Brain structural maturation and the foundations of cognitive behavioral development

Kristine B Walhovd[1], Christian K. Tamnes[1] and Anders M. Fjell[1]

[1]Research Group for Lifespan Changes in Brain and Cognition, Department of Psychology, University of Oslo, Norway

Contact details: e-mail: k.b.walhovd@psykologi.uio.no, mailing address: University of Oslo, Department of Psychology, LCBC, POB 1094 Blindern, 0317 Oslo, phone +47 22845130

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Abstract

Purpose of review Thorough knowledge of normal neural foundations for cognitive behavioral development is fundamental to understand mechanisms of both neurodevelopmental disorders and normal adaptation. This review aims at identifying trends in magnetic resonance imaging (MRI) studies published within the last 18 months illuminating maturational structural brain foundations for normal cognitive behavioral development.

Recent findings Development is coordinated within neurocognitive systems, with predictable functional correlates. There is great individual variability within the normal range. Relationships between brain and cognitive variance at any given age are moderate, and appear to be of a complex and dynamic nature. Importantly, current studies point to a dimensional component to cognitive and behavioral psychopathology, where differences among healthy and clinical developmental groups exist along a continuum. Finally, factors influencing and detectable in early development are likely to have lifespan consequences.

Summary Brain development is highly coordinated, but the normal individual variation at any given age is substantial. Relationships between brain and cognitive measures are typically moderate and may fluctuate with age. A dimensional component to neural foundations for multiple developmental disorders makes the study of normal individual brain differences in development even more important to understand both normal and clinical cognitive behavioral outcomes throughout life.

Keywords: brain, cognition, normal development, MRI, dimensional

Introduction

Recently, researchers from the Child Psychiatry Branch of NIMH cautioned against biases in pediatric head circumference norms having influenced findings on early brain overgrowth in Autism Spectrum Disorder (1). This reflects a continuously troublesome fact: we need thorough knowledge of normal development in order to accurately detect and understand mechanisms of neurodevelopmental disorders. We also need to understand normal development and adaptation in and of itself. Here, we review recent magnetic resonance imaging (MRI) studies of normal brain structural development and its relations to cognitive and behavioral outcomes.

Developmental patterns and normal individual differences of brain and cognition

The most dramatic brain changes take place early, but large longitudinal studies on normal brain development in infancy have until recently been lacking.

Early brain and cognitive development uncovered

Recent longitudinal data show that cortical gray matter (GM) volumes more than double (108%) during the first year of life, with lesser increase (19%) during the second (2). Likewise, subcortical volumes increase sharply during the first year (2). Cortical surface area expansion (3*) appears region-specific, paralleling cognitive and functional development at different stages: Relatively

more expansion in the first year is seen in parts of superior temporal and parietal, postcentral and occipital cortices, perhaps reflecting rapid development of sensory functions. In the second year, particular expansion is seen in superior frontal, inferior temporal, and inferior and superior parietal cortices, involved in motor planning, higher order visuospatial, sensory and attentional processing (3).

White matter (WM) microstructure also shows faster rate of change in the first than second year, with rapidly increasing fractional anisotropy (FA) and decreasing radial (RD) and, to a somewhat lesser extent, axial (AD) diffusivity (4*) (see Figure 1). Again, region-specific maturational patterns are observed: Colossal tracts exhibit larger RD changes in the first year. Motor and sensory tracts are more mature at birth and develop more slowly (4), in correspondence with GM volume in sensory-motor regions (2). Association tracts continuously show lower maturation degree in the first two years of life (4). A leftward development of arcuate fasciculus has been found, with more than 20% larger FA values than the right in the first year, suggestive of language-related lateralization differences appearing (4). Individual differences in WM microstructure in neonates yield higher heritability estimates than in adults, with more mature regions showing less genetic variation (5). Multimodal and network approaches show maturation from a local to distributed organization (6-8). Both the dorsal attention and default-mode network (DMN) start from an isolated region in neonates, but evolve to synchronized networks at 1 year of age, when they also become

anticorrelated (8). This pattern of development is enhanced, but less dramatic in the second year (8), echoing structural maturation (2, 3).

