to shift from the perspective and mindset implied by one language to that implied by another, and one may need to flexibly switch languages in a conversation with a person who speaks Language A and person who speaks Language B (Green, 1998; Hermans et al., 1998; Klein et al., 1995; Paradis, 1997; Perani et al., 1998). Thus bilingualism taxes executive functioning and early bilingualism exerts environmental pressure for the accelerated development of EFs.

Children only 4–7 years old, who are fluently bilingual, are 1–2 years ahead of their monolingual peers on cognitive tasks that require inhibiting distractors or prepotent responses, changing perspectives, or flexibly adapting to changed rules (Bialystok, 1999; Bialystok and Majumder, 1998; Bialystok and Martin, 2004; Bialystok and Shapero, 2005; Martin-Rhee and Bialystok, 2008). Even infants show advanced executive functioning if bilingual (Kovács and Mehler, 2009a,b). Indeed, before infants are even speaking, simple comprehension seems to produce this effect, for it has been elegantly demonstrated that infants of only 7 months, exposed to bilingual input from one parent speaking one language and the other parent speaking another, show more advanced executive functioning than their peers exposed to only one language (Kovács and Mehler, 2009a). These effects are specific; bilingual children are not ahead on recognition or recall memory, learning, or IQ. Older adults who continue to be actively bilingual preserve their executive functioning longer into old age than do monolingual older adults matched for IQ, SES, and health (Bialystok et al., 2005, 2004, 2006).

Vygotsky (1967, 1978) emphasized the importance of social pretend play (e.g., playing doctor and patient, or grocery store) for the early development of EFs. If you think about it, during dramatic make-believe play, children must *inhibit* acting out of character, *hold in mind* the role they have chosen and those of others, and *flexibly adjust* in real-time as their friends take the play scenario in directions they never imagined. Thus, social pretend play exercises and challenges all three of the core EFs (inhibitory control, working memory, and cognitive flexibility).

Bodrova and Leong (2007) developed an early education program, *Tools of the Mind*, based on the theories and research findings of Vygotsky and his protégés. Bodrova and Leong initially tried social dramatic play as an add-on to existing curricula. Children improved on what they practiced in those modules, but the benefits did not generalize. They did not generalize to other contexts or other demands on EFs. For benefits to generalize, supports for, training in, and challenges to EFs had to be part and parcel of what the children did all day long. The children's actions throughout the day had to be exercising EFs to really see a benefit. Thus, Bodrova and Leong embedded aspects of EF training in all academic activities, including literacy and math, as well as having activities whose primary focus was to improve EFs.

A *Tools of the Mind* literacy activity with an embedded EF component is *Buddy Reading*. Children of 4 or 5 years each select a book, get into pairs, and take turns "reading" the story in

their picture books. With each child eager to tell his or her story, no one wants to listen. To help them succeed at exercising inhibitory control (one of the EFs), the teacher gives one child a drawing of lips and the other a drawing of an ear, explaining, "Ears don't talk; ears listen." With the concrete, visible reminder, the child with the ear is able to inhibit talking, wait his or her turn, and listen (see Fig. 5). Otherwise the child would not be able to do that. After a few months, the pictures are no longer needed; the children have internalized the instructions and are able to listen and wait their turn without the visible reminders.

Scaffolds, such as the simple line drawing for *Buddy Reading*, enable children to practice skills they would not otherwise be able to practice. If a teacher assumes that children are not capable of something and so structures the class so that the children never need to do that, children do not get the benefit of practice to help them improve. If a teacher, with the same assumption, scaffolds or supports children to help them perform at a level they could not perform at on their own, then they get practice (and the pride of doing something that may have seemed far beyond their reach) and through repeated practice, they improve. In the *Buddy Reading* example, instead of being scolded or ashamed for being a poor listener (as would happen without the visual "ear" reminder), children have the boost to their self-esteem from having been able to be a good listener, and increased self-confidence that they can successfully do what's required of them.

Fig. 5. Photograph of two children engaged in *Buddy Reading*. Note the line drawing of an ear in the hand of the girl listening to the other girl. Photograph by Morey Kitzman, reprinted from the supplementary online material for Diamond et al. (2007) with permission.

