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Dr. Tomáš Paus, University of Toronto, Canada

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Synthesis

How important is it?

The brain is the most important organ of the human being. It is a very complex organ which has a preponderant role in all the functions of the body. Moreover, the absence of brain activity defines clinical death. Brain maturation, which is significant before birth – with the generation of over 100 billion nerve cells – and during the first two years of life with a continuing growing brain volume, is a period of great vulnerability. The developing brain is particularly sensitive to environmental influences, such as toxic early life stress. Brain development may be affected through sensing pathways by sound, touch, vision, smell, food, thoughts, drugs, injury, disease and other factors.

In the developing course, brain areas do not mature at the same time. For example, auditory perception begins before birth. The newborn brain is already able to recognize familiar voices and tunes from the foetal period. On the contrary, the cerebral areas implicated in declarative memory and in vision are not mature at birth. To become fully developed, these systems, including the *auditory cortex*, need the stimulation that occurs after birth.

An important aspect of the very young brain is its capacity for change. When maturing, the brain becomes less plastic; for example, by the end of the first year, the parts of the brain that differentiate sounds are becoming specialized according to the language the baby has heard. At the same time, the brain is already starting to lose the ability to recognize different sounds found in other languages.

What do we know?

IMAGING TECHNIQUES

Since the advent of imaging techniques which allow us to see structural images of the brain (magnetic resonance imaging [MRI]), to measure brain activity (functional MRI [fMRI]) in living people and more recently to detect changes in *white matter microstructure* (diffusion tensor imaging [DTI]), numerous studies have been conducted to explore cerebral anatomical changes and to try to relate them to behavioural changes. Because they are non-invasive, these

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techniques can be used to study the development and the effects of experience on the brain.

DEVELOPMENT

Recent evidence in young children indicates that total brain volume increases 101% in the first year, followed by a 15% increase in the second year. In the first year, the major growth is that of *grey matter* (149%), *white matter* increase is less important (11%). The *cerebellar* volume increases 240% in the first year, whereas increase by 90%. From ages 3 to 30, white matter volumes increase, while grey matter volumes rise and then fall, peaking at a characteristic time specific for each brain region during childhood and adolescence. Concurrently, connectivity between brain areas increases both structurally and functionally and the balance between *limbic*/*subcortical* and *frontal lobe* functions changes until young adulthood. Moreover, studies using *genomic imaging* indicate that genes are involved in shaping the brain. Twin studies carried out in adults as well as in children and adolescents show the high heritability of volume measured in different regions of the grey matter.

EARLY LIFE STRESS

Early life stress may also affect the brain volume. Animal models have shown that the *amygdala*, the *prefrontal cortex* and the *hippocampus* undergo stress-induced structural remodelling, which alters behavioural and physiological responses, including anxiety, aggression, mental flexibility, memory and other cognitive processes. Research in humans increasingly suggests that severe early life stressors (e.g., trauma, maltreatment, neglect) may result in decreased brain volumes. However, numerous scientific studies support the conclusion that providing supportive, responsive relationships as early in life as possible can prevent or reverse the damaging effects of toxic stress.

ATTENTION

Recording the electrical activity of the brain is a less recent method than imaging techniques; however it allows researchers to obtain event-related potentials (ERPs) which are electrical potentials in the brain in response to specific stimuli. Attention ERPs studies conducted in infants reveal a *Negative central (Nc) component* which is greater in amplitude when heart rate indicates attention.

VISION

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In the early months of life, the visual system is still developing. At birth, the infant vision is mainly controlled at a subcortical level, with the cortex starting to mature at about 2 months postnatally. Due to immaturities of the eye components, the newborn is moderately farsighted. Visual attention and visual searching begin by 3 months; the infant begins to associate visual stimuli with an event (e.g., the bottle and feeding). Using variants of the simple visual orienting task known as the Gap task, studies indicate that the disengage operation becomes operative between 3 and 4 months of age. Prior to age 4 months, infants are able to selectively focus their attention, but once engaged on a particular stimulus, they have difficulty disengaging and moving their attention elsewhere. Rather, they tend to fixate for prolonged periods.

AUDITION

Auditory cortex shows a very prolonged developmental trajectory, with completely mature responses to simple sounds not achieved until about 18 years of age. At the same time, the brain's responses to occasional changes in a repeating auditory stimulus can be measured in 2-month old infants.

MEMORY

Dramatic changes in the brain areas implicated in memory occur in the first two years of life. To assess declarative memory ("remembering") in preverbal children, researchers have used elicited imitation (infants are shown an action (i.e., ringing a bell) and given opportunities to imitate the modelled action). Improvements in memory with age are consistent with brain development.

What can be done?

Once the infant born without any problem neither during pregnancy nor at birth, his/her developing brain is shaped by interactive influences of genes and experience. The brain architecture will form as expected if the parents and caregivers respond attentively to the interaction initiated by their child. Nurturing relationships in the early years promote physical and mental health and benefit for learning throughout the life cycle. Not only is supportive, attentive and sensitive care from adults required for an optimal infant's brain development, it also protects the developing brain from potentially harmful effects of stressors. Moreover, if an infant's brain has already been affected by toxic stress, scientific evidence shows that supportive

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and responsive relationships as early in life as possible can prevent but also reverse the damaging effects of toxic stress.

DEVELOPMENT

Work investigating the impact of experience on brain maturation during development and vice versa is still scarce. Adolescent neurobiology has also been relatively understudied. Therefore, the full complexity of the issue cannot yet be understood. The hypothesis telling that developmental changes in brain structure are prerequisites of a particular cognitive ability could be obsolete as the role of experience in shaping the brain could be stronger than previously thought. The image data add up with genetic information, behavioural scores, family history, blood tests, and much more. This flood of data is more than researchers can currently understand, and new bioinformatics and statistical methodologies are required to better grasp what information is most relevant to patient care.

EARLY LIFE STRESS

Research on early life stress needs more studies to elucidate the effect of childhood stress on brain structures and processes. The field also lacks an adequate understanding of the genetic variations among children that moderate the reactivity, regulation, and impact of stress responses. Future research should analyse the impact of different types of trauma at different developmental stages, in order to identify sources of outcome variability. Furthermore, the use of salivary cortisol measure (a non-invasive measure of the effect of chronic stress) has boosted research on the neuroendocrine system involved in stress response, namely the hypothalamic-pituitary-adrenocortical (HPA) axis (or *stress hormone axis).*

ATTENTION

To determine which brain areas are the likely cause of Event Related Potentials measured on the scalp, researchers can now use age-appropriate MRI templates which are allowing them to move from using adult templates to interpret infant data. New research can focus on specifics such as individual variability and neurodivergent populations.

Problems with visual disengagement, often expressed in infants as prolonged visual fixation, together with high levels of distress, are very worrisome and challenging for parents. They should be detected early and seen as flags that warrant referral.

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VISION

Visual experience is crucial for a child's vision to develop normally – a “use it or lose it” situation; treatment of common childhood eye diseases should begin much earlier than standard practice dictates.

AUDITION

Brain’s response to a sound event (the auditory event-related potential) could be used in infants as a diagnostic indicator of early abnormal central auditory development; these are a method of choice for examining early auditory development and the maturation of auditory cortex. Passive learning, for example learning from tapes or from speaking toys, is one of the interventions that is suggested to remediate to problems in speech perception and language acquisition.

MEMORY

Although a lot of recent progress has been made, learning about memory and brain development in infancy will require more studies conducted in humans because much information comes from animal models (rodents and nonhuman primates).

As we increase our understanding of the relations between brain and behaviour, we will be able to develop interventions to help infants and children in the at-risk groups (e.g., infants born to mothers with blood sugar control problems during pregnancy, infants adopted from international orphanages and healthy preterm infants).

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Imaging the Growing Brain

Tomáš Paus, MD, PhD

University of Toronto, Canada

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Introduction

When does your brain stop growing? A simple answer is: never.

Of course, the most dramatic growth happens in the womb. During the short period of nine months, the initial “mother” cell gives rise to over 100 billion nerve cells, and a brain that weighs about 400 grams when a child is born. As the child learns to walk and talk, her brain continues to grow, reaching the size of 1,200 grams by the time she is four years old; this is only about 200 grams less than an adult. But it does not stop there.

Over the next 10 to 15 years, until the child becomes a young adult, the brain growth continues: it now affects different brain compartments in a slightly different way. For example, the thickness of the different regions of *cerebral cortex* changes between 5 and 18 years of age at different paces, with the regions important for reasoning, planning and social communication maturing last. The white matter containing the pathways that connect the different brain regions continues to mature as well during this period. In boys, the volume of white matter increases sharply during adolescence, perhaps under the influence of the rising levels of the sex hormone, testosterone. In girls, changes in white matter seem subtler and may reflect a process called myelination, by which axons gain additional layers of a fatty substance called myelin, which makes them conduct nerve impulses faster.

What happens next? Does the brain of an adult stop growing? Not really.

It seems that experience continues to shape our brains even in our early 20s. For example, if you are trying to learn how to juggle three balls and you practice every day for two months, the parts of your cerebral cortex that are tracking the moving balls grow. Although we do not know which cells are growing, it is likely that all the additional brain activity in this brain module, specialized for tracking movement of visual stimuli, elicits a cascade of events leading to a structural change in this region. However, this is not permanent – if you stop juggling, it is gone a couple of months

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later.

Finally, what about the “aging” brain? Does it grow or shrink?

This seems to depend on where in the brain we look and whose brain we look at. For example, older professional musicians playing in an orchestra are possibly gaining, and certainly not losing, grey matter in the *cortical region* that may be engaged repeatedly during their work, such as frequent sight-reading of musical scores. This observation suggests that the brain structure continues to be plastic and amenable to experience even later in life.

How do we know all this? To a great extent, the above knowledge was gained through the use of magnetic resonance imaging (MRI) to visualize the living brain in healthy participants, from infancy, through childhood and adolescence into adulthood. MRI is a powerful non-invasive technique that allows us to take detailed 3-dimensional pictures of the brain in less than 15 minutes. These are then analysed using various computational algorithms that quantify, automatically and precisely, many different features, such as thickness of the cerebral cortex, volume of grey and white matter or properties of major white-matter pathways. The widespread availability of magnetic resonance (MR) scanners and the relative ease of acquiring structural images of the brain makes MR an ideal tool for large-scale studies of brain development and the various factors that may influence it, both in relation to an individual’s genes and her environment. The emerging discipline of “population neuroscience” provides laboratory-based research to the field. Measuring the human brain on a population level allows us to study the complexity of human existence and the circumstances, whether psychological (e.g., early life stress) or biological (e.g., nutrition), under which we grow.[1] I will now describe in more detail the basic principles of MRI, the use of computational tools to quantify the brain growth and a few conceptual issues related to the interpretation of findings obtained with these techniques.

MRI: Basic principles

For imaging brain structure, the most common acquisition sequences include T1-weighted (T1W) and T2-weighted (T2W) image *diffusion-tensor images (DTI)* and magnetization-transfer images (MT). The T1W and T2W images are typically used for quantifying the volume of grey and white matter (both global and regional), and estimating the cortical thickness or other morphological properties of the cerebral cortex, such as its folding. Using DTI and MT imaging, one can assess different properties of white matter, again both globally and regionally. The various features of

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brain structure that can be extracted from these four types of images are described below. In addition to the above sequences, less common but often even more informative acquisitions include T1 and T2 relaxometry (i.e., measurement of the actual relaxation times)[2] *magnetic resonance spectroscopy (MRS).*[2]

For imaging brain function, the most common MR parameter to measure is the blood oxygenation-level dependent (BOLD) signal. The BOLD signal reflects the proportion of oxygenated and de-oxygenated blood in a given brain region at a given moment. A strong correlation between the amount of synaptic activity and regional cerebral blood flow is the reason why the BOLD signal is a good, albeit indirect, measure of brain "function."[3] In the majority of *functional MRI (fMRI)* studies, one measures changes in BOLD signal in response to various sensory, motor or cognitive stimuli. Therefore, only brain regions that are likely to respond to such stimuli can be examined using a given paradigm.

Structural MRI: Measuring the brain growth

As pointed out above, the different acquisition sequences capture various properties of grey and white matter and, in turn, provide a wealth of information that can be extracted from the images using an ever-growing array of computational algorithms. Here I provide an overview of the most common techniques used in developmental studies:

Computational analysis of high-resolution structural brain MR images (typically T1W and T2W images) is used to extract in a fully-automatic fashion two types of measurements: (1) Voxel- or vertex-wise features derived for each X, Y and Z (i.e., three-dimensional) location (e.g., grey- and white-matter "density" maps, cortical thickness, cortical folding); and (2) Volumetric measures (volumes of grey or white matter in particular brain regions, or the area of specific brain structures, etc).

Density maps are generated by (1) registering T1W images with a template brain (e.g., the average MNI-305 atlas);[4] (2) classifying the brain tissue into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF); and (3) smoothing the binary 3-D images (i.e,. GM, WM and CSF) to generate 3-D maps of GM/WM density. These maps are then used in voxel-wise analyses of age- or group-related differences in GM or WM density.[5]

Cortical thickness can be measured, for example, using FreeSurfer; this is a set of automated tools for reconstruction of the brain cortical surface.[6] The local cortical thickness is measured

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based on the difference between the position of equivalent vertices in *pial* and grey/white surfaces. Local estimates of cortical folding can be obtained by measuring, for every point x on the cortical surface, the area contained in a small sphere centred at x.[7]

The volume of brain tissues (grey matter or white matter) can be estimated by registering images to a labeled template brain on which lobes have been defined traced by an expert. One can then count the number of grey and white matter voxels belonging to a given anatomical region, such as *frontal lobe*.[8,9] More sophisticated algorithms are often developed to segment small structures with poorly defined boundaries, such as *hippocampus amygdala*.[10]

In addition to the density maps and volumetric measurements of white-matter structures, such as the *corpus callosum*, two other techniques are used to evaluate structural properties of white matter: diffusion tensor imaging (DTI) and magnetic transfer (MT) imaging. Using diffusion tensor imaging, one can estimate local differences in the magnitude and directionality (fractional anisotropy) of the diffusion of water in the extra-cellular space around the axons. It is assumed that fractional anisotropy varies as function of structural properties of white matter, such as *myelination* and fiber arrangement of a given white-matter tract.[11,12]

The magnetization transfer ratio (MTR) is another measure employed for the assessment of white-matter properties; it provides information on the macromolecular content and structure of the tissue.[13] Given that the macromolecules of myelin are the dominant source of MT signal in white matter,[14,15] one can use MTR as an index of myelination. Note, however, that myelin is not likely to be the sole factor influencing MTR.[11]

The above techniques provide a wealth of information about structural properties of the human brain. Work described in the reviews by Durson[16] and Giedd[17] used some of these approaches to chart brain development from childhood to adolescence.

Interpreting brain images

A number of conceptual frameworks have been put forward to interpret some of the findings reviewed above vis-à-vis underlying neurobiology. Unfortunately, the indirect nature of the available measures makes it very difficult to verify the validity of some of these propositions.