While patterns appearing to correspond to functional development can be identified from studies of early brain development (2-4, 9), scarce data exist to assess these relationships directly for normal individual differences. As a striking example, better working memory scores at 12 months of age relate to higher FA and lower RD values in select WM tracts (10**). FA explained 10-16 %, and RD (see Figure 1) 12-25% of the variance (10). This testifies that relationships between indices of brain and cognitive development are of a moderate nature.

[Insert figure 1]

Trends in preschool, school age and adolescent brain and cognitive development – some apparent discrepancies and emerging patterns

Dynamic changes take place in GM and WM throughout childhood and adolescence, along with protracted cognitive development (11*,12-15,16*, 17,18). Neuroanatomical variance among individuals tends to increase with age (16). There are increases in total and regional cerebral WM (17), along with increasing FA, and regionally decreasing MD and RD (19). As for GM, the picture appears complex, as discussed below.

Peak development of cortical thickness and volume

A number of previous studies have pointed to increases in cortical thickness well into school age (20-22), followed by later maturational thinning. However, a recent report based on the cross-sectional large sample from the Pediatric Imaging and Neurocognitive Genetics (PING) study, indicates monotonous decrease in cortical thickness in the age range 3-21 years (16). In contrast, cortical surface area expanded up until the age of 12 years (16). Thus, regional volume increases and decreases are ongoing simultaneously in different parts of the cortex, including increases in temporal and prefrontal cortices in preschool years and decreases in occipital and primary somatosensory areas (23). While there are sex differences also in development, this is out of scope for the current review, and interested readers are referred to e.g. (22). The overall picture is one of average GM and cortical volume decrease in school age and adolescence (16, 17, 24).

Cortical foundations of cognitive development – when less becomes more

The maturational cortical volume reduction and thinning is associated with cognitive development. Cortical reductions in a fronto-parietal network has been related to improvement in working memory and executive function in the age range 5-10 (25) and 8-22 years (11). Independently of age, sex and general abilities, volume reductions explained 5-7% of the variance (11). However, indices of general intellectual ability and executive function showed

positive correlations with temporal, frontal, cingulate and precuneus as well as early visual area GM in children aged 6-18 from the NIH study of normal brain development (26). Other variables showed both negative and positive weightings (26). Relationships appear to vary with age (27), with partly a reversal of the pattern where “more is more” with respect to local GM volumes and measures of everyday executive functions switching to a ”more is less” pattern (26). This might be related to pruning, dendritic changes and myelination processes. Similarly, thinner parietal cortices have been found to predict better verbal learning and memory, visuospatial functioning and problem solving in the age range 12-14 years (13). There is regional variability (28), e.g. thinner left orbitofrontal cortex predicted better 30 minutes visuospatial recall, possibly reflecting executive components of memory processes in one study, while hippocampal volume was positively associated with retention over one week, possibly relating to consolidation of memory traces (28). There is currently great interest in how the noted brain changes in adolescence relate to social processing and risk taking, as recently reviewed elsewhere (29-31).

Multimodal approaches to brain developmental foundations of cognition

Multimodal imaging may illuminate the neurobiological properties underlying maturational cortical thickness and volume reductions. In a recent study, regional superficial WM patterns in development (age 10-18 years) diverged from the more widespread GM maturation, indicating that the cortical thickness changes cannot largely be explained by encroachment of WM into

deeper cortical layers (19). Multimodal approaches may also yield a fuller picture of cognitive foundations (32). Intraindividual variability (33), inhibition and task switching (34) in development are related to microstructural properties of WM tracts, including FA. Exploring the association further, Grydeland and colleagues (35), used T1- and T2-weighted MRI Myelin Mapping combined with DTI to show that intracortical myelin links with intraindividual variability in a speeded inhibition task across the human lifespan. In the PING study, multimodal imaging properties were also found to relate to cognitive control, which increased rapidly in preteen years (36). Surface area of the anterior cingulate cortex accounted for a significant proportion, while properties of large-fiber connections explained additional variance in cognitive performance (36). Maturation of neural tracts and progressive myelination appear critical correlates of the development of stable performance of cognitive control (33-36).