When we evaluated the effect of *Tools of the Mind* on EF development compared with a high-quality program newly developed by the school district, we specifically chose EF measures quite different from anything the children had ever done before. To see a difference by condition, the children would have to transfer their training in EFs to utterly new situations. All children came from the same neighborhood and were closely matched on demographics. Stratified random assignment of teachers minimized confounds due to teacher characteristics.

Our results reported in *Science* (Diamond et al., 2007) showed that children in *Tools* performed better on measures of EFs than their peers in the district's curriculum (see Fig. 6). This difference increased as the EF requirements of the tasks increased. Other children in *Tools of the Mind* in other schools and states, with different comparison programs, have been found to consistently outperform comparison children on standardized academic measures (Barnett et al., 2008). Staff at one school in our study became so convinced that children in *Tools of the Mind* classes were so markedly outperforming other children that they halted the study early in their school and switched all classes to the *Tools of the Mind* curriculum.

The significance of these findings is that they indicate that (1) EFs can be improved in preschoolers. Some had thought preschool too early to try to improve EFs, but this research indicates it is not. (2) EFs can be improved in regular public-school classes, without expensive, high-tech equipment or specialists. (3) The program that embraced the importance of play produced better EFs and academic outcomes than

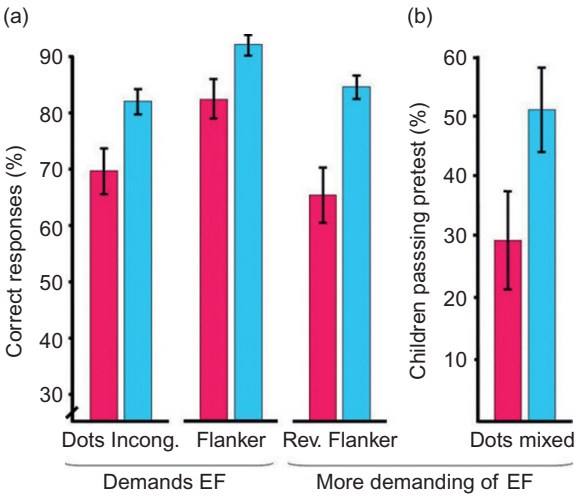


Fig. 6. Photograph of a child performing the Hearts & Flowers task (which used to be called Dots-Mixed [see Fig. 3]) and comparison of the performance of Kindergarten children in *Tools of the Mind* (lighter gray in print version; blue in online version) with the performance of children from the same neighborhood, closely matched on demographics, in a different kindergarten program (darker gray in print version; pink in online version) on tasks that assess EFs. All differences are significant, but the benefit of *Tools of the Mind* on the easier conditions (Hearts & Flowers Incongruent and Flanker) was much smaller than on the more EF-demanding conditions (Hearts & Flowers Mixed and Reverse Flanker). For the first set of three graphs (A), the dependent measure is percentage of correct responses. For the last graph (B), the dependent measure is percentage of children. Photograph is by Martin Dee. The graphs are reprinted from Diamond et al. (2007) with permission.

one that devoted more time to direct academic instruction, indicating that play may *aid* academic goals rather than taking time away from achieving them. (4) If throughout the school-day EFs are supported and progressively challenged, it appears that benefits generalize and transfer to new activities, as the outcome measures were different from anything the children had done before.

Just as our brains (especially PFC) work better when we are not feeling stressed, our brains (especially PFC) work better when we get exercise and are physically fit. There is considerable evidence that aerobic exercise improves how the brain works (especially PFC) and how we think (with EFs showing the greatest benefit from improved aerobic fitness). "[T]he positive effects of aerobic physical activity on cognition and brain function [are evident] at the molecular, cellular, systems, and behavioral levels" (Hillman et al., 2008: 58). "Physical activity-related modulation is disproportionately larger for task components that necessitate greater amounts of executive control" (Hillman et al., 2008: 61). The positive effects of aerobics on EFs, long demonstrated in adults, can also be seen in children (Hillman et al., 2005, 2009).