Cortical grey-matter and synaptic pruning

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It is the case that MR-based estimates of the volume of cortical GM and cortical thickness appear to decrease during adolescence. This has been often interpreted as an indication of "synaptic pruning," a process by which "redundant" synapses overproduced in the early years of life are being eliminated.[18] The initial evidence for accelerated synaptic pruning during post-natal development came from post-mortem studies by Huttenlocher, who described a decrease in the number *dendritic* spines in the human cerebral cortex during childhood and adolescents.[19,20] But these studies were limited by the low number of specimens available for the different stages of human development. A more definite evidence of synapse elimination during adolescence was provided by studies carried out by Rakic and colleagues in non-human primates.[21,22] Using electron microscopy, they observed a dramatic decrease in the number of synapses in the monkey visual cortex during puberty, whether expressed as a number of synapses per neuron or per cubic millimetre of neuropil (unmyelinated nerve fibers) (about a 45% loss). But it is unlikely that this decrease in synaptic density translate into a decrease in cortical volume. Bourgeois and Rakic[21] commented that "changes in the density of synapses affect very little either the volume or surface of the cortex because the total volume of synaptic boutons … is only a very small fraction of the cortical volume" and concluded that "… a decline of synaptic number during puberty should have a rather small effect on the overall volume of the cortex."[21]

If the number of synapses per se is unlikely to change the cortical volume/thickness than what other cellular elements could affect it? As discussed in detail elsewhere,[23] age-related variations in (cortical) grey matter observed in vivo with MRI could be related to the variations in neuropil (60% of the mouse cortex), which consists of dendritic and axonal processes. It is also conceivable that the apparent "loss" of grey matter reflects an age-related increase in the degree of myelination of intra-cortical axons. The higher the number of myelinated fibres in the cortex, the less "grey" the cortex would appear on regular T1-weighted images. Such a "partial-volume" effect could result in an apparent loss of cortical grey-matter.

White matter and myelination

Given the well-documented histology-based increase in the degree of myelination during the first two decades of human life,[24] it is perhaps not surprising that any changes in the volume or "density" of white matter revealed by computational analyses of T1-weighted images are attributed to changes in myelination. Again, assumptions based on previous knowledge are influencing interpretation of new data. Quite often, articles reporting age-related changes in myelination have merely measured volumes of white matter. We have shown a clear example of

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dissociation between age-related changes in the volume of white matter during adolescence and changes in magnetic transfer ratio (MTR), an indirect index of the amount of myelin in white matter.[25] Although white-matter volume increased with age during adolescence among males, MTR values decreased, thus indicating a decrease in the amount of myelin in the unit of volume.[25] If not increases in myelin, what could be driving the observed increase in white-matter volume during male adolescence? Our tentative answer is that this may be due to changes in axonal caliber. The larger the caliber, the fewer axons fit in the same unit of the imaged volume, producing a relative decrease in the myelination index.[26] Although more work is needed to confirm this initial observation, it serves as a reminder that most of the MR sequences from which inferences are often drawn are not specific enough to interpret MR-based findings as reflecting a single neurobiological process, such as myelination.

Brain images and causality

The use of structural and functional neuroimaging provides a powerful tool for the study of brain maturation and cognitive development during adolescence. In addition to the need to keep in mind the many specific challenges associated with the interpretation of structural and functional findings discussed in the previous section, one also needs to be cautious about the general meaning of "brain images." In particular, we should not confuse a manifestation with a cause.

Observing a difference between children and adolescents in the size (or activation) of a particular structure simply points to a possible neural mechanism mediating the effect of age on a given behaviour; it is not the cause of this behaviour. For example, a stronger activation of the ventral *striatum* during the performance of a reward task by adolescents, as compared with adults, should not be interpreted as causing the adolescent's reward-seeking behaviour; it merely indicates possible age-related differences in the probability of engaging this structure during this particular task. In this sense, neuroimaging-based assessment should be treated in the same way, and at the same level, as any other quantitative phenotype describing cognitive, emotional, endocrine or physiological characteristics of an individual. To look for causes of a given behaviour and its higher or lower probability during adolescence, we need to turn our attention to the individual's environment and his/her genes.

Role of genes and environment in shaping the brain

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It is clear that both genes and experience influence many structural features of the human brain. In a special issue on genomic imaging, published by Human Brain Mapping,[27] a number of articles reported high heritability of regional volumes of grey matter estimated from twin studies carried out in adults, as well as in children and adolescents. At a single-gene level, several previous reports revealed differences between (adult) individuals with different allelic variations in brain morphology.[28,29]

Findings of genetic influences on brain morphology are often seen as the consequence of a direct effect of the genes on brain structure, perhaps occurring as early as in utero. But it is also possible, in fact quite likely, that these effects are mediated by the different level of functional engagement of given neural circuits in individuals with different genes and experiences. Several studies have confirmed that a repeated (functional) engagement of a particular neural circuit leads to changes in its structural properties, which can be detected in vivo with MR (e.g., in musicians;[30,31] London taxi drivers;[32] bilingual subjects;[33] initially inexperienced jugglers[34]). Although determining directionality of such structure-function relationships is impossible in the majority of current studies (with the exception of the juggler study), the existing animal experimental literature confirms the possibility of experience impacting brain structure.[35]

Overall, there is an increasing body of evidence that challenges a simple, deterministic view of genes influencing the brain directly and, in turn, the individual's behaviour. As indicated by a number of studies on the effect of experience on brain structure, MRI-derived anatomical measures may very well reflect a cumulative effect of the differential experience (behaviour) rather than the other way around. This point speaks directly to the issue of biological determinism. Quite often, we view developmental changes in brain structure as (biological) prerequisites of a particular cognitive ability. For example, the common logic assumes that cognitive/executive control of behaviour emerges in full only after the prefrontal reaches the adult-like level of structural maturity. But given the role of experience in shaping the brain, it might also be that high demands on cognitive control faced, for example, by young adolescents assuming adult roles due to family circumstances, may facilitate structural maturation of their prefrontal cortex. This scenario, if proven correct, will move us away from the passive view of brain development into one that emphasizes active role of the individual and his/her environment in modulating the "biological" (e.g., hormonal) developmental processes.

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Brain Maturation of Newborns and Infants

[1]Guido Gerig, PhD, [2]John H. Gilmore, MD, [2]Weili Lin, PhD

[1]Scientific Computing and Imaging Institute (SCI), University of Utah, USA

[2]Departments of Psychiatry and Radiology, University of North Carolina, USA

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Introduction

Recently, imaging studies of early human development have received more attention, as improved modeling methods might lead to a clearer understanding of the origin, timing, and nature of differences in neurodevelopmental disorders. Non-invasive*magnetic resonance imaging (MRI)* can provide three-dimensional images of the infant brain in less than 20 minutes, with unprecedented anatomical details and contrast of brain anatomy *cortical and subcortical* structures and brain connectivity.[1,2,3] Repeating MRI at different stages of development, e.g., in yearly intervals starting after birth, gives scientists the opportunity to study the trajectory of brain growth and compare individual growth trajectories to normative models. These comparisons become highly relevant in personalized medicine, where early diagnosis is a critical juncture for timing and therapy types.

Subject

Clinical research questions related to pediatric neuroimaging focus on a better understanding of the variability and plasticity of early development, as well as differences between typical and atypical growth trajectories. Likewise, other questions are essential to patient care: maturation delays, accelerated growth, atypical development eventually rejoining typical trajectories, possible effects in different timing of brain maturation, a better understanding of developmental processes in view of risks for mental illness, and possibilities for early diagnosis. Ultimately, improved understanding of dynamic brain-development processes in the healthy and the sick will lead to better preventative care and more options for treatment.

Problems

Infant neuroimaging poses multiple challenges related to subject preparation for imaging and choice of optimal scanning parameters, given the strong constraints on shortest possible imaging time (preferably limited to 15 and 20 minutes). As a general rule in early brain development

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studies, infants are not sedated, so the optimal preparation of subjects and parents is essential to achieve high-quality images that are not corrupted by subject motion.

Image analysis is concerned with extracting quantitative information from image data, which include volume measurements of brain and cerebrospinal fluid, but also more detailed measurements on subcortical structures and localized cortical regions. Due to significantly different brain shapes, sizes and tissue contrast properties between infants, research laboratories have developed specialized analysis software[4,5,6] to account for regional contrast changes in the rapidly growing brains.

Research Context

Advanced imaging and image-processing capabilities have honed visualization studies in infant-brain analysis and advanced our understanding of early brain growth.[7] Getting detailed quantitative information about the individual growth of brain structures and connectivity via quick, non-invasive brain scans will benefit early diagnosis, decisions about early intervention and subject management, and improved comparison between groups of healthy infants and infants with psychiatric disorders or neurological disease. Neuroimaging is thus becoming a new tool to provide in vivo measurements of detailed anatomical and functional properties throughout the first few years of human brain development – information that has, so far, only been available during post-mortem brain studies. Most importantly, the ability to image individual subjects over time results in growth trajectories of clinically relevant brain measurements. This is also a radically new development, and it enables new clinical research to study the dynamic process of the path of early development.

Key Research Questions

A key issue for advancing imaging science is the question of how to incorporate statistics with image data, which is the domain of computational anatomy. While we know how to analyze and compare standard measurements (e.g., height, weight, head circumference) and how to calculate longitudinal regression to predict the time-change of these features, extending similar statistics to image data requires significant future research efforts. Early success has been achieved by novel concepts that calculate the average 3D image based on a group of image data[8] and its extension to age regression,[9] resulting in a continuous model of brain images as a function of age. Similarly, longitudinal regression on shapes of brain structures has demonstrated how delayed or accelerated growth can be quantified.[10] This research is essential to answer questions

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about brain development in healthy infants and deviations thereof in the presence of illness. By examining changes of brain anatomy and white-matter connectivity, novel methodologies have examined the maturation of brain white-matter via longitudinal analysis of fibre tracts, structures that are closely correlated with the development of cognitive function.[11]

Recent Research Results

A study of 84 children at 2-4 weeks, 35 at 1 year, and 26 at 2 years of age[12] showed that total brain volume increased 101% in the first year, followed by a 15% increase in the second year. The major growth in the first year was attributed to gray matter (149%) and to a lesser extent, white matter (11%). The cerebellar volume increased 240% in the first year, whereas cerebral hemispheres increased by 90%. Such descriptive analysis of first- and second-year growth patterns will lead to significantly improved insight into the timing and growth rates of brain structures that are closely associated with cognitive brain function.

In a similar neuroimaging analysis of neonates, including *monozygotic* (MZ) and *dizygotic* (DZ) twins, researchers found significant group differences in intracranial volume on neonatal MRIs, with DZ twins showing significantly greater discordance than MZ twins.[13] Structural equation modeling was used to estimate additive genetic, common environmental, and unique environmental effects on brain structure.[14] Heritability of intracranial volume was found as 0.73, with a higher value in white matter (0.85) and lower heritability in gray matter (0.56). By comparing these studies with existing studies of older children, we can begin to answer questions about the influence of the environment on the growth trajectories of infant brains.

By including risk factors for mental illness, researchers found that prenatal mild *ventriculomegaly* might predict abnormal early brain development in neonates[15] and serve as a symptom for neuropsychiatric disorders associated with ventricle enlargement. A similar study was conducted to identity structural brain abnormalities in the prenatal and neonatal periods associated with the genetic risks for schizophrenia.[16] Results showed no large abnormalities of neonates at risk and concluded that structural brain abnormalities arise during postnatal brain development.

These studies demonstrate the importance of neuroimaging and image analysis to assess brain development differences between specific age groups, as well as the need to extend *cross-sectional studies to longitudinal data analysis*. This includes information on the early development of individual subjects.

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Research Gaps

Whereas progress in advanced neuroimaging and image-analysis methodology is advancing rapidly, there are significant gaps in understanding the relationship between observed imaging data and the underlying neurobiology and function of the human brain. Researchers can measure and provide more data than we can currently understand, and new bioinformatics and statistical methodologies are required to better grasp what information is most relevant to patient care. Measurements include data as heterogeneous as image data, genetic information, behavioural scores, family history, blood tests, and much more. This flood of data creates a significant translational gap between technological advances in data collection and its subsequent interpretation and comprehension.

Conclusions

The scientific community sees significant progress in neuroimaging technology related to studies of the developing brain. Whereas initial efforts were directed towards improved imaging for the specific age range of the first few years of life, current research focuses on longitudinal aspects of early brain growth. Repeated imaging across the age window of interest only became possible with new scanner technologies, which provide non-invasive imaging with short scan times while increasing spatial resolution and contrast. Extracting trajectories of brain growth, in addition to regular cognitive assessments, will give clinicians a clearer insight into individual brain maturation. A comparison of individual growth trajectories is significantly different from cross-sectional evaluation at specific time points, as longitudinal data analysis naturally incorporates the correlation of repeated measure, thereby preserving subtle temporal changes versus cross-sectional variability.

Implications for parents, services and policy

Progress in pediatric neuroimaging and associated image analysis will improve our understanding of healthy development and the eventual risk for mental illness and brain disorder. There is great hope that this additional information will lead to more accurate early diagnosis, so that optimal therapeutic intervention that can start as early as possible, with the aim to align an eventual atypical developmental path with a typical trajectory. Autism research,[17,18] for example, is one major clinical research area that has increased its effort to study early brain development. Following the practice of personalized medicine, individual treatment plans might be developed to optimally serve the patient. Non-invasive neuroimaging will therefore

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become an important instrument in gathering important information about the variability of human brain development, assessing individual growth patterns, and potentially defining structural correlates with critical periods of human cognitive development. Ultimately, early diagnosis and intervention might hopefully lead to improved patient management, successful prevention, and reduced health care costs.

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Interactions Between Brain Maturation and Experience in Driving Behavioural Development

Sarah Durston, PhD

Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Netherlands

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Introduction

Childhood is a time when the brain undergoes significant change. Intuitively, many people would expect brain development to involve linear increases in size with age. However, this is not the case. Brain development encompasses individual developmental trajectories for different brain areas, with both increases and decreases in size over time. For example, cortical gray matter typically shows a peak in volume during adolescence, whereas white matter continues to show linear increases in volume over this period. The age at which the peak thickness occurs varies across the cortex, with *cortical regions* supporting primary functions, such as motor and sensory systems, maturing first and higher-order association areas, such as the *prefrontal cortex* maturing last.[1] Subcortical structures that are *phylogenetically* older than cortex also show differential developmental trajectories. For example, *striatum* shows peak volume in middle childhood.[2] *Magnetic Resonance Imaging (MRI)* lacks the spatial resolution to inform us on what the cellular underpinnings of these volumetric changes are, but some have speculated that they may reflect events at the neural level, such as increases in the number of connections between brain areas and the pruning of underused connections and nerve cells.[3]

To understand the role of brain maturation in behavioural development, it is key to relate these anatomical changes to changes in behaviour. For example, peak volumes of striatum may be linked to sensitive periods for motor learning, as these also occur in middle childhood.[2] Such temporal coincidences between brain and behavioural maturation make it tempting to conclude that there are causal relationships between brain and behavioural development. Such conclusions are supported by reports of correlations between developmental changes in the brain and cognitive measures, where these relationships hold across individuals. For example, Sowell and colleagues[4] showed an association between prefrontal lobe structural maturation and memory function. Similar associations have been reported between prefrontal volume and measures of behavioural control.[5] While such studies do suggest that functional changes in the brain during development are reflected in anatomical changes, they do not inform us of the directionality or causality of such relationships. What is driving the correlation between brain

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structure and function? In addition to using MRI to investigate brain structure, *functional Magnetic Resonance Imaging (fMRI)* techniques are now available that allow investigators to study brain activity during cognitive tasks or rest. Activity is usually assessed by contrasting a baseline condition with a task condition of interest.