Patterns of coordinated maturational anatomical coupling and change across subcortico-cortical and cortico-cortical regions are now being delineated (37-39). To some extent, such structural/maturational networks are also predictive of functional connectivity and network organization as measured by resting state fMRI (38). Both resting state (40) and task fMRI (41) patterns develop with age, but patterns of task-induced DMN deactivations with age appear task-specific (42). Stronger DMN coupling has been linked to greater cognitive skill for vocabulary (37), as well as for quality of past remembering and, marginally, future imagination (43). In the latter study, higher score for past

remembering correlated with default-mode functional connectivity in the precuneus. Again, multimodal imaging added to the picture: temporal and frontal cortical surface arealization explained additional variance in quality of past remembering and future imagination, respectively (43). As functional cortical areas grow in size developmentally, they may influence the structural properties of the fibers transmitting signals to and from these regions (44**). In principle the same could apply to individual differences broadly, as experience-dependent plastic changes have been shown (45-47).

In sum, a number of studies point to parallel developments of brain and cognition. Age-independent brain-cognition correlations are often moderate, but rest on the principle that there is much variance in brain and cognitive development at any given age. This is illustrated in Figure 2. Striking variance even among high functioning children and adolescents leads one to question how well normal ranges can be defined. Recently, studies have focused on the continuity of individual differences in brain, cognition and behavior across the normal and clinical range.

[Insert figure 2]

A dimensional component to variation in neurodevelopmental normal differences and psychopathology

The need to understand normal brain development as a foundation for cognition and behavioral adjustment is becoming increasingly clear. Features contributing to neurodevelopmental diagnoses may not be unique to pathology, but represent quantitative differences along a continuum, elevations of characteristics also present in broader, and healthy populations, as illustrated in Figure 3. Inattention and hyperactivity symptoms in healthy children have been associated with decreased regional cortical thickness and thinning rate in attention networks, including frontal areas (48*, 49). These results correspond to findings in populations with ADHD (50). In another study (51), the association of attention problems and cortical thickness was not found, but symptoms of conduct problems within the normal range were related to thinner prefrontal cortices in a manner similar to that previously observed in conduct disorder (52). Similarly, antisocial traits have been associated with thinner prefrontal cortices, and autistic trait ratings with thinner superior temporal cortex in typically developing youth (53).

In some of the studies supporting a dimensional view of psychopathology (48, 51), the relationships are primarily found in younger children. Differences observed at a given time point in development may not necessarily be as evident later on (27). However, absence of age interactions has also been observed (53), and neural foundations and cognitive symptoms of developmental behavioral problems do not invariably vanish with maturation. For instance, a study of adults with ADHD and their unaffected siblings showed impairments in both groups in sustained attention and regional

neuroanatomical reductions in frontal GM and WM relative to controls (54). Recently, developmental trajectories of cortical thinning with a convergence toward typical dimensions in networks supporting attention and cognitive control were shown to predict remittance versus persistance of ADHD in adulthood (55).

[ınsert Figure 3]

The long term and complex impact of early brain development for lifespan cognitive and behavioral function

The long-term impact of early events in brain development on cognition is becoming increasingly clear. Risk groups (56*,57-59), may show subtle deviances in brain development early on. However, while some correlates may be found in terms of cognitive behavioral function in infancy (60), such may not necessarily be easily identifiable. This may in part be due to difficulties with testing young children, but also, consequences on complex cognitive function cannot be observed until these develop. Recent studies have pointed to prolonged development of brain and cognitive function throughout adolescence, especially for aspects of attention and executive function (11-14, 16, 17, 34, 36, 37, 61, 62). Hence, some early impacts may in in principle be observed only decades after. Neonatal brain development and abnormalities have been shown to predict memory, learning and language outcomes, as well as social-emotional development and psychiatric diagnostic

status at school age (56, 63-65). Inder and colleagues showed associations between neonatal brain measures and socio-emotional development at age 5 years that were similar whether those difficulties were reported at both age 2 and age 5 or only at age 5 (56). Multiple interpretations are possible, but it is plausible that further brain maturation is necessary before the impact of regional alterations on particular symptom domains becomes evident (56). Woodward and colleagues (66) showed that neonatal WM abnormalities were important predictors of neurocognitive outcome for very preterm children at age 4 and 6 years, with a tendency for impairments to become increasingly apparent with age. Such tendencies in our opinion call for a refinement of the concept of “developmental delay”. The implicit assumption is that one would expect catch-up with time, but often, evidence does not support this. Effects of early adversities may be continuous, or even become more pronounced with age. This should, however, not lead to a pessimistic view where early intervention is halted – a number of studies point to positive effects of early intervention (67-69). Rather, it should alert us to the continuing needs for studies of at risk groups, ensuring that appropriate measures and follow-up are continued also for a prolonged time.