Intervention studies show that children's increased participation in physical activity leads to better cognitive skills and grades. For example, a 2-year physical activity intervention with over 4500 elementary-school children produced improvements in children's math and reading scores (Hollar et al., 2010). Children who received extra physical education showed better academic achievement on average than that of a control group (Shephard et al., 1994). Among 6th graders randomly assigned to condition, those who met at least some of the Healthy People 2010 guidelines for vigorous activity had significantly higher grades than those who performed no vigorous activity (Coe et al., 2006). Among 13–16 year olds randomly assigned to physical exercise or a control group, those in the exercise

group improved more in selective attention and concentration (Budde et al., 2008). When the results from many studies were pooled in a meta-analysis, a positive clear relation between physical activity and both verbal skills and math emerged for all ages (4–18 years) and especially for those 13 years of age or younger (Sibley and Etnier, 2003).

Dance provides physical exercise and can be quite physically demanding and taxing, but it also directly exercises and challenges EFs by requiring sustained attention and concentration and by requiring that one hold complex sequences in mind. There have been few scientific studies of the benefits of dance for other than fitness, posture, or balance. Two noteworthy studies have been conducted with older adults, however. Verghese et al. (2003) examined the relation between leisure-time cognitive or physical activity and the incidence of dementia. At the study's outset all subjects were over 75 years old and dementia-free. Five years later, reading or doing crossword puzzles was associated with a 35% reduced risk of dementia. Almost none of the physical activities offered protection against dementia—except dance. Dance conferred the greatest risk reduction of any activity studied, cognitive or physical; a 76% reduced risk of dementia. Kattenstroth et al. (2010) studied the impact of many years of regular, amateur ballroom dancing on neurologically healthy elderly subjects, compared to education, gender, and age-matched controls with no record of dancing or sports. The dancers performed better on the Raven Matrices (a measure of fluid intelligence very highly correlated with EFs [Duncan, 1995; Duncan et al., 2008; Jaeggi et al., 2008]) and on a nonverbal test of selective attention and concentration (Gatterer, 1990).

Many different activities can probably improve executive functioning, from tae-kwon-do (Lakes and Hoyt, 2004), tai chi (Lam et al., 2010; Matthews and Williams, 2008; Taylor-Piliae et al., 2010), or yoga (Pradhan and Nagendra, 2010) to playing chess, from storytelling to playing a musical instrument, from sports to choral singing to acting in plays. The most important element is probably that the person loves what he or she is doing, so that doing it brings great joy. If a person enjoys the activity enough he or she will spend a lot of time at it, practicing and pushing him- or herself to do better. It is the discipline, the practice that produces the benefits. Even the best activity for improving EFs if done rarely will produce little benefit.

Why try to improve EFs early? Just because it is possible to improve them early does not necessarily mean that we should. Why not wait? Perhaps slower-developing children will catch up over time. Alas, evidence indicates that rather than early EF delays disappearing, they tend to grow larger (Nagin and Tremblay, 1999; Brody et al., 2003). Consider children who start school with poor EFs: They tend to blurt out answers, jump out of their seats, have trouble paying attention and completing assignments, and impulsively butt in line and grab things from other children. They get poor grades and are always getting scolded. School is no fun and before long they would just as soon not be there. Teachers come to expect poor performance from them, and the children come to expect poor performance from themselves. A self-reinforcing negative feedback loop develops with the frustrated child deciding school is a place of failure.

Conversely, consider children who start school with good EFs: They wait to answer until they are called on, stay in their seats, pay attention, complete their assignments, and are well behaved. For them, school is a place of success and praise. Teachers enjoy them, expect them to do well, and the children expect to succeed. A self-reinforcing positive feedback loop is created.

Small differences at the beginning can lead to bigger and bigger differences over time. A small difference in children's EFs at the outset of schooling could lead to disparities in EFs and achievement that grow larger with each passing year. Children at risk fall progressively farther behind other children in academic achievement over the school years. That "widening achievement

gap" (O'Shaughnessy et al., 2003) may result from two opposing dynamisms (negative and positive feedback loops) going in opposite directions. Reducing or erasing the disparity at the outset might nip that dynamic in the bud.

"Brain-based" does not mean immutable or unchangeable. EFs depend on the brain, yet they can be improved by the proper activities. Reducing stress and improving physical fitness yield benefits to EFs. Using your EFs, exercising and challenging them improves them, much as physical exercise hones our physical fitness. Such EF "exercise" may be beneficial for our mental health just as physical exercise is beneficial for our bodily health.

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