Subject

Understanding brain development – and in particular its relationship to behavioural development – is important for constraining our understanding of what children are capable of at different stages of development. For example, the protracted development of prefrontal cortex has been linked to relatively protracted development of behavioural control, whereas subcortical areas in striatum mature more rapidly. This may be related to impulsive and reward-seeking behaviour in adolescence.[6] Furthermore, understanding typical brain development is relevant to understanding developmental changes from typical in child neuropsychiatric disorders, such as attention-deficit hyperactivity disorder (ADHD). Here, imaging studies have consistently suggested that changes in cognition are related to changes in volume and activity of prefrontal cortex, related to poor development of behavioural control.[7] Furthermore, it has been suggested that the attenuation of ADHD symptoms with development in some affected individuals may be related in to normalization of cortical development in key areas.[8]

Problem

Perhaps the biggest challenge in studying brain development is addressing what is driving it. While clearly there is an interaction between environmental factors (e.g., learning and experience) and changes in brain structure and functioning, it is hard to tease these interactions apart. This represents a classic chicken-and-egg problem in whether it is brain maturation that supports behavioural development or whether the brain is maturing under the influence of cumulative behavioural experience. Currently, most investigators would probably argue that it is both. However, to be able to provide a comprehensive answer and to understand the mechanisms at work, we need to tease these processes apart.

Research Context

This question is being addressed by several research groups worldwide, often using non-invasive imaging techniques, such as MRI. This technique can be used to produce structural images of the brain for anatomical studies, where the size or shape of brain areas can be assessed. In fMRI,

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blood oxygenation level is assessed allowing for an in-vivo measure of brain activity. A relatively new Magnetic Resonance (MR) technique that is being used increasingly is *Diffusion Tensor Imaging (DTI)*. This technique can detect changes in white matter microstructure based on properties of diffusion of water in the brain.[9] All three of these MR techniques are particularly suited to studying development and/or effects of experience on the brain, as they are noninvasive. Individuals can be scanned repeatedly in the course of several days or several years, allowing for tracking of brain changes over time.

Key Research Question

The key research question in this area is how experience and brain maturation interact in driving behavioural development.

Recent Research Results

One example of how imaging techniques can be applied to linking brain maturation to behaviour in development comes from Galvan and colleagues. They took a correlational approach to investigating reward-seeking behaviour in adolescence using functional imaging. This behaviour is supported by structures in striatum (notably the *nucleus accumbens*) that are controlled by top-down prefrontal systems. Striatum is phylogenetically older and shows a developmental peak volume around age 7 years, while prefrontal cortex is known to develop relatively late, with a peak volume at the end of adolescence/early adulthood. In adolescents, the earlier maturing striatum showed a pattern of activation similar to adults, whereas later maturing prefrontal regions looked more similar to children, suggesting that increased reward-seeking behaviour in adolescence is related to differential developmental trajectories of the regions underling this behaviour.[10] While this example informs us of how brain and behavioural maturation go together, it does not yet address how experience comes to play in these processes.

A recent example of the impact of experience-driven learning in adulthood comes from Klingberg. It is established that working memory is supported by the *frontal-parietal cortical network*.[11] Recently, these authors showed that– in addition to changes in cortical structure– working memory training is associated with changes at a molecular level: Training changed the binding of dopamine (a neurotransmitter that modulates working memory) to its receptors in key cortical areas.[12] Such findings are exciting as they hold the promise of informing us on how changes at an anatomical level seen using MRI are supported at the molecular level. However, further technical advances are needed before such effects can be investigated in development: Dopamine receptors cannot yet be visualized using MR techniques. Therefore studies such as

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this one make use of radioactive *ligands* (in this case, one that binds to the relevant dopamine receptor), meaning that they cannot be conducted with children and that the number of scans that can be collected within a given time frame is limited.

Research Gaps

The interplay between brain and behavioural development is a topic of interest and much progress has been made in recent years. However, much of this work has been based on cross-sectional comparisons of individuals at different ages. There is a relative lack of longitudinal imaging studies addressing brain changes within individuals, although this is being addressed by a number of comprehensive studies worldwide (see[13] for a review). One exception is the work by Giedd, Rapoport and colleagues at the National Institute of Mental Health. This group has collected thousands of longitudinal anatomical MRI-scans from both typically and not-typically developing children and adolescents.[14] Furthermore, there has been significant progress on experience-driven brain changes in adults. However, relatively little work has addressed the interplay between experience and brain maturation directly by using imaging techniques in training studies in developing children.

Conclusions

The interactions between experience-driven changes and maturational changes in brain development are complex. Brain maturation is characterized by both progressive and regressive events and these changes are related to changes seen at the behavioural level. However, to date these relationships have often been classified using correlations. While this can inform us on the relationship between brain and behaviour indirectly, it does not provide information on the directionality of these relationships: Is brain maturation driving behavioural development or is it the reverse? Or is it more complex, with each driving the other? While initiatives to investigate childhood brain development within the same individuals are underway, few studies have yet addressed the impact of experience on these changes. As such, our understanding of the relationship between these various aspects of development is still incomplete.

Implications for Parents, Services and Policy

Brain development is an ongoing process that continues throughout childhood and adolescence. It is likely driven by innate factors and by experience. Furthermore, the reverse also appears to be true: brain maturation drives experience and the impact that experiences have on the

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developing child. However, the mechanisms by which this occurs are not fully understood. Nor is it established whether they apply equally at all stages of development. Research efforts using neuroimaging techniques are addressing trajectories of brain development in typical and atypical populations. Similarly, work with adult samples is addressing how experience shapes the brain. However, work investigating the impact of experience on brain maturation during development and vice versa is still scarce. One important implication of this is that generalizations from work in adults and on typical brain maturation should be viewed with caution, as the full complexity of the issue cannot yet be understood.

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Adolescent Brain Maturation

Jay N. Giedd, MD

Child Psychiatry Branch, National Institute of Mental Health, USA

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Introduction

The teen years have long been noted as a time of dramatic changes in body and behaviour. Insight into the neurobiology underlying these cognitive and behaviour changes has been greatly enhanced by the advent of *magnetic resonance imaging (MRI)*, which allows safe and unprecedented access to the anatomy and physiology of the living brain. Longitudinal MRI studies are beginning to map out the developmental trajectories of brain maturation and to explore the genetic and environmental influences on these trajectories in health and illness.

Subject

Most teenagers successfully navigate the transition from the dependency of childhood to the self-sufficiency of adulthood. However, adolescence may also be a time of substantial turmoil and, for some, the emergence of psychopathology. Understanding the course, mechanisms and influences of adolescent brain maturation may illuminate the path to more effective interventions for illnesses and to the optimization of healthy development.

Problems

Although adolescence is a time when many major life decisions are made and societies grant broader freedoms and responsibilities, surprisingly little research has been done to explore how changes in cognition, emotion and behaviour affect the decision-making processes. Adolescence is also the most common time for the onset of several classes of psychiatric illnesses including anxiety and mood disorders, psychosis, eating disorders, personality disorders and substance abuse. Even though the risk for somatic illnesses such as cancer or heart disease is relatively low, mortality increases from childhood rates with motor vehicle accidents the leading cause of death.

Research Context

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In recent years adolescent neuroscience research has been bolstered by ever-increasing advances in the fields of *neuroimaging* and genetics. Because MRI does not use ionizing radiation it allows not only the scanning of healthy children and adolescents but of repeated scanning throughout the course of development. This longitudinal data regarding the anatomy and physiology of the brain can be integrated with genetic, environmental, cognitive, emotional and behavioural assessments to explore the mechanisms and influences of healthy and unhealthy development.

Key Research Questions

As the goal of characterizing the general trajectories of brain maturation has progressed, research has begun to focus on elucidating: (1) the mechanisms giving rise to anatomical and physiological changes; (2) the relationship between neuroimaging measures and the cognitive, behavioural and emotional changes seen in adolescence; (3) the role of genetic and environmental influences; (4) how and when the developmental trajectories differ between healthy and clinical populations; and (5) what interventions may best optimize healthy development, enhance education, prevent psychopathology and treat disorders in age-appropriate ways if they do happen.

Recent Research Results

Longitudinal studies of subjects from ages 3 to 30 have shown that white matter volumes continue to increase until well into the third decade of life, while gray matter volumes rise and then fall, peaking at a characteristic time during childhood and adolescence which is specific for each brain region. These changes underlie a general pattern of functional and structural increases in connectivity and integrative processing, and a changing balance between *limbic subcortical* and *frontal lobe* functions that extend well into young adulthood.

One of the tenets emerging from a cumulative body of research is that in neuroimaging, as in life, the journey is often as important as the destination. Assessing the trajectories (i.e., size by age) of neuroimaging measures has shown to be more discriminative than static measures in studies examining male/female differences, linking neuroimaging measures to cognitive abilities, discriminating healthy from clinical populations, and characterizing heritability of brain anatomy.[1] For instance, males and females have differently shaped trajectories, with females tending to reach peak volumes of gray and white matter earlier than males.[2] Regarding brain/cognitive ability correlates, individuals with a very high IQ have differently-shaped trajectories of cortical thickness than individuals with a normal range IQ, with key brain regions

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actually starting with thinner cortex, but then growing more rapidly to end up at a similar final value.[3] Diagnostically, in Attention-Deficit/Hyperactivity Disorder versus healthy controls, the delay in cortical maturation predicts clinical status better than the final size.[4] Also, twin studies examining the relative contributions of interacting genetic and environmental factors indicate a robust effect of age on heritability of neuroimaging measures.[5] For example, brain regions associated with primary and motor sensory functions appear to be most strongly affected by genetic factors early and by environmental factors later in development, while areas associated with more complex functions such as language become more heritable with time. These findings may imply that different brain regions may be more susceptible to environmental interventions at some times than others.

Research Gaps

Although there is a trend toward an increasing number of people, training programs, journals and funding directed toward research of adolescent neurobiology, historically it has been relatively understudied.

One aspect of adolescent decision making that has been targeted for future research is to characterize the distinctions between traditional laboratory assessment done with subjects acting alone in low-stress testing environments with hypothetical scenarios (i.e. “cold” cognition) versus real-world decision making which often occurs in group settings with peer pressure, high-conflict/high-stress situations and actual consequences (i.e. “hot” cognition).

Another research challenge is to deepen our understanding of the relationship between neuroimaging findings and specific cognitive abilities or psychological characteristics. As mental functions arise from the activity of distributed neural networks, the practice of attempting to correlate the size of any single structure with a particular ability is giving way to the recognition of the need to understand the complex relationships amongst different nodes of the networks. Mathematical approaches such as graph theory are beginning to be used to explore the network properties of the brain.

Conclusions

A fundamental aspect of adolescent brain maturation is that it is a time of dramatic change. This changeability or “plasticity” has served our species well, allowing us to adapt to the unique challenges of our environment at a time when we leave the protection of our natal families to become self sufficient members of the community. The plasticity of the human adolescent brain

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makes adolescence a time of great risk and great opportunity.

White matter increases, *functional magnetic resonance imaging (fMRI)* studies showing greater correlation across disparate regions on certain tasks, and *electroencephalogram (EEG)* changes in coherence support a notion of increased "connectedness" among brain subcomponents during adolescence and into adulthood. *Inverted U gray matter* changes may reflect the brain's increasing refinement for specialization, driven by the demands of the environment – although much work remains to assess this speculation. Studies of twins, male/female differences, specific genes, environmental effects, and psychopathology are underway to examine influences on trajectories of brain development.

Implications for Parents, Services and Policy

Of the neuroimaging findings, the finding that the prefrontal cortex (a critical component of networks involved in judgment, decision making and impulse control) continues to mature into a person's mid 20s, has most prominently entered discourse, affecting social, legislative, judicial, parenting and educational realms. Despite the temptation to trade the complexity and ambiguity of human behaviour for the clarity and aesthetic beauty of colorful brain images, we must be careful not to over-interpret neuroimaging findings as they relate to public policy. Age-of-consent questions are particularly enmeshed in political and social contexts. For example, currently in the United States a person must be at least 15 to 17 years old (depending on the state) to drive, at least 18 to vote, buy cigarettes or be in the military, and at least 21 to drink alcohol. The minimum age for holding political office varies as well: some municipalities allow mayors as young as 16, and the minimum age for governors ranges from 18 to 30. On the national level, 25 is the minimum age to be a member of the U.S. House of Representatives, and 35 to be a senator or the President. The age of consent to sexual relations varies worldwide from puberty (with no specific age attached) to age 18. Clearly, these demarcations reflect strong societal influences and do not pinpoint a biological "age of maturation." The optimal use of advances in understanding of adolescent brain maturation will require an integrated effort involving parents, legislators, educators, neuroscientists, clinicians and the teens themselves.

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Auditory Perception and Early Brain Development

Minna Huotilainen, PhD, Risto Näätänen, PhD

University of Helsinki, Finland

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Introduction

Auditory perception begins before birth.[1] During development, the human brain becomes a highly-specialized system for the perceptual, memory and semantic functions required for understanding and producing language and enjoying music. The milestones of this step-by-step development have their underpinnings in neural development and are strongly related to the auditory exposure and communicative actions in childhood.

Subject

Several skills for speech and music perception are present in the infant brain as early as birth.[2] Already the newborn brain can recognize familiar voices and tunes from the foetal period. Also, neonates learn new sounds quickly and pay a lot of attention to combining visual and auditory information. They are interested in matching what they hear with what they see. Soon they learn the correspondences between certain phonemes and their sounds, and the way lips, tongue and larynx move to produce them. Some speech and music perception skills have developed during the foetal period, whereas others are more “hard-wired.” During the first few years, auditory perception becomes so accurate and efficient that it allows the understanding of fast speech even in noisy conditions, the enjoyment of music and the fine-grained retrieval of information from environmental sounds.[3]

Problems

Without brain research methods, it would be very difficult to determine perceptual and memory skills in infants. Most research methods currently permit the use of only very simple behavioural paradigms comparing two short sound patterns, but research is moving towards more ecological paradigms. A major problem in using behavioural methods is that results depend not only on the perceptual and memory skills of the child but also his/her motivational and arousal state.

Research Context

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The tradition in cognitive brain research is moving towards more ecologically valid research paradigms that use natural words and speech. *Event-related potentials (ERPs)*,[4] extracted from the *electroencephalogram (EEG)*, provide millisecond-accurate information on brain processes underlying auditory perception and memory functions (i.e., recognizing voices, phonemes, remembering sound patterns, finding similarities between sounds), whereas *functional magnetic resonance imaging (fMRI)*[5] provides a good spatial resolution on the areas involved in perceptual tasks in infants and children. The mismatch negativity (MMN),[6,7,8] especially when recorded in the new, efficient paradigms like the multi-feature paradigm,[9,10,11] is a key tool in the field of ERP research since it currently provides a measure of the perceptual accuracy for all most important acoustic parameters such as frequency, intensity, duration, temporal structure and sound-source location.[10,11] Furthermore, for speech sounds, parameters like vowel or consonant identity, pitch of speaking voice, among others, can also be studied.[11] In addition, this type of paradigm is currently being developed in order to determine the capabilities for perceiving different aspects of natural speech and musical sounds which can also be used in infants. If problems in speech perception are observed in infancy, some experimental training methods are available for strengthening the perceptive skills. In future, very early speech perception training methods may become part of the standard care of these infants.

Key Research Questions

What are the developmental milestones related to auditory perception and memory? What are the neural correspondents of these milestones? What is the role of auditory exposure in auditory development? Can the early auditory perception problems of a child that possibly lead to problems like dyslexia or delayed speech be observed with brain measurements? What are the countermeasures available when such problems are observed? Currently, research is focused on both understanding the underlying mechanisms of auditory perception in the infant brain and applying this information to understand speech perception problems in individual infants and children and to show results of different training methods.

Recent Research Results

Recent results from studies with healthy individuals revealed that the newborn brain is surprisingly skilled in detecting sounds, differences in sound features, even regularities in the auditory environment.[12] Recent results from applied studies show that there are clear deficiencies, in particular in the MMN response, already in newborns and in young infants when they are born prematurely,[13] have an elevated risk for dyslexia,[14] or have suffered from metabolic problems during pregnancy.[15] In some infants, the brain responses related to detecting changes

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in speech sound duration or change of phoneme are very weak or non-existent. This means that the automatic mechanisms detecting speech sound changes in a healthy infant brain are not functioning as usual, making the detection of speech sounds compromised.