Continuous influences across the lifespan

Influences of early life characteristics on brain and cognition can affect the whole lifespan, as illustrated in Figure 4. Normal variation in birth weight has been found to predict neuroanatomical volumes and cortical surface area in later childhood, adolescence and early adulthood (70, 71*). This may be due

to a mixture of prenatal environmental and genetic effects. A number of common variants in risk genes for psychiatric disorders were recently found predictive of brain structure at birth, with some effects being highly similar to those reported in adults (72**). While pre-and perinatal development have long been seen as critical in the etiology of mental illness such as schizophrenia, present data call for a widening of this perspective to also comprise disorders typically associated with aging, such as Alzheimer`s dementia (AD). Here, effects of select genes have been interpreted within an antagonistic pleiotropy perspective, where evolutionary changes beneficial to survival in youth increase the vulnerability to diseases in aging (73). However, neonates carrying APOE ε4, the major genetic risk factor for AD, were recently reported to have reduced volumes of temporal cortex in much the same manner as that reported in elderly (72). This indicates that the contribution to brain characteristics associated with AD risk is likely present before birth and may represent a stable risk factor. Similarly, for variants of the fat mass and obesity (FTO) –associated gene, associated with reduced brain volumes in healthy aging and risk of AD (74, 75), smaller brain volumes were recently shown also in adolescents (76).

[Insert Figure 4]

Developmental trajectories of brain and cognition unfold over time and genetic and constitutional risk factors interact with postnatal experiential and

environmental factors, but it is becoming increasingly clear that influences very early in life are important predictors. Remarkable predictive validity of intelligence tests at age 11 for cognitive performance at age 90 years has been observed (77). This calls for a developmental lifespan perspective. If we were able to take these early factors into account in a more precise way, we might be more successful at identifying other important influences in lifespan development.

Conclusion

A number of principles can be outlined from the current literature. First, brain structural development is coordinated within neurocognitive systems, but relationships between brain and cognitive measures are often moderate and of a complex and dynamic nature. Second, there is great individual variability within the normal range, where differences between healthy and pathological development can typically be of dimensional, rather than categorical nature. Finally, factors influencing and detectable in early development are likely to have lifespan consequences. Future research in these areas will be important to inform on the mechanisms of both normal and pathological development of brain and cognition.

Key points:

- Development is coordinated within neurocognitive systems, but relationships between brain and cognitive measures are often moderate and of a complex and dynamic nature.
- There is great individual variability within the normal range and differences between healthy and pathological development can typically be of dimensional, rather than categorical nature.
- Factors influencing and detectable in early development are likely to have lifespan consequences.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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**Besides providing evidence for the impact of early cerebral development in preterm infants on later behavioral adaptation, this study points to

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** While polymorphisms in putative risk genes for psychiatric and dementing disorder have been associated with brain and cognition in a adults, it has been unknown when in the lifespan these associations arise. Some effects have been interpreted within a framework where genetic variants may yield characteristics beneficial to survival in reproductive years, but become disadvantageous late in life, e.g. for the APOE ε4 allele. This study is the first to show that multiple risk genes predict brain structure also at birth, highlighting the importance of prenatal brain development even for “old age” disorders such as Alzheimer´s disease.

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Figure titles and legends

Figure 1 Early brain development and relation to cognitive function A) Development of radial diffusivity in infancy. The scatter plot shows average radial diffusivity in seven tracts vs. postnatal age. Horizontal lines represent the overall means. It is evident that changes in the first year are greater than in the second year. (Genu and splenium, anterior and posterior part of corpus callosum, respectively, ArcInfTemp = arcuate inferior temporal tract, UF= uncinate fasciulus, ILF = inferior longitudinal fasciculus, PLIC= posterior limb internal caspule, ALIC = anterior limb internal capsule, all left hemisphere (L)). Adapted from (4). B) Relationships between individual differences in working memory performance and white matter development. Anterior cingulum (shown in upper panel) radial diffusivity correlated with visuospatial working memory performance in healthy 12 months old infants (lower panel). Adapted from (10).