Research Gaps

Currently, several ideas exist for the very early remediation of problems in speech perception and language acquisition. These methods often utilize passive learning (i.e., learning from tapes or from speaking toys etc.). We need scientific evidence as to whether and how these methods work and which of them would be most optimal.

Conclusions and Implications

The auditory system is under fast development in the foetal and neonatal brain. It is important to guide this development towards its natural direction. This is ensured by providing the infant and child with an auditory environment that is safe from strong or continuous noises and includes a lot of child-directed speech and music, especially singing. Background speech or music, for example from the television, has not been found to foster the linguistic development of a child; speech and music need to be directed to the child in a live situation and in a communicative manner. Even babies can engage themselves in communication. Babies are very fast learners. Communication between babies and older children is very effective for speech learning.

The auditory system is especially vulnerable after a premature birth. For these infants, a quiet environment with infant-directed speech and singing, paced according to the infant's individual schedule should be provided, if possible, even during the intensive care period.

Infants learn to produce phonemes by trial and error, by listening and looking at the speaker. For speech learning, it is important that the infant and the speaker are in eye contact. The duration of eye contact is determined by the child or infant and it depends on the infant's age starting from just a few seconds.

It is essential that children who have problems learning to speak, have a quiet background when listening to speech.

Shared attention is vital for speech learning. Adults should actively search for shared moments of attention with infants. When the infant is pointing at an object and the adult pronounces the name of the object a few times, the infant will learn the name very quickly.

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Using Electroencephalography (EEG) to Measure Maturation of Auditory Cortex in Infants: Processing Pitch, Duration and Sound Location

Laurel J. Trainor, PhD

McMaster University, Canada

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Introduction

The auditory system serves three main functions: identifying and locating objects, perceiving music, and understanding language. All of these rely on efficient processing of basic sound features. *Electroencephalography (EEG)* can be used to measure, for example, how auditory cortex processes pitch, fine temporal differences and sound location in infants. In particular, the brain's response to a sound event (the *event-related potential or ERP*) changes across age in morphology (i.e., what positive and negative peaks are present at which recording sites on the scalp) and in the amplitude and latency of the peaks present.[1] ERPs can also be analyzed developmentally in the frequency domain in terms of changes across age in phase-locked and non-phase-locked activity in different frequency bands such as alpha, beta and gamma.[2,3] Many factors likely contribute to these changes. Processes such as waves of *myelination*, *synaptic proliferation*, *synaptic pruning*, and the presence and amounts of various *neurotransmittors* are largely under genetic control.[4,5] These processes enable the development of more efficient circuits for processing auditory features. At the same time, the details of the networks formed are largely affected by experiential factors, such that synaptic connections receiving concurrent input are strengthened while others are weakened or eliminated. Thus, specific experience with sounds with pitch, with sound containing fine timing differences, and with sound from different spatial locations all affect auditory development. At a higher level, the specific musical system and language to which the infant or child is exposed also contribute substantially to auditory maturation, enabling efficient processing of certain musical pitch systems, rhythmic structures and phonemic categories.[6] Here we outline the dramatic changes seen in ERPs during development and indicate how these changes could be used as diagnostic indicators of early abnormal auditory development.

Subject

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Basic auditory abilities are crucial for the linguistic and music acquisition that will enable communication and healthy social and emotional development. Auditory ERPs derived from EEG recordings in response to sound can track the development of auditory processing. Here we describe what is known about the normal development of ERP responses to basic auditory features, how they change with age, and how they are affected by musical experience. Auditory ERPs could be used as a diagnostic indicator of early abnormal central auditory development.

Problems

Diagnosing auditory processing difficulties early in development would be very useful as the earlier problems are identified, the greater the chance for successful remediation. Currently, hearing thresholds can be established with the *auditory brainstem response (ABR)* in newborns[7] and with behavioural measures such as *conditioned head turn* in older infants.[8] However, ABR does not give information about processing sound features such as pitch, duration and sound location, and it also does not address cortical sound processing. Behavioural measures are limited in that they typically do not have the power and experimental control to give reliable information about individual infants. Due to movement constraints and the noise of the scanner, functional Magnetic Resonance Imaging (fMRI) is very difficult to run with infants and young children. Thus, ERPs derived from EEG recordings are a method of choice for examining early auditory development and the maturation of auditory cortex.

Research Context

In adults, the presentation of a sound results in a series of obligatory evoked potentials (EPs) that originate in auditory areas. Because auditory cortex is located around the *Sylvian fissure*, synchronous depolarizations of neurons whose axons span cortical layers tend to create electrical fields at the scalp with opposite polarity at frontal and occipital sites. The series of EPs include the P1 (first frontally positive potential) around 50 ms after stimulus onset, the N1 around 100 ms and the P2 around 180 ms. Attention to the stimulus and performing a stimulus-related task result in further EP components. One other obligatory or preattentive component is the *mismatch negativity (MMN)*. MMN is elicited in an *oddball paradigm* in which repeated (standard) sounds (or tokens from a category) are occasionally replaced with a different (deviant) sound (or token from a different category).[9] The deviant sound elicits an additional negativity between 150 and 250 ms after its onset. MMN is of particular interest as it is thought to reflect an automatic change detection mechanism.

Key Research Questions

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What are the developmental trajectories for the P1, N1, P2 and MMN? Is their development affected by experience? Can the maturation of auditory cortex be determined by measuring ERPs to sound?

Recent Research Results

Despite the fact that N1 and P2 are obligatory responses in adults, they are not seen clearly in children until after 4 years of age in response to music tones and sine tones.[10,11] Interestingly, N1 and P2 increase in amplitude and decrease in latency with age, reaching a maximum amplitude around ages 10 to 12. Amplitude decreases thereafter, reaching adult levels around 18 years of age. The developmental trajectory of N1 and P2 appear to be related to maturation of neural connections in layers II and upper III.[12] Data from human autopsies show that neurofilament expression, which enables fast transmission of neural signals, only begins to be expressed in these layers around 5 years of age, and does not reach adults levels until 12 years of age. The majority of connections to other cortical areas arise in these layers, suggesting that this protracted immaturity may be related to immature top-down processing or executive control of auditory perception. Interestingly, preschool children engaged in music lessons show N1 and P2 components equivalent to children 2 to 3 years older, suggesting that music lessons affect auditory executive control.[11]

Although N1 and P2 are difficult to measure in infants, MMN can be measured very early in development.[1,13] Interestingly, our research shows that in very young infants, occasional changes in the pitch, size of a temporal gap, or location of a sound result in an increase in the amplitude of a slow frontal positivity. This component is not present in adults. Some months after birth, an adult-like MMN (faster frontally negative component) emerges in the ERP. For simple pitch discrimination, MMN is present by 3 months,[14,15] but for hearing the pitch of the missing fundamental, MMN is not seen until 4 months,[16] and for hearing changes in a pitch pattern, the immature slow positive response remains at 6 months.[17] For detection of small silent gaps in a tone, the adult-like MMN emerges around 4 to 6 months.[18] Sound localization remains immature for a very long time, such that even by 8 months the slow positive response is still present, but not the adult-like MMN.[19] Thus, the age at which adult-like MMN emerges depends on the sound feature under investigation.

Research Gaps

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There are few studies in this area to date, so our knowledge of normal developmental trajectories is still quite limited. Furthermore, there are few studies concerning multisensory interactions and how they develop. One promising area of recent research is to examine the development of oscillatory activity through frequency analysis of EEG data. Early data suggest protracted developmental time courses for activity in beta and gamma frequencies, and effects of musical training.[2,3] Finally, in order to understand how the functional development of the auditory cortex is related to anatomical development, interfaces between human and animal studies will need to take place.

Conclusions

Auditory development and the maturation of auditory cortex can be examined for different sound features with event-related potentials (ERPs) derived from EEG recordings. Auditory cortex shows a very protracted developmental trajectory, with completely mature responses to simple sounds not achieved until about 18 years of age. At the same time, the brain's responses to occasional changes in a repeating auditory stimulus can be measured in very young infants. When adult-like ERP morphology for detecting sound changes emerges depends on the particular sound feature, with early emergence for pitch (3 months), later emergence for small temporal changes (4-6 months), and latest emergence for pitch patterns and sound localization (after 8 months).

Implications for Parents, Services and Policy

Early detection of central auditory processing problems (when hearing thresholds are normal) is critical because much language and musical acquisition takes place during infancy. ERPs derived from EEG offer the potential for identifying the age norms at which various developmental milestones are achieved. These could be used to assess whether individual infants are on a normal maturational trajectory.

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Visual Perception and Early Brain Development

Teresa Farroni, PhD, Enrica Menon, PhD

Dipartimentodi Psicologia dello Sviluppo e della Socializzazione, University of Padua, Italy
Centre for Brain and Cognitive Development, School of Psychology, Birkbeck College, University of London, United Kingdom

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Introduction

A significant part of our *cerebral cortex* is devoted mainly to visual processing. Vision provides information about our environment without the need for proximity involved in taste, touch and smell. Vision has an overriding importance in every aspect of our day-to day-lives.

Subject

Different brain areas, as well as different processes of perception, are responsible for particular visual functions, such as perception of movement, colour and depth. There are even specific brain regions that deal only with facial recognition or biological (i.e., non-object) movements, and others that process only object recognition. Localized brain damage affecting these regions can lead to specific disorders, such as prosopagnosia, in which the ability to recognize faces is lost, while object recognition is unaffected. Vision would therefore seem to be a good starting place for studying the functional manifestations of brain development.

Problems

It is difficult to determine whether changes in visual abilities during development are due to limitations in peripheral structures, such as the eye, lens and muscles, or whether they are due to changes within the brain. The perceptual capacities of young infants are clearly limited by immaturities in peripheral sensory systems (e.g., spatial acuity limited by the immature retina); the developing visual circuits may benefit by being protected from “information overload” caused by too many extraneous fine details.[1] However, the question remains: What is the major constraint on the development of perception?

Research Context

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Visual sensitivity is poor in newborn primates and develops gradually to adult levels during the early postnatal years. Numerous studies of visual development have described this process. Generally, contrast sensitivity and acuity, measured psychophysically, are mature by 5 to 6 years in humans and by 1 year in monkeys. Behavioural measurements show sensitivity and acuity improving together, but electrophysiological measurements suggest that the contrast sensitivity of neural elements may mature considerably sooner. [2,3,4,5]

Recent Research Results

In the last decades, there have been considerable advances in our understanding of the development of vision in the early years. It has become obvious that visual function includes various aspects that begin and mature at different times and that the visual system includes several *cortical* and *subcortical areas*, each with its own role in processing specific aspects of visual information.[6] The main breakthrough has been the ability to assess different aspects of visual function, such as acuity, visual fields or visual attention, longitudinally from the neonatal period.

This has allowed us to establish the onset and maturation of each of these aspects in normal infants, providing age-dependent normative data.[7] The combined use of *neuroimaging* and *electrophysiological* techniques has further helped to elucidate the correlation between different aspects of visual function and different areas of the brain, and to suggest possible mechanisms of maturation of visual function in normal children and in those with neonatal brain lesions. Several recent studies have provided evidence that normal development of vision depends on the integrity of a complex network which includes not only optic radiations and the *primary visual cortex* but also other cortical and subcortical areas, such as the *frontal* or *temporal lobes* or the *basal ganglia*, which are known to be associated with visual attention and with other aspects of visual function.[8]

Although the anatomy of several distinct routes from the retina to the brain had already been identified at the beginning of the 20th century,[9] the functional distinction between two separate systems, defining “where” an object is located and “what” it is, is the result of pioneering studies in the 50s and 60s, looking at the effect of brain stimulation and brain lesions. In the 70s, Bronson suggested a model for human visual development, in which newborn vision is mainly controlled at a subcortical level, with the cortex starting to mature at about 2 months postnatally.[10]

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The relevance of subcortical control has also been confirmed by imaging studies showing normal ability to fix and follow in infants who had extensive cortical occipital lesions.[11]

Other studies have subsequently confirmed that the cortex takes over executive control from subcortical modules and have also suggested that cortical function involves different streams processing specific aspects of visual information.[12] Each of these aspects becomes operational at different postnatal ages and interacts with subcortical circuits to form distinct modules.[13] In the 80s, a model of visual function was proposed, involving *dorsal* and *ventral streams*, two different *cortical pathways* assumed to process different visual information. While the dorsal stream is involved in localizing “where” an object is in the space, with the *parietal lobe* as the end point of this pathway, the ventral stream and temporal lobe are engaged in “what” an object is in terms of form, colour and face recognition.[14] Further support for this theory came from other studies on primates postulating that “where” and “what” responses are largely under cortical control, whereas subcortical structures are mainly engaged in “reflex” actions.[15] Other authors have suggested another model based on two anatomically distinct streams, named *parvocellular* and *magnocellular*. The two streams, morphologically distinct at ganglion cell and lateral geniculate nucleus levels, project to different parts of primary visual cortex, V1, and continue within independent cortical streams to the colour-specific area, V4, and to the motion-selective area, V5. While the parvocellular-based system is used for form and colour vision, the magnocellular system subserves movement perception and some aspects of stereoscopic vision.[16,17] More recently, Milner and Goodale[18] proposed a further version of these models, suggesting that one stream, the ventral, is used for perceptual processing, and one, the dorsal, for controlling actions.

While the ventral stream, containing specialized areas for face perception, was proposed as the “who” system, the dorsal stream, holding areas for managing eye movements, reaching and grasping, was suggested as the “how” system. In other words, one system is devoted to deciding what and who we are looking at, and the other one decides the appropriate responses and actions to be made.

In the early months of life, the visual system is still developing. From birth to complete maturity, the eye increases to three times its size at birth, and most of this growth is complete by age 3; one third of the eye's growth in diameter occurs in the first year of life. The following information gives indicators of normal visual development in young children from birth to 3 years and the relative brain functional implications.

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In a premature infant (depending on the extent of prematurity): The eyelids may not have fully separated; the iris may not constrict or dilate; the aqueous drainage system may not be fully functional; the choroid may lack pigment; retinal blood vessels may be immature; optic nerve fibres may not be myelinized; there may still be a pupillary membrane and/or a hyaloid system. Functional implications: lack of ability to control light entering the eye; visual system is not ready to function.

At birth: The pupils are not yet able to dilate fully; the curvature of the lens is nearly spherical; the retina (especially the macula) is not fully developed; the infant is moderately farsighted and has some degree of astigmatism. Functional implications: The newborn has poor fixation ability, very limited ability to discriminate colour, limited visual fields and an estimated visual acuity of somewhere between 20/200 and 20/400; because of the mainly subcortical orienting mechanisms, there is limited orienting to single targets from birth to 3 months; there is a preference for black and white designs, especially checkerboards and designs with angles.

By 3 months: Cortical control of eye/head movements starts to make the integration for attention switching possible; ventral and dorsal stream neural systems start to contribute together to the infant’s visual behaviour; ocular movements are coordinated most of the time; attraction is to both black and white and coloured (yellow and red) targets; the infant is capable of glancing at smaller targets (as small as 2.5 cm, or about 1 in.); visual attention and visual searching begin; the infant begins to associate visual stimuli with an event (e.g., the bottle and feeding).

By 5-6 months: The infant is able to look at (visually examine) an object in his/her own hands; ocular movement, although still uncoordinated at times, is smoother; the infant is visually aware of the environment ("explores" visually), and can shift gaze from near to far easily; the infant can "study" objects visually at near point and can converge the eyes to do so; can fixate at 1 m, or about 3 ft.; eye-hand coordination (reach) is usually achieved by now; the infant may be interested in watching falling objects and usually fixates on the point where the object disappears.

Between 6 and 9 months: Acuity improves rapidly (to near mature levels); the infant "explores" visually (examines objects in hands visually and watches activity in surroundings); can transfer objects from hand to hand and may be interested in geometric patterns.

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Between 9 months and 1 year: The child can visually spot a small (2-3 mm) object nearby; watches faces and tries to imitate expressions; searches for hidden objects after observing the "hiding"; is visually alert to new people, objects, surroundings; can differentiate between familiar and unfamiliar people; vision motivates and monitors movement toward a desired object.

By 2 years: Myelinization of the optic nerve is completed; there is vertical (upright) orientation; all optical skills are smooth and well coordinated; acuity is 20/20 to 20/30 (normal); the child can imitate movements, match same objects by single properties (colour, shape), and point to specific pictures in a book.

At 2-5 years of age: the child’s brain functions are characterized by nearly adult basic sensory processing abilities. However, further development of brain mechanisms for analyzing complex visual scenes, specific objects and faces will occur later. While basic understanding of the social world is good, further development in the ability to predict the intentions and goals of others will continue to occur.

By 3 years: Retinal tissue is mature; the child can complete a simple form board correctly (based on visual memory), do simple puzzles, draw a crude circle and put 2.5 cm (1 in.) pegs into holes.

By 5-7 years: It is known that the basic functions of early sensory areas of the cortex have completed their development; nevertheless, the functional development of brain substrates for perception of complex visual scenes takes still longer. These changes involve continuing myelinization of connections and changes in the density of synapses within the prefrontal cortex. Specifically, there is a spurt of synapse growth followed by a period of pruning around the time of puberty.

Conclusions

The contribution of peripheral system (retinal) development in the emergence of basic visual functions can only partially explain improvements in visual behaviour, indicating that brain changes are also important.

We can conclude that sensory experience from the external world can influence the way the brain wires itself up after birth; visual experience is crucial for a child's vision to develop normally—a "use it or lose it" situation; and that treatment of common childhood eye diseases

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should begin much earlier than standard practice dictates.

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Attention and Early Brain Development

[1]Kelly C. Roth, PhD Candidate, [2]Stefania Conte, PhD, [1]Greg D. Reynolds, PhD, [2]John E. Richards, PhD

[1]Department of Psychology, University of Tennessee, USA

[2]Department of Psychology, University of South Carolina, USA

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Introduction

Attention serves several functions related to information processing. It selects certain events or objects in the environment to focus on and maintains focus on the object of interest while information provided by that object is processed. Additionally, while attention is focused on one object, shifts in attention to distractors are inhibited. These aspects of attention show major developmental change throughout infancy.

Subject

In infants, attention is thought to change with age concurrently with changes in brain function. Models of attention in early development are based upon behavioural findings in human infants, integrated with findings on changes in brain function of non-human and human adults, or clinical populations.[1-7] Many of these models are influenced by Schiller's research[8] on eye movement systems in non-human primates. In infants from birth to two months of age, it is proposed that eye movements are primarily driven by a "reflexive system" largely under the influence of primitive brain areas located beneath the cerebral cortex (i.e., subcortical). Thus, eye movements and visual attention are generally reflexive in early infancy. Between three and six months of age, a voluntary orienting network becomes functionally mature. This network includes areas within the parietal and temporal cortices and the frontal eye fields and is involved in the ability to voluntarily shift visual attention from one stimulus to another.[9-11] From six months on, the anterior attention network (or executive attention system) becomes functional, as areas within the prefrontal cortex and the anterior cingulate cortex begin to play a significant role in maintaining visual attention while inhibiting shifts of attention to distractors.

Problems

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Traditionally, infant visual attention and brain development have been measured using looking time and eye tracking measures during “marker tasks”. These are behavioural tasks for which the brain areas involved have been firmly established, thus they can be used to indirectly study brain development in infants and children.[12] Instead, Richards and colleagues[13,14] suggest that integrating direct physiological measures of brain activity provides a fuller picture of the development of attention. Most of the major approaches to direct measurement of cortical activity (e.g., positron emission tomography, functional magnetic resonance imaging) cannot be used with human infant participants because of ethical and/or practical concerns. Both near infra-red spectroscopy (NIRS) and electroencephalography (EEG) can measure neural responses during cognitive tasks in pediatric populations. Moreover, source localization methods allow us to reconstruct the neural generators of the activity recorded on the scalp. We describe how these techniques can be applied to track the development of human infant brain activity.

Research Context

Infant attention is measured in the laboratory using looking time, heart rate, and the electroencephalogram (EEG).[15-18] Infant heart rate shows a sustained decrease during periods of attention, triggered by activity within the brain stem.[19] The EEG measures electrical activity that is produced in the brain with electrodes on the scalp. Event-related potentials (ERPs) are time-locked changes in EEG that are in response to a specific event or task. Source localization algorithms can be utilized to determine which brain areas are the likely sources of EEG/ERP electrical activity or NIRS blood oxygen level dependent (BOLD) response measured on the scalp.[16-18,20] This approach can provide a more direct measure of infant brain activity involved in attention.

Key Research Questions

The key research questions addressed by this line of work are what areas of the brain are involved in infant attention, whether the areas involved in attention change across the course of infant development and, whether electrophysiological measures of attention are consistent with behavioural measures of attention. Ultimately, all these questions relate to the need to learn more about brain-behaviour relations in infancy by focusing on the growing field of direct neurophysiological measures.

Recent Research Results

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In infant ERP research, a component labeled Negative central (Nc) is more active following salient stimuli and likely related to attention.[15,21,22] Reynolds and Richards[16] found areas of the brain involved in the Nc component are located within the prefrontal cortex and the anterior cingulate. Remember these are areas associated with the executive attention system. The Nc component increases in amplitude with age, indicating increased attention-related activity in the prefrontal cortex during infancy.[15,23,24] This parallels increased voluntary control of attention, demonstrating the Nc component can be used to index attentional engagement in the brain.[25] Infants generally prefer novel stimuli,[26] showing increased look durations and head turns to novel faces compared to familiar faces.[27] With stimulus repetition, the Nc component shows a decrease in amplitude.[28] For example, infants habituated to one category of faces show greater Nc amplitude to novel compared to familiar faces.[29] This sensitivity to faces is linked to heart rate defined attentional states. Infants show larger Nc amplitude during heart rate defined periods of attention when viewing faces compared to objects, and they show larger Nc amplitude overall during attentive states compared to inattentive states.[24,30] Taken together, these findings show consistency between behavioural, heart rate, and neural correlates (i.e., ERP and sources) of infant attention. Recently, EEG source analysis has been applied to the investigation of different attentional mechanisms[31-33] and face[24,30] and language[34,35] processing, suggesting the importance of the technique as an imaging modality to investigate neural development.

Research Gaps

Although the application of source analysis to infant ERP data represents a major step in measuring attention-related infant brain activity, there is still much room for progress. Source analysis models for pediatric populations are becoming more precise thanks to the realistic description of the head anatomy provided by structural MRIs. Age-appropriate MRI templates necessary for accurate source analysis studies[36] are made available in the Neurodevelopmental MRI Database.[37] These templates have been successfully used to reconstruct the neural generators of both EEG and NIRS signals during attentional tasks.[16,18,31–33,38] Further application of this approach should be done for a better understanding of the developmental changes in attention. Moreover, further progress must be made in designing new procedures to simultaneously measure behavioural and neural correlates of infant attention. Until these research gaps are addressed, our knowledge of infant brain activity and brain-behaviour relations will remain constrained by methodological limitations.

Conclusions

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There is a rich history of behavioural research on the development of attention in infancy. Additionally, several scientists working in the area have proposed models of infant brain development, integrating behavioural findings from infant research with research on brain development in animals and adults.[1-7] While many of the models may accurately describe the progression of infant brain development in relation to attention, at present the models remain untested because of methodological constraints. However, major progress has been made, and we now know that there is consistency between commonly used behavioural, heart rate, and electrophysiological correlates of infant attention.[15,17] We have made an initial step in identifying areas of the brain related to cognitive development by demonstrating that areas of the prefrontal cortex and the anterior cingulate are involved in infant attention.[16-18,30,31,33] Infant templates have also been developed, allowing us to move from using adult templates to interpret infant data.[37] New research can focus on specifics such as individual variability and neurodivergent populations now that we have a solid foundation in place.[39] We are confident that steady progress will continue in research on infant brain development and attention.

Implications

One of the major implications of research on infant attention relates to attention deficit hyperactivity disorder (ADHD). It is currently estimated that ADHD affects approximately 10% of school-aged children.[40] Symptoms of ADHD include poor control of attention, inattentiveness, hyperactivity, poor impulse control, and behaviour management problems. Evidence indicates that the inattentive aspect of ADHD may be related to deficits in the voluntary orienting network, whereas the hyperactive aspect of ADHD may be related to a poorly functioning executive attention system.[41,42] Children with ADHD show a delay in the development of cortical thickness[42] in the prefrontal cortex as well as altered functioning of executive attention and default mode networks.[43] These systems involve the prefrontal cortex and anterior cingulate, areas identified as sources of attention-related cortical activity in our research on infant attention.[16,17] ADHD is typically not apparent in affected children until the school years. These children may be referred to health-care professionals for problems controlling their behaviour in classroom settings. It would be ideal to have an earlier identification method for children at risk of developing ADHD. The promise of basic research on infant attention and brain development is the potential identification of atypical patterns of infant development that may predict later onset of ADHD.

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The Early Development of Visual-Spatial Attention

Susan E. Bryson, PhD

Dalhousie University and IWK Health Centre, Canada

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Introduction

Successful adaptation to our ever-changing world depends on our ability to move attention quickly in space. From very early in life, our ability to selectively orient or redirect attention allows us to connect with key others, to learn about and make sense of the world, and to regulate our emotional reactions.[1,2] As currently conceived, "spatial selectivity" is achieved through the component disengage, shift and engage operations of the posterior visual attention system.[3,4] In order to move attention in visual space and thereby optimize the quality of "new" visual input, the infant must first disengage from the current focus and then shift and engage attention at the new target location, bringing with it the processing resources of the visual system.

Subject

The posterior attention system and its spatially-selective component operations form part of a larger network of interconnected attention systems that are organized at distinct levels and mediated by different neural regions.[3,5] These include both a sub-cortical vigilance system, which maintains alertness and sustained attention, and an anterior (frontal) executive system, which exerts volitional (voluntary) control and recruits resources necessary for goal-directed behaviour. Toward the latter part of the first year of life, development of the *frontal cortex* allows the infant to increasingly exert volitional control over visual-spatial orienting.[6-8] Prior to this, the infant's attention is driven largely by external input, to which responses of the posterior attention system are relatively quick and automatic.

Relevance and Statement of the Problem

Given the fundamental importance of visual orienting to overall adaptation, research has focused on its early development in both typical and atypical populations. Development of the disengage operation is of particular interest because of its critical role, not only in virtually all forms of learning, but also in the regulation of emotion.[1] When over-aroused by novelty, unfamiliarity or excessive stimulation, infants regulate state by disengaging and moving their attention

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elsewhere.

Research Context and Key Research Questions

Evidence on the early development of the shift and disengage operations comes largely from a simple visual orienting task known as the "Gap task." In this task, the infant's attention is engaged on a centrally-located attractor stimulus, and then the time taken to initiate an eye movement (saccade) to onset of a second peripheral stimulus is measured. The critical distinction is whether the two stimuli overlap or not. Conditions under which a gap occurs provide a measure of the shift operation: offset of the attractor stimulus prior to onset of the peripheral stimulus serves to automatically disengage attention such that a shift alone is required. Conditions in which the two stimuli overlap (i.e., the two compete for attention) provide a measure of the disengage operation: attention must be disengaged first from the attractor stimulus before it can be shifted to the peripheral stimulus.

This task has been used to address a number of key research questions, notably:

1. When in development does the disengage operation become operative?
2. Is development of the disengage operation associated with infants being easier to soothe? and
3. Are disengage problems early in life predictive of autism, and associated with increased distress/irritability?

Recent Research Results

Typical development

Using variants of the Gap task, findings consistently indicate that the disengage operation becomes operative between 3 and 4 months of age[9-11] (also see[12] for evidence of development into early childhood). Overall, saccadic latencies (reaction times) to disengage and shift attention decrease from 1½-6 months of age. At all ages, responses are slower during the overlap (disengage) than the gap (shift) condition, although this effect is largest in the younger infants. Prior to age 4 months, infants are able to selectively focus their attention, but once engaged on a particular stimulus, they have difficulty disengaging and moving their attention elsewhere. Rather, they tend to fixate for prolonged periods, as captured by the terms "obligatory looking"[13] or "sticky fixation."[14]

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While the precise neural circuitry underlying development of the disengage operation remains to be elucidated, evidence of a major change during the first 3-4 months is thought to reflect the increasing influence of cortical input.[15,8,16] At the behavioural level, the ability to disengage attention is implicated in the development of various cognitive and social-cognitive milestones (e.g., back-and-forth looking, as required in discrimination leaning;[17] contingency learning;[10] and joint attention;[18,19] as well as the regulation of state.).[2] Indeed, in 4- to 6-month-olds, ease of disengaging attention is associated with less distress, more positive emotion and with infants being easier to soothe, as measured by parent reports on a temperament questionnaire.[20,10,11] Thus, consistent with the claims of Rothbart et al.,[2] disengagement or distraction appears to be a basic mechanism by which infants regulate their emotional states.

Atypical development

In related work using the Gap task, delays in development of the disengage operation have been documented in various high-risk groups, including infants with William's syndrome and those with frontal lobe injuries.[21,22] In autism and its related disorders (autistic spectrum disorders, or ASDs) – conditions defined by atypical social-communicative development and a lack of behavioural/cognitive flexibility[23] findings are particularly striking. Children with ASD are distinguished from developmentally-matched controls by long reaction times to disengage visual attention, as well as a preponderance of associated distress or avoidance behaviours (e.g., rapid and shallow breathing, gaze aversion and excessive mouthing).[18,24,25] Note further that in ASD the disengage problem persists into adulthood, and in adults, like children, the problem is particularly marked when moving attention to the left side of space.[26-30] Finally, in research on at-risk infants with an older sibling with ASD, disengage problems at 12 months are predictive of a later ASD diagnosis, and to a lesser extent are characteristic of the broader autistic phenotype (i.e., non-ASD cases) (Bryson SE et al., unpublished data, 2009).[31-33] Again, the ASD cases were distinguished by abnormally long left-directed disengage reaction times, and these were linked with parent-reported temperament, notably low reactivity, high irritability and reduced capacity to be soothed. Both the left-sided asymmetry in disengagement and its association with negative affect implicate right hemisphere dysfunction in ASD, which, given the age of onset of the problem (12 vs. 6 months), may be compromised by impoverished development of frontal/executive control (Bryson SE et al., unpublished data, 2009).