Figure 2 Normal individual variation in brain and cognitive development and their relationship

A) Spaghetti plot for superior frontal cortex volume (mm^3) by age (years) in development. Blue lines denote boys and red lines denote girls. An assumption-free general additive model as a function of age was fitted. The lower panel shows the superior frontal region in the right hemisphere. B) Spaghetti plot for working memory performance (% of words recalled correctly on the Keep Track task) by age (years). The lower panel shows a schematic

illustration of the last part of a single trial of the task. In each trial, sixteen words were presented serially, and the number of categories increased throughout the task. C) Partial regression plot obtained from a multiple regression analysis on annual percentage volume change in prefrontal cluster in the right hemisphere (as shown in the lower panel), with sex, age and annual change in working memory performance as independent variables. The plot shows volume change against working memory change (both in z scores), and the linear fit line corresponds to the partial correlation, controlled for sex and age. Adapted from (24) and (11).

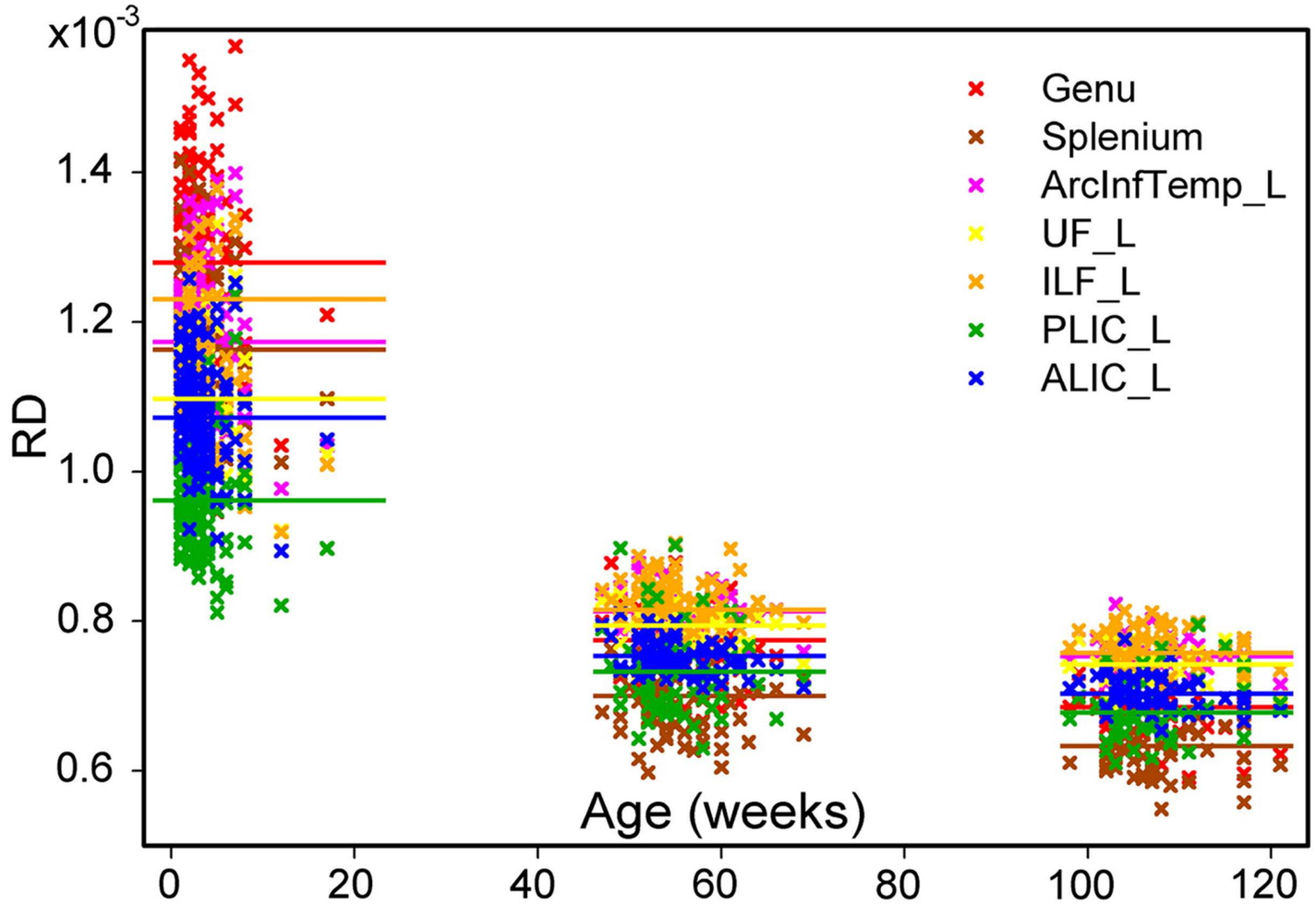
Figure 3 A dimensional component of neurodevelopmental disorders