Conclusions, Research Gaps and Implications for Parents, Services and Policy

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To summarize, visual-spatial attention and its component disengage, shift and engage operations allow developing infants to selectively orient to key people and events, and to regulate their emotional reactions to incoming sensory information. Findings indicate that these operations develop early in life, and that they become increasingly under the control of the anterior attention system, thus allowing infants to exert volitional control in the face of incoming stimulation. Delayed development of the disengage operation is not restricted to but is particularly marked in children with ASD. Indeed, evidence for both the early emergence and stability of impaired disengagement suggests that this is a core dimension of the autistic phenotype.[34] Among the outstanding questions is whether and to what extent disengagement underlies other key features of development, including the development of joint attention and related social-communicative skills, as well as the ability to flexibly shift set and to process information at both a global and local level.[18,7,34,35]

At the more applied level, learning and adaptation in the typically-developing infant is made possible by the ability, from very early in life, to control attention and regulate states of emotional distress. Problems with disengagement, often expressed in infants as prolonged visual fixation, together with high levels of distress, are very worrisome and challenging for parents, and should be seen as flags that warrant referral. Early detection and appropriate treatment of these behavioural signs will go a long way in preventing the cascading negative effects so well documented in children with autism and related disorders.[36] Rather, we need to reduce distress and enhance states of positive affect in order to optimize learning and adaptation in all children.

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Memory and Early Brain Development

[1]Thanujeni Pathman, PhD, [2]Patricia J. Bauer, PhD

[1]York University, Canada; [2]Emory University, USA

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Introduction

Memory is a fundamental capacity that plays a vital role in social, emotional and cognitive functioning. Our memories form the basis for our sense of self, guide our thoughts and decisions, influence our emotional reactions, and allow us to learn. As such, memory is central to cognition and cognitive development. Yet, historically, it was believed that children under three or four years were unable to form stable representations of events and thus, were unable to remember them. This belief came in part from findings that adults rarely recall personal events from before the age of 3½ years (a phenomenon known as infantile or childhood amnesia). However, research with infants and young children has made it clear that they can and do form memories of events. This research, coupled with studies from behavioural neuroscience (using animal models) and developmental neuroscience (using electrophysiology and neuroimaging), has given us insights into the ways in which memory, and the brain structures that support it, change with development.

Subject

There are many ways to divide the construct of memory. For example, we distinguish working memory, which allows maintenance of representations for seconds, and long-term memory, which allows us to remember events over a life-time. Long-term memory can be further divided into two types: non-declarative (or implicit) and declarative (or explicit). Non-declarative memories are inaccessible to conscious awareness and include skill learning (e.g., knowing how to ride a bike) and priming (i.e., facilitated processing of a stimulus as a function of prior experience with it). Non-declarative memory is apparent virtually from birth. For example, infants show more robust processing of faces they have seen before relative to novel faces. However, when most people think of memory or “remembering” they think of declarative memories. Declarative memory requires conscious recollection and includes the recognition and recall of names, objects, and events. This chapter is a review of what we know about declarative

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memory development in typically developing infants, and the relations between declarative memory and brain development.

Problems

Studying the development of declarative memory and the brain areas that support it are challenging for various reasons. The first problem researchers face is how to reliably measure declarative memory in preverbal children. Traditional tests of declarative memory rely on verbal report, and so are better suited for older children and adults. Second, it is challenging to link behaviour with the brain. Researchers must determine whether the timing of changes in behaviour corresponds with the timing of changes in the brain. Last, researchers must make tests that measure behaviour and brain function sensitive to potential deficits.

Research Context

Infants and young children experience rapid brain development. When brain weight is examined from birth to old age, the largest change in the weight of the brain occurs in the first year of life.[1] However, not all parts of the brain develop at the same time[2] and there are slower developments in some regions. This is especially true for the areas of the brain that are implicated in declarative memory. The hippocampus, a brain structure in the medial temporal lobe necessary for the formation of declarative memories, is formed prenatally.[3,4] Yet the cells in the dentate gyrus of the hippocampus, an area that links the structure with cortical regions of the brain, do not appear adult-like until well after birth.[5,6] More subtle structural changes continue even in late childhood.[7] Another area of the brain implicated in memory function is the prefrontal cortex. The density of synapses in this area increases dramatically around eight months and peaks between 15 and 24 months.[8] Changes continue to occur after this period, until well into adolescence.[9,10] Overall, we see dramatic changes in the brain areas implicated in memory in the first two years of life.

Key Research Questions

1. How does long-term memory develop? What behavioural changes are seen in memory performance in infancy and early childhood?
2. How do changes in memory performance relate to postnatal changes in the brain?

Recent Research Results

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Researchers have used *elicited imitation* to assess declarative memory in preverbal children. In elicited imitation, infants are presented with novel objects and are shown how to use them to create short "events," such as making and ringing a bell. Immediately and/or after a delay, infants are given the opportunity to imitate the modeled actions. Memory is assessed by comparing the number of actions (individual actions and actions in correct temporal order) to the number of actions during baseline performance (before modeling).[11,12] Researchers have used this paradigm with infants as young as six months and have found that with age, infants remember for increasing lengths of time. For example, six-month-olds remember actions for 24 (but not 48) hours, nine-month-olds remember for one month (but not three months), and by 20 months of age, infants remember for as long as one year. In addition, with age the effect becomes increasingly reliable—a greater number of infants in each successive age group show evidence of recall (see reference 13[13] for review).

In general terms, the time course of improvements in memory with age (indexed behaviourally) is consistent with brain development. Late in the first year of life, the medial temporal lobe structures are functionally mature, and there are increases in the density of synapses in the prefrontal cortex. This corresponds to the improved recall abilities of infants near the end of the first year of life. Further improvements in the reliability of recall occur throughout the second year of life, corresponding to the continued increases in synapse formation in both the prefrontal cortex and dentate gyrus.[14]

Research Gaps

We have made a lot of progress in learning about memory and brain development in infancy, yet there is much we do not know. More information is needed on the time course of development of memory areas in the human brain. Although a lot of recent progress has been made, much information comes from animal models (rodents and nonhuman primates) and so it is unclear how precisely this time course would map onto human brain development. Further work in developmental neuroscience could help to fill this gap. Studies that relate behavioural measures of memory to brain activity are vital to a complete understanding of the development of declarative memory. An advance in this direction comes from research relating event-related potentials (ERPs, an electrophysiological technique that measures brain activity associated with specific stimuli) to the robustness of behavioural recall in infants.[15] Further work using this technique and neuroimaging techniques, spanning various ages and different types of memory measures, will be useful.

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Conclusions

The ability to form memories and remember them is a vital part of human experience. Historically, people believed that infants lacked this ability. The use of a nonverbal task has allowed researchers to challenge and disprove this assumption. Declarative memory is apparent in the first year of life, as evidenced by behaviour on nonverbal, imitation-based tasks. It develops substantially throughout the first and second years of life. The timing of improvements in performance corresponds to the timing of changes in the developing brain. For example, the rise in synapse production in brain areas implicated in memory roughly maps onto the ages at which we see improvements in recall. Research combining measures of neural processing (assessed via ERPs) and behaviour (assessed via imitation) promises to bring greater resolution to the question of relations between developments in brain and in behaviour. Further work is needed to better understand the development of the human brain and relate it to memory performance in infancy and beyond.

Implications

This research has theoretical and practical implications. First, the work will inform the adult memory literature—one cannot fully understand the mature end-state of a function without understanding its beginning. Moreover this research adds to the literature on infantile amnesia. Infants are able to form memories, even if as adults, they are unable to recall them. The work also has practical implications. Once we understand the typical development of the brain areas associated with memory and the typical recall abilities of infants, we can apply this knowledge to special populations who are at risk. For example, infants born to mothers with blood sugar control problems during pregnancy are more likely to have perinatal brain iron deficiency which may have deleterious consequences for the normal development of the hippocampus. These infants show deficits in delayed recall compared to control infants of the same age.[16] Other groups that show deficits in delayed recall are infants adopted from international orphanages and healthy preterm infants.[17] As we increase our understanding of the relations between brain and behaviour, we will be able to develop interventions to help infants and children in these at-risk groups.

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Stress and Early Brain Development

Megan R. Gunnar, PhD, Adriana Herrera, MA, Camelia E. Hostinar, BS

University of Minnesota, USA

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Introduction

Stress is a condition in which an individual experiences challenges to physical or emotional well-being that overwhelm their coping capacity. While some experience with manageable stress is important for healthy development, prolonged, uninterrupted, overwhelming stress can have toxic effects. This type of toxic stress is often associated with childhood abuse and neglect.

In the early years of life when the brain is developing rapidly it is particularly sensitive to environmental influences. Toxic early life stress (ELS) may induce persistent hyper-sensitivity to stressors and sensitization of neural circuits and other neurotransmitter systems which process threat information. These neurobiological sequelae of ELS may promote the development of short and long-term behavioural and emotional problems that may persist and increase the risk for psychopathology and physical health disorders into adulthood.[1,2]

Subject

Research has begun to identify the neural circuits, brain structures, and endocrine systems affected by ELS and their role in emergent psychopathology and medical problems. Multidisciplinary research in the areas of risk and resilience, developmental psychopathology, psychoneuroendocrinology, neuroscience, and molecular and behavioural genetics has elucidated factors that increase vulnerability to stressors and those which protect children from their deleterious effects. Understanding the mechanisms through which ELS “gets under the skin” should help us to identify intervention and prevention targets, thus having broad implications for policy and practice.

Problems

The stress response system involves the *sympathetic nervous system*, the various neurotransmitter systems, the immune system, and the *hypothalamic-pituitary adrenocortical*

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(HPA) axis.

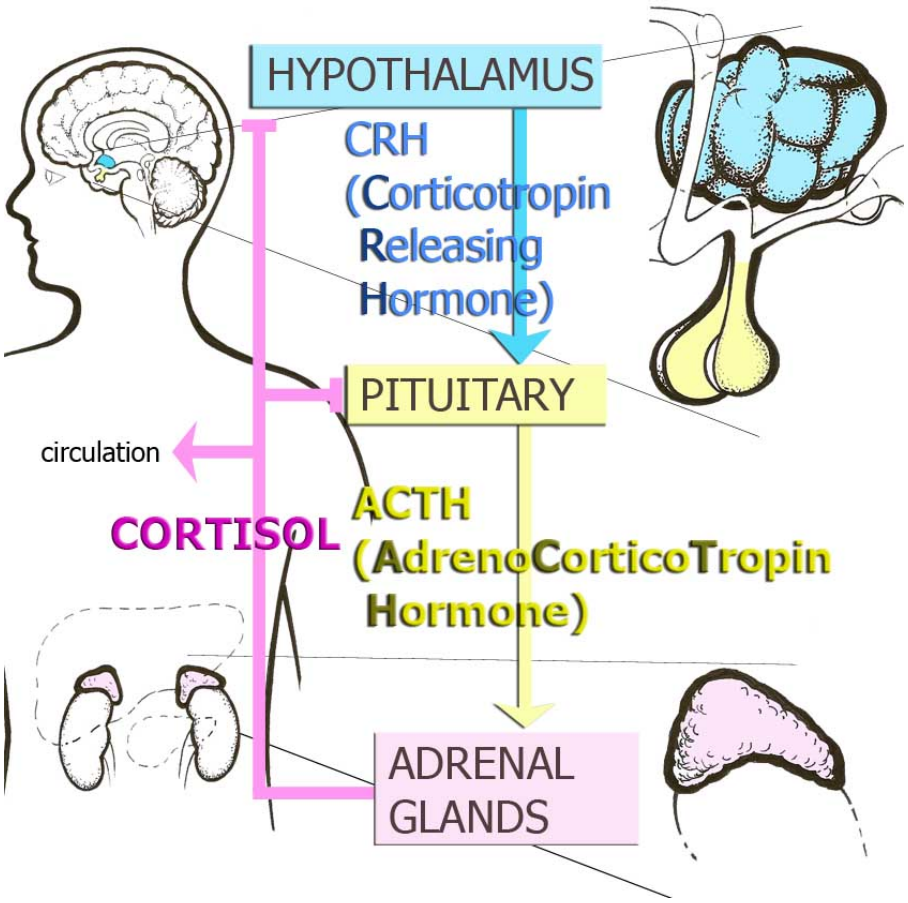


Figure 1. Hypothalamic-Pituitary Adrenocortical Axis or Stress Hormone Axis

The HPA axis maintains the organism's capacity to respond to acute and prolonged stressors and is a major focus of ELS research, as the brain is a major organ targeted by steroid hormones produced by this system. In response to a stressor, the HPA axis becomes activated and the hypothalamus and other brain regions release *corticotropin-releasing hormone (CRH)*.

CRH produced in the *amygdala*, a structure involved in orchestrating emotional responses, activates behavioural stress responses such as *fight/flight responses*, heightened vigilance, and defense-related learning and memory.[3] CRH produced in the *hypothalamus*, a structure involved in maintaining *homeostasis*, stimulates production of *adrenocorticotropin hormone (ACTH)* by the *pituitary gland*, which then signals the cortex of the *adrenal glands* to produce and release *cortisol (corticosterone in rodents)*. Cortisol facilitates adaptation and restores homeostasis through changing internal dynamics.

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One problem for researchers studying stress in children is that, although the chronic effects of stress are often revealed by measures of ACTH and CRH,[4] their measurement is invasive and not feasible with children.[5] Therefore, most researchers rely on samples of cortisol obtained in saliva, which imposes certain limitations in explicating the regulation and dysregulation of this system. Additionally, researchers must consider that other factors affect cortisol levels such as time of day, child age, sleep/wake cycles, and social context. Nonetheless, research on this neuroendocrine system has burgeoned because of the use of salivary cortisol measures.

Another critical challenge is the complex and multifaceted nature of stress in childhood. Researchers must consider: (1) the type(s) of stressors the child faces, their chronicity and severity, (2) the family environment, (3) psychological mechanisms of coping and defense, (4) individual differences in reactivity, (5) and developmental status. The pathway from stress to psychopathology and/or medical problems likely involves many environmental factors, which continuously interact with an individual's unique genetic code to shape HPA functioning and brain development.

Research Context

Examining the relationship between stress and brain development in humans relies on technology which has only recently become available, including imaging techniques to assess brain development and activity (e.g., structural and functional *MRI*, *MEG*, and so on), *electrophysiological* measures of brain activity, and more advanced and sophisticated techniques for measuring HPA axis functioning. These procedures have been used mostly in studies of the adult consequences of ELS. Only recently have researchers begun to examine the effects of ELS on child development. Here is where the scientific literature lags behind. Fortunately, animal models have played a critical role in helping researchers understand phenomena which has not yet been addressed or cannot be answered by studies of children. Findings in non-human primates and rodents[6-11] have provided a framework by which researchers can formulate testable theories on the psychological and neurobiological impacts of stress in humans.

Key Research Questions

1. What sources promote individual differences in how children respond to stressors?
2. Which genetic and environmental factors protect children against the deleterious effects of ELS thus promoting resilience?

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3. What are the long-term consequences of ELS and are they reversible?
4. What is the role of ELS in the development of psychopathology and medical health problems?

Recent Research Results

Research in humans increasingly suggests that *severe* early life stressors (e.g., trauma, maltreatment, neglect) may result in decreased brain volumes, dysregulation of the neuroendocrine stress response system, and *limbic dysfunction* involving regions such as the *hippocampus*, *medial prefrontal cortex*, and amygdala.[12-18] Consistent with these findings, animal studies of severe ELS yield evidence of inhibition of *neurogenesis*, disruption of *neuronal plasticity*, *neurotoxicity*, and abnormal *synaptic connectivity*. Sensitive periods and stages of enhanced *brain plasticity* are particularly vulnerable to the long-term effects of stress hormones and may result in altering the typical pathways and organization of the young brain. Research also suggests that severe ELS may have mental and physical consequences that last into adulthood, including increased risk of depression, anxiety, post-traumatic stress disorder, *metabolic syndrome*, and cardiovascular disease.[2,3,19-21]

Notably, research has revealed that the child's access to supportive, attentive, and sensitive adult care plays a salient role in buffering the activity of the HPA system and protecting the developing brain from potentially harmful effects of stressors.[2,22-24] Children within secure parent-child relationships learn that when faced with a stressor, they can experience distress, communicate their negative emotions, and effectively elicit aid from caregivers. It is likely that this sense of safety prevents activation of the HPA axis and other critical stress-mediating systems.[22-26]

A small body of emerging literature suggests that the negative effects of stress are not always irreversible. Interventions which enhance the economic and emotional support of children undergoing considerable stress have been shown to improve both behavioural and emotional adjustment, and normative regulation of the HPA axis.[27] Research has also found that behavioural therapy as well as drug therapy may bring about neurobiological changes in individuals suffering form the psychological effects of stress.[28] Furthermore, there is increasing evidence that some experience with stressors early in life, particularly experiences that enhance the child's capacity to cope effectively, may have *stress inoculation* effects. That is, they may decrease the reactivity of stress responsive neurobiological and neuroendocrine systems to stressors experienced later

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in life.[29,30]

Research Gaps

Most of the adult research on ELS relies on retrospective reports of ELS experiences. Prospective studies are needed to elucidate how the types of stressors children experience at different points in development impact the development of physiological and behavioural responses to subsequent challenges. Additionally, stress research has yet to elucidate the processes and mechanisms through which social support buffers against the harmful effects of stress. It is also unclear how childhood stress, in combination with concurrent psychopathology, differentially affects HPA axis regulation. Furthermore, neuroanatomical and neurophysiological studies are needed to more fully explicate ELS effects on specific brain structures and processes. Finally, although an active area of research, the field still lacks an adequate understanding of the genetic variations among children that moderate the reactivity, regulation, and impact of stress responses.

Conclusion

As children grow into mature adults, they will inevitably be faced with challenges, both predictable (e.g., beginning the first day of school) and unpredictable (e.g., the loss of a loved one). These challenges provide children with the opportunity to learn how to effectively manage stress, regulate emotions, and develop the social, behavioural, and cognitive coping resources needed to overcome these obstacles. The presence of sensitive and responsive caregivers can help equip children with the tools needed to handle stress in a healthy manner.

The early years of life constitute a particularly sensitive period during which chronic stress may lead to dysregulation of the stress system and may compromise brain development. Not all individuals are equally at-risk for developing neurobiological, behaviour and health consequences of ELS. It is likely that genetic factors, emotional and behavioural predispositions, stress history, social support, mental health status, age, and sex all play a role in stress reactivity and regulation. Tracing the pathways through which early adversity impacts later development is the key challenge for developmental stress research in the coming decade.

Implications

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Although we do not yet have a full understanding of the neurobiological and neuroendocrine processes through which ELS affects development, the present state of the science is sufficient to draw implications for policy and practice. Many of these implications are outlined in a working paper on stress and brain architecture produced by the National Scientific Council on the Developing Child and available on the council's website.[a,31] These implications include: (1) The need to strengthen a range of informal and formal services to support parents who are struggling to provide care for their children; (2) The need to make affordable expert assistance available to parents and early child care professionals to equip them with the knowledge and skills to help children who have symptoms of abnormal stress responding before these problems produce pathology; (3) The need to increase the availability of assessment and treatment for young children with serious stress-related mental health problems; (4) And, because parental substance abuse and mental illness are associated with increased risk of toxic stress exposures for young children, these conditions and the economic circumstances associated with them are a major public health problem needing significant public attention.

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Note:

[a] See also the National Scientific Council on Child Development Publications available at: http://www.developingchild.net/pubs/wp.html Accessed February 13, 2009.

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Childhood Trauma and Adult Stress Responsiveness

Christine Heim, PhD

Emory University, USA

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Introduction

The past decades have witnessed an increasing societal awareness of child maltreatment, such as abuse and neglect, which is now considered a public health problem of epidemic dimensions.[1] In addition, large numbers of children experience the loss of a parent or live with a mentally ill parent who is likely unable to provide continuous or adequate parental care. Compelling evidence suggests that childhood trauma is a major risk factor for the development of mood and anxiety disorders as well as certain medical diseases, including heart disease and disorders such as chronic fatigue and pain syndromes.[2] In adulthood, these disorders often manifest or worsen in relation to acute or chronic life stresses and, importantly, persons with childhood stress experience appear to be sensitized to the adverse effects of subsequent stressors on health.[3-4] It appears that adverse experience during development induces vulnerability to the effects of stress later in life and thereby induces risk for developing stress-related disorders.

Subject

The precise mechanism that mediates the effects of early adversity on later stress vulnerability and disease risk has been the subject of intense inquiry in neuroscience research. Studies in rodents and non-human primates have focused on effects of early experience on the structure and function of the brain, including effects at the level of the *genome*, which may result in altered stress responsiveness. Results suggest that adverse experience, such as maternal separation or low maternal care, induces persistent changes in neural circuits implicated in integration of cognitive and emotional processing, controlling the *stress hormone axis* and *autonomic nervous system*, and regulating of arousal and vigilance. These changes produce increased physiologic responses to subsequent stressors, as well as depression-like behaviour, anxiety, cognitive impairment, pain sensitivity, and altered sleep.[5-6] It is conceivable that early adverse experience may be causally associated with developing a variety of emotional and bodily

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disorders, particularly in response to challenge.

Problem

Little is known as to whether findings on the neurobiological effects of early stress observed in animal models can be translated to humans and to what extent such effects may contribute to the development of disorders linked to early stress in epidemiological studies.

Key Research Question

A key question for clinical research concerns is whether adverse experience in childhood is associated with neurobiological changes similar to those observed in animal models and whether these changes are related to disorders such as major depression.

Research Context

Clinical studies conducted in recent years have attempted to identify mechanisms that link childhood trauma to adult disease risk. A primary candidate in investigating this link has been the *hypothalamic-pituitary-adrenal (HPA) axis*, the organism's main stress hormone system. At the brain level, a hormone called *corticotropin-releasing hormone (CRH)* stimulates the HPA axis. The end product of the HPA axis released from the adrenal gland is the stress hormone *cortisol*. Cortisol exerts multiple effects on metabolism, behaviour, and the immune system that help the organism adapt to challenge. Several brain regions modulate the HPA axis. Brain regions that inhibit the HPA axis are the *hippocampus* and *prefrontal cortex* (PFC). The *amygdala* and *noradrenergic fibers* from the brain stem activate the stress response. Cortisol in turn shuts off the HPA axis in several parts of the brain. Sustained or increased glucocorticoid (GC) exposure can have adverse effects on the hippocampus, which causes decreases of *synapses* and decreased production of new neurons. Overexposure to cortisol also negatively affects the PFC. Such damage might progressively reduce the control of the HPA axis and lead to increased stress responses. [7-8]

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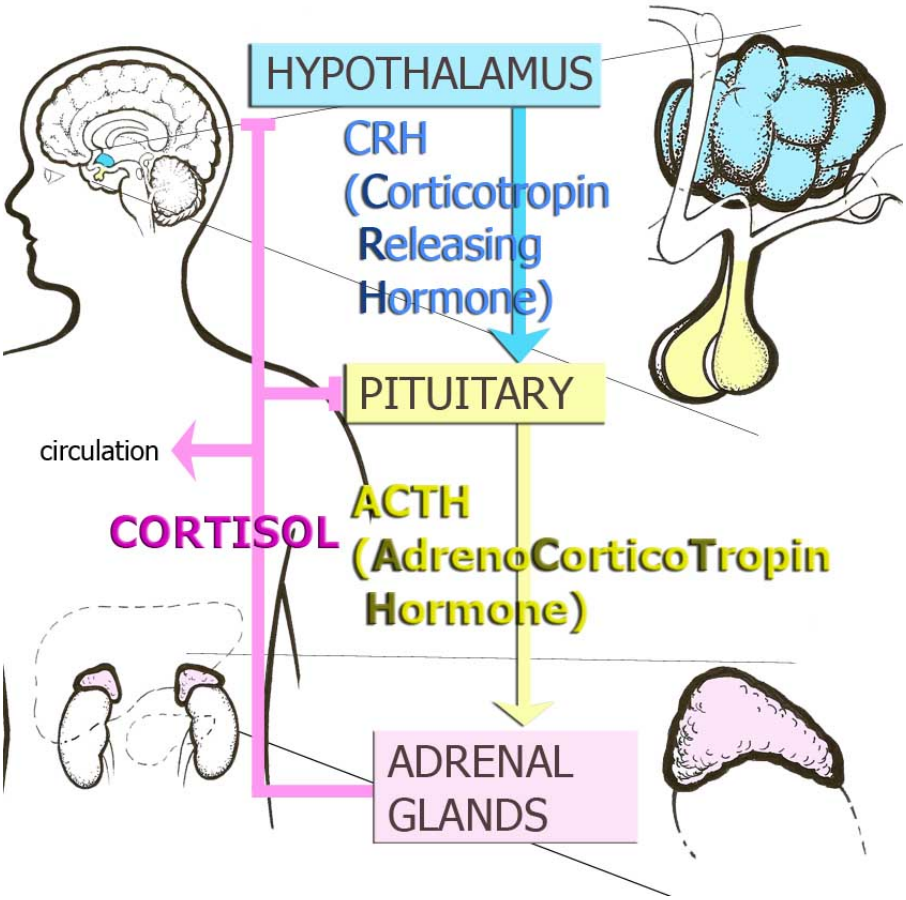


Figure 1. Hypothalamic-Pituitary Adrenocortical Axis or Stress Hormone Axis

CRH neurons also integrate information relevant to stress in several brain areas outside of the *hypothalamus*. Direct administration of CRH into the brains of animals produces integrated *endocrine*, autonomic and behavioural responses that parallel signs of stress, depression and anxiety. CRH and another neurotransmitter, norepinephrine, interact in a circuit that connects the amygdala and the hypothalamus with the area in the brain stem called *locus coeruleus*, in order to regulate vigilance, anxiety and fear, and to integrate endocrine and autonomic responses.[9-10]

Any disruptions in these systems, as a consequence of early stress, could plausibly lead to altered stress reactivity and the emotional, cognitive and physical changes that are characteristic of disorders related to stress.

Research Results

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Retrospective clinical studies in adult humans with childhood trauma histories yielded the following main results:

a. Women abused as children exhibit markedly increased stress hormone and heart rate responses to psychosocial laboratory stress, consisting of public speaking and mental arithmetic, compared to controls. The increaseis most pronounced in abused women with current depression.[11] Similar results have been reported for adults with early parental loss[12], suggesting that results can be applied to other forms of early stress.

b. Some abused women, particularly those without depression, exhibit relatively decreased cortisol output under resting conditions[13], although findings are not uniformly consistent. Upon further stress, lack of cortisol availability may promote activation of stress systems in the brain, resulting in enhanced stress responsiveness and behavioural changes.

c. Lack of regulatory cortisol effects may further be promoted by relative resistance of brain regions to cortisol. Cortisol exerts its effects through special receptors and these receptors can decrease in number or become insensitive. To test this hypothesis, a dexamethasone/CRH test can be applied. Dexamethasone is a synthetic *glucocorticoid* that suppresses the HPA axis. Subsequent CRH injection induces a rise of cortisol, overriding the suppression, in some persons. This is called an escape. Such escape is the most sensitive marker of HPA axis hyperactivity in depression. Recently, childhood trauma has been associated with marked escape from dexamethasone suppression in adult men, particularly in those with depression, suggesting decreased sensitivity to cortisol's feedback actions under stimulated conditions.[14]

d. Enhanced autonomic stress reactivity coupled with impaired cortisol sensitivity might enhance immune activation after childhood trauma. Thus, depressed men with high levels of childhood trauma exhibit increased immune activation in response to psychosocial stress, as measured using *inflammatory markers*.[15] Increased inflammatory markers were also associated with childhood adversity in a recent prospective cohort study.[16] Messengers in the immune system, such as *cytokines*, may further stimulate central CRH systems and contribute to risk for several medical diseases, e.g. cardiovascular disease and chronic fatigue.

e. The above findings are consistent with increased central CRH activity. Accordingly, levels of CRH in the fluid that surrounds the brain have been found to be associated with perceived childhood stress and abuse experiences.[2,17]

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f. As mentioned before, the hippocampus is one of the most plastic regions of the brain which is critically involved in HPA axis control, explicit memory and context conditioning. Maternal separation and central CRH injections during development alter the structure and plasticity of the hippocampus in laboratory animals. A smaller than normal hippocampus is a hallmark feature of depression. Childhood trauma has been associated with small hippocampi in several studies.[18-20] Moreover, small hippocampi in patients with depression have been linked to childhood trauma.[21] Repeated bursts of CRH during development and/or increased cortisol reactivity over time may contribute to smaller hippocampi after childhood trauma, leading to further sensitization of stress responses.

g. Not all individuals exposed to childhood trauma go on to develop a disorder, even upon further challenge. One approach to understand risk versus resilience is to consider interactions between early stress and dispositional factors, such as genetic variations in neurobiological stress response systems. For example, moderating effects have been demonstrated for variations of genes in various brain systems, including the *serotonin* and CRH system.[22-25] These gene-environment interactions likely reflect genetic moderation of the brain's functional response to stress.

Research Gaps

Future research should elucidate the neural and molecular basis of increased risk after childhood trauma, and integrate these mechanisms with hormonal findings and clinical symptoms. Studies using *functional imaging* are needed to develop neural system models of failed adaptation to stress as a consequence of childhood adversity. Interactions between genetic dispositions, gender, and environmental factors in inducing brain changes should be studied. Particular emphasis should be given to studying differential impact of different types of traumas at different developmental stages, in order to identify sources of outcome variability. Such research may identify biological markers of risk and generate precise targets, and time windows of opportunity, for the prevention of adverse outcomes. Longitudinal studies are needed to meet this goal and describe developmental trajectories of adverse outcomes versus resilience.

Conclusions and Implications

In conclusion, results from clinical studies suggest that early stress in humans is associated with long-term neurobiological changes that are comparable to those described in animal studies and suggest sensitization to stress. Genetic variations in stress response systems moderate the link

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between childhood trauma and adverse outcomes. It must be noted that, in the above studies, changes in stress response systems were only seen in cases with childhood trauma and depression, but not in depressed patients without significant early stress. The implication of these results, taken together, is that several of the classic features of depression may derive from early stress, reflecting vulnerability to develop depression and likely other disorders in response to challenge. This also implies that there may be biologically discernable subtypes of depression and other disorders, as a function of childhood trauma. This notion is also supported by findings of differential treatment responsiveness to psychotherapy versus pharmacotherapy in chronically depressed patients depending on childhood trauma[26] and in patients with *irritable bowel syndrome*.[27] Thus, consideration of developmental factors may be useful in improving diagnostic classification of mental and functional somatic disorders and may ultimately help in guiding differential treatment decisions.

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The Brain: The Central Organ of Stress and Adaptation Across the Lifecourse

Bruce S. McEwen, PhD

The Rockefeller University, USA

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Introduction

The important topics discussed by Gunnar, Herrera, Hostinar and by Heim rely upon a basic knowledge of brain-body interactions over the lifecourse. That is, effects of stress early in life clearly have a lasting effect on later mental and physical processes, increasing the risk for both mood and anxiety disorders, as well as cardiovascular and other systemic diseases. As a result of the recent progress of modern neuroscience and medicine, there is a growing understanding of brain-body interactions that underlie adaptation to stress and the accumulated pathophysiology that is associated with excessive and prolonged stress. Among the important concepts that have emerged is the notion that the brain is the central organ of stress because it regulates the major systems involved in adaptation and pathophysiology and is itself influenced both structurally and functionally by those systems. As summarized by both Gunnar et al.[1] and by Heim,[2] these effects begin early in life. Another major concept is that of "*allostasis*" and "allostatic overload," reflecting the protective and damaging effects of the mediators of stress and adaptation and cumulative change resulting from prolonged stress and the lifestyle and behaviours associated with chronic stress. Related to this is the concept of biological embedding, namely, that those early life influences "get under the skin" and increase the impact of the cumulative aspects of prolonged stress and lifestyle.[3]

Subject

Research has made progress in understanding the role of the brain as the central organ of stress. Indeed, the brain is the key organ of the adaptive and maladaptive responses to stress because it determines what is threatening and, therefore, potentially stressful, as well as initiating the behavioural and many of the physiological responses to the stressors, which can be either adaptive or damaging.[4,5] Stress involves two-way communication between the brain and the cardiovascular, immune and metabolic system via the *autonomic nervous system* and via

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endocrine mechanisms. The effects of stress involve measurements of multiple endpoints related to mediators of stress and adaptation and cumulative change in the body and brain.