The figure shows areas where cortical thickness relates to (A) group differences of healthy control children and children with ADHD, with thinner cortices in the patient group marked, and B) a child behavior checklist (CBCL) attention problems by age interaction in healthy children, explained by negative associations of attention problems and cortical thickness in younger subjects up to the age of 10 years. There is an apparent overlap of the neural substrates, suggesting a dimensional component to behavioral disorders, where brain correlates of normal variation can be seen along a continuum with those of clinical behavioral disorder. Adapted from (48) and (50).

Figure 4 Early life characteristics relate to development of brain and cognition over prolonged time

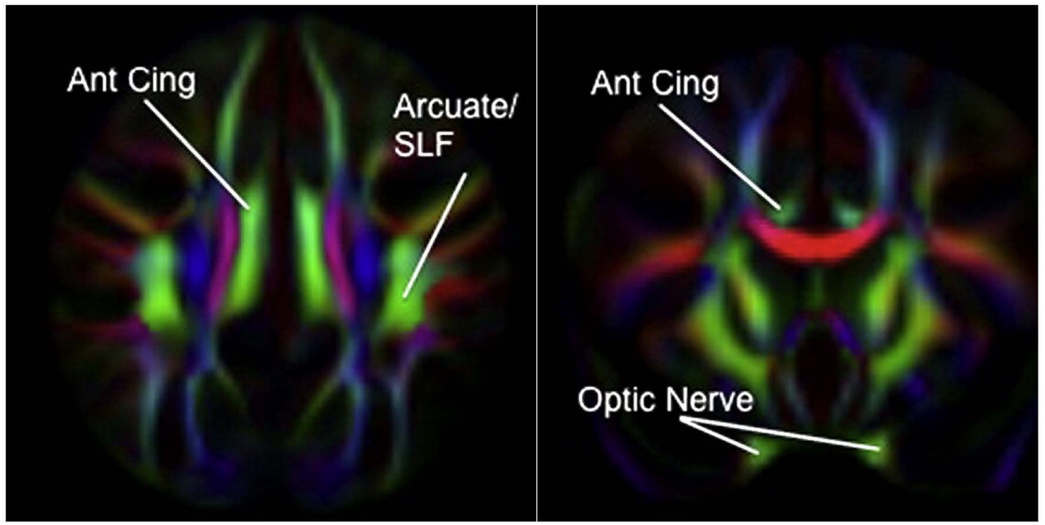
The figure shows (A) Areas where normal genetic variation in the APOE gene associated with risk for Alzheimer´s disease is associated with gray matter (GM) volume at birth (blue areas show lesser gray matter for carriers of the APOE ε4 risk allele in the temporal lobes, including bilateral hippocampus, parahippocampus, fusiform, middle and inferior temporal areas, whereas greater volume was observed in parietal, and partially frontal and occipital cortex. (B) Areas of positive relationships between a measure of cognitive control/self-regulation and cortical arealization in children and adolescents, and 4) Areas where birth weight differences within the normal range in two independent samples from the NIMH (1) and PING (2), respectively, showed positive relationships to cortical arealization. Adapted from A: (72), B: (36), and C: (70 and 71).