Problems

The mediators of stress and adaptation operate in a non-linear manner (Figure 1) meaning that many of these mediators regulate each other in both positive and negative ways and also operate in a "U" shaped manner that is now referred to by the term *hormesis*.[7] Beyond the “flight or fight” response to acute stress, there are events in daily life, including the individual life style, that produce a type of chronic stress and lead over time to wear and tear on the body (“allostatic overload”). Yet, the hormones and other mediators associated with stress and adaptation protect the body in the short-run and promote adaptation (“allostasis”).[4,5,8] These systems are regulated by the brain via the *hypothalamus* and outputs via the autonomic and *neuroendocrine systems*. Input to the hypothalamus involves brain areas, such as the *amygdala*, the *hippocampus* and the *prefrontal cortex*, and these brain areas, along with the hypothalamus, respond to hormonal signals.

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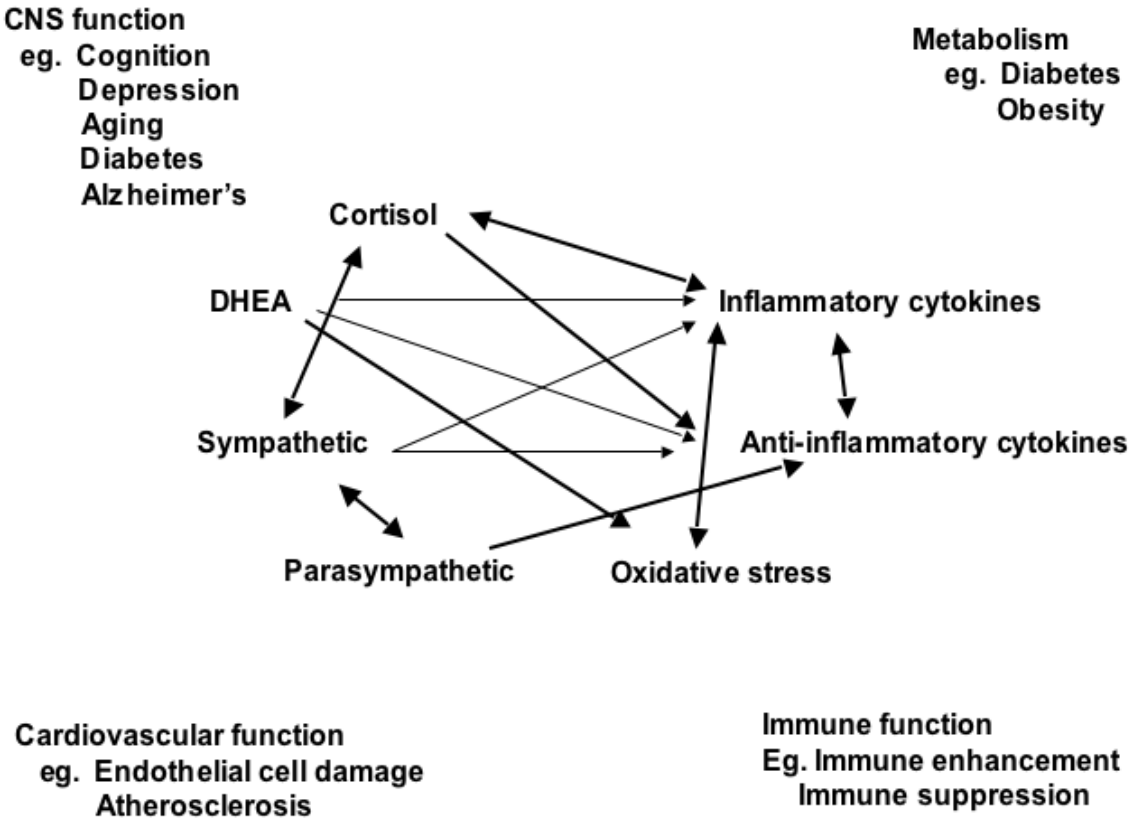


Figure 1. Non-linear network of mediators of allostasis involved in the stress response. Arrows indicate that each system regulates the others in a reciprocal manner, creating a non-linear network. Moreover, there are multiple pathways for regulation – e.g. inflammatory cytokine production is negatively regulated via anti-inflammatory cytokines, and via parasympathetic and glucocorticoid pathways, whereas sympathetic activity increases inflammatory cytokine production. Parasympathetic activity, in turn, modulates and limits sympathetic activity. Furthermore, mediators, such as cortisol and inflammatory cytokines, produce biphasic effects that are described now by the term *hormesis* (see text). Reprinted from McEwen[6] by permission.

Research Context

The assessment of allostasis and allostatic overload is based upon collection of clinical information for the multiple systems involved in stress and adaptation; namely, the *Hypothalamic-Pituitary-Adrenocorticol (HPA) axis*, the autonomic nervous system, and metabolic parameters.[9,10-12] Brain mechanisms involved in allostasis and allostatic overload can be studied in animal models using methods of modern neuroscience and translated to human subjects by brain imaging techniques that are rapidly developing.[13]

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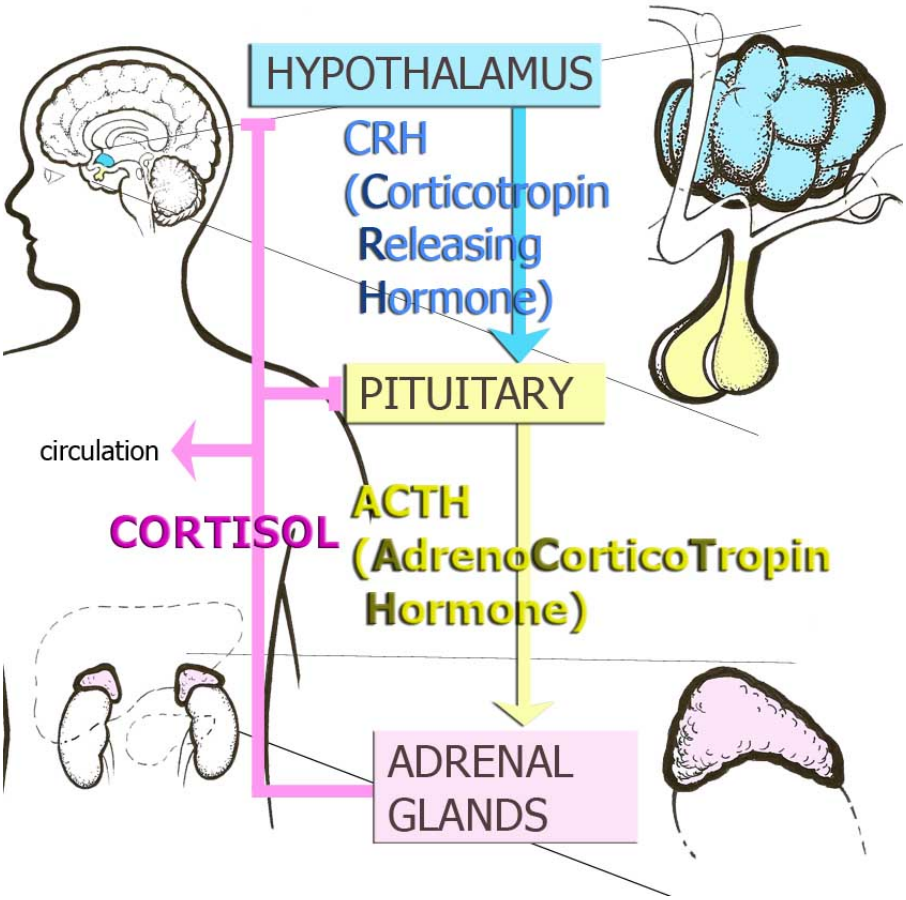


Figure 2. Hypothalamic-Pituitary Adrenocortical Axis (HPA) or Stress Hormone Axis.

Key Research Questions

Experiences involving social interactions and events in the physical environment are processed by the brain and are usually referred to under the rubric of “stress.” We now know, from animal models, that the brain changes in structure and function with experiences, including those of chronic stress, and that these changes in brain represent “adaptive plasticity,” in that they are largely reversible and appropriate for the conditions that cause them.[5] With the exciting advances in *neuroimaging*, the living human brain can now be studied in some detail as it responds to stressful experiences during the life course, as well as how its structure and functions relate to physiologic states in the body.

Recent Research Results

Animal models have provided insights into how the brain responds to stress.[5] The brain is a target of stress and the hippocampus was the first brain region, besides the hypothalamus, to be

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recognized as a target of *glucocorticoids*. Stress and stress hormones produce both adaptive and maladaptive effects on this brain region throughout the life course. Early life events influence lifelong patterns of emotionality and stress responsiveness and alter the rate of brain and body aging. The amygdala and prefrontal cortex, as well as the hippocampus, undergo stress-induced structural remodeling, which alters behavioural and physiological responses, including anxiety, aggression, mental flexibility, memory and other cognitive processes; glucocorticoids play a role in this remodeling along with excitatory amino acids, metabolic hormones and other intracellular and extracellular mediators.[5]

Human brain structural imaging has begun to reveal how the human hippocampus changes with experience. Recent evidence includes the relationship of 20 years of elevated perceived stress to reduced hippocampal volume,[14],and how the hippocampus shrinks in disease states, such as *Cushing's disease*, major depression, diabetes and posttraumatic stress disorder (PTSD)[15,16] and pre-disease conditions, such as resulting from chronic jet-lag[17] and elevated circulating inflammatory *cytokines*.[18] Hippocampal volume is also smaller in both young and older people with low self esteem, accompanied by elevated HPA activity and lack of habituation to repeated stress.[19]

Based on animal models, and as noted above, the mechanisms for these changes are complex and are likely to involve not only glucocorticoids, but other hormones and mediators. Furthermore, physical activity and fitness in elderly subjects is associated with greater hippocampal volume and better memory function,[20] just as greater activation of prefrontal cortical activity is associated with fitness and regular exercise and leads to better executive function.[21,22]

The prefrontal cortex, which is reversibly, functionally impaired by increased levels of perceived stress in medical students studying for the board exam[23] is smaller in major depression[24] and is smaller in people who self-report lower socioeconomic status.[25] Functional activation of the prefrontal cortex is related to blood pressure responses,[26] whereas functional activation in the amygdala is related to the negative response to fearful faces,[27] which is exaggerated in people with early life adversity.[28] Elevated amygdala functional activity is also related to the development of *atherosclerosis*.[29]

Animal models teach us that experiences, including stress-induced changes in brain structure, are largely reversible and that resilience in both brain structure and behaviour is the name of the game in adapting to changing environments.[5] A corollary of this is that failure to show resilience

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is a feature of maladaptation and pathophysiology, including anxiety and depressive disorders and the downstream effects that these have on the rest of the body via the autonomic, neuroendocrine and immune systems. But how plastic is the human brain in response to interventions that effectively treat disorders that affect the brain as well as the rest of the body?

Although there is limited information, a few studies have shown longitudinally, in the same subjects, changes, for example, in functional activity[30] and prefrontal cortex (PFC) structure[31] in patients who successfully responded to behavioural therapy treatment for *obsessive–compulsive disorder OCD* and chronic fatigue, respectively. Another, albeit cross-sectional, study reports thicker cortical volume in *right anterior insula* and prefrontal cortex of subjects who had meditated for many years compared to matched controls.[32] It is well known that, as an adjunct to pharmaceutical therapy, social and behavioural interventions, including regular physical activity and social support, are able to reduce the chronic stress burden and benefit brain and body health and resilience.[5] Therefore, studies of how the brain is changed by behavioural, as well as by pharmaceutical therapies, are important future applications of brain imaging.

Research Gaps

Experience tells us that the social and physical environments in which people live and work have a huge effect upon psychological states. The nature of these environments also affects physical and mental health and risk for disease. Yet the scientific study of this important topic has been frustrated and fragmented by disciplinary boundaries between such fields as environmental toxicology, social psychology, sociology, health psychology, economics, epidemiology, psychiatry, pediatrics, neurology and medicine. As a result, only some of the considerable knowledge has penetrated, albeit inconsistently, into the mainline of medical teaching and practice, and neuroscience has been largely out of the picture until recently. As a result, a coherent conceptual framework has been missing, because the brain has not been fully recognized as playing a central role in physiological adaptation and the effects of stress, as well as being a target of stress and related behaviors.[5] This is beginning to change with the translation of animal research findings to the human being via brain imaging techniques that are summarized above.

With brain imaging, most of the information has come from cross sectional studies, which can be only suggestive as to causality. With the advent of interventions that improve brain function and treat behavioural disorders, longitudinal studies of brain structure and function are not only possible, but essential, to show causality. As noted above, the best example thus far is that of the

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beneficial effects of physical activity. Another important area is that of the brain effects of Type 2 diabetes, noted above, but an important gap that must be filled is that such studies be carried out in the context of the developing brain and the consequences of Type 2 diabetes in childhood.

Conclusions

The lasting effects of stress on the body beginning early in life must be considered in the context of the whole lifecourse and the central role of the brain in the protective and damaging effects of the physiological mediators of stress and adaptation. The powerful effects of early life stress on the brain are beginning to be understood from animal models, as well as some brain imaging studies.[33] These are now being considered in relation to measures of the mediators of allostasis and allostatic overload,[34] since, as summarized above, circulating stress and metabolic hormones have important effects on the brain. In relation to the papers by Gunnar et al.[1] and by Heim,[2] it is possible to envision heroic life-long longitudinal studies of the brain beginning early in life, but perhaps more realistic to imagine shorter term studies of the effects of adversity on brain development in parallel with cognitive and physiological measures patterned after recent studies of a more limited nature.[34,35] However, it would be even more valuable to follow longitudinally the effects of interventions designed to ameliorate effect of early life adversity, based, for example, on the nurse-family partnership program.[a]

Implications

Brain-body interactions are strongly influenced by the social and physical environments in which we live, and these are, in part, the products of practices and policies of private enterprise and government and these can be changed by changing those policies. Indeed, virtually all of the policies of government and business have effects upon health, and they are likely to have a top down effect via the brain on all the physiological systems involved in stress and adaptation.[5] For example, programs that promote physical activity are likely to benefit brain function (see above), just as programs such as the Experience Corps produce benefits to the elderly volunteers in both physical and mental health.[36] Likewise, studies of the efficacy of programs for children, such as the Perry School Project,[b] would benefit from assessment of cognitive function and brain health. Therefore, monitoring how the brain is affected by such policies is another important future direction of neuroimaging research because animal models can only give clues, but the study of the adaptability of the human brain is the ultimate goal!

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Notes:

[a] See also the Nurse Family Partnership website available at: http://www.nursefamilypartnership.org. Accessed December 17, 2009.

[b] See also: HighScope Educational Research Foundation. HighScope Perry Preschool Study: Lifetime effects: The HighScope Perry Preschool Study through age 40; 2005. Available at: http://www.highscope.org/Content.asp?ContentId=219. Accessed December 17, 2009.

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