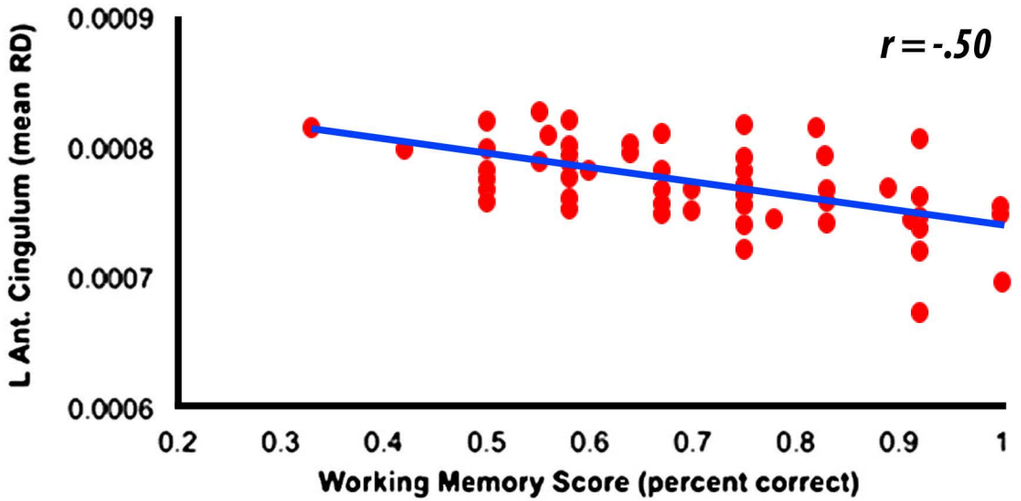
(A) Development of white matter microstructure in infancy



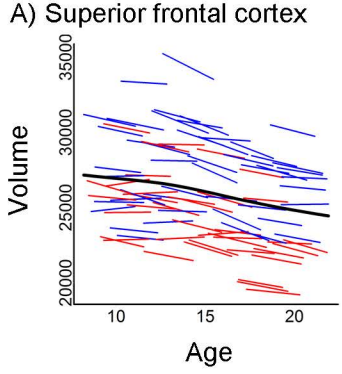
Geng et al. (2012)

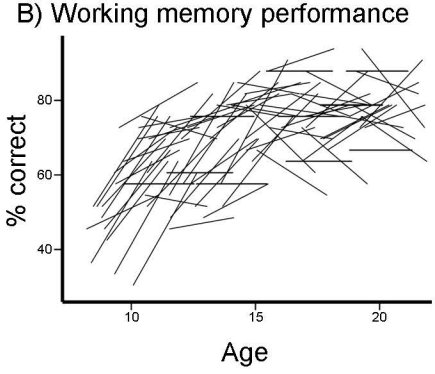
(B) Relationship between white matter microstructure and working memory in infants

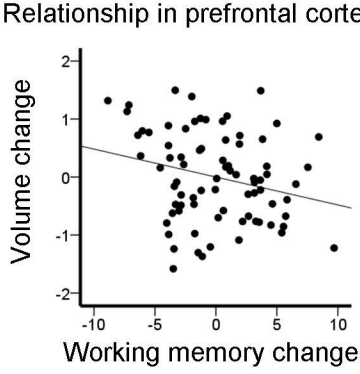


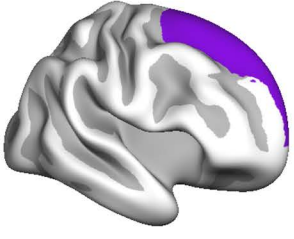


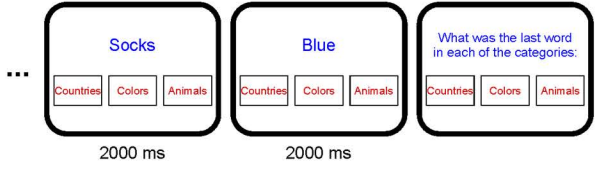
Short et al. (2013)

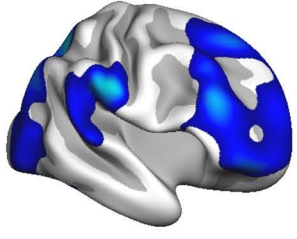

A) Superior frontal cortex
Volume
35000
30000
25000
20000
10
15
20
Age


B) Working memory performance
% correct
80
60
40
10
15
20
Age


C) Relationship in prefrontal cortex
Volume change
2
1
0
-1
-2
-10
-5
0
5
10
Working memory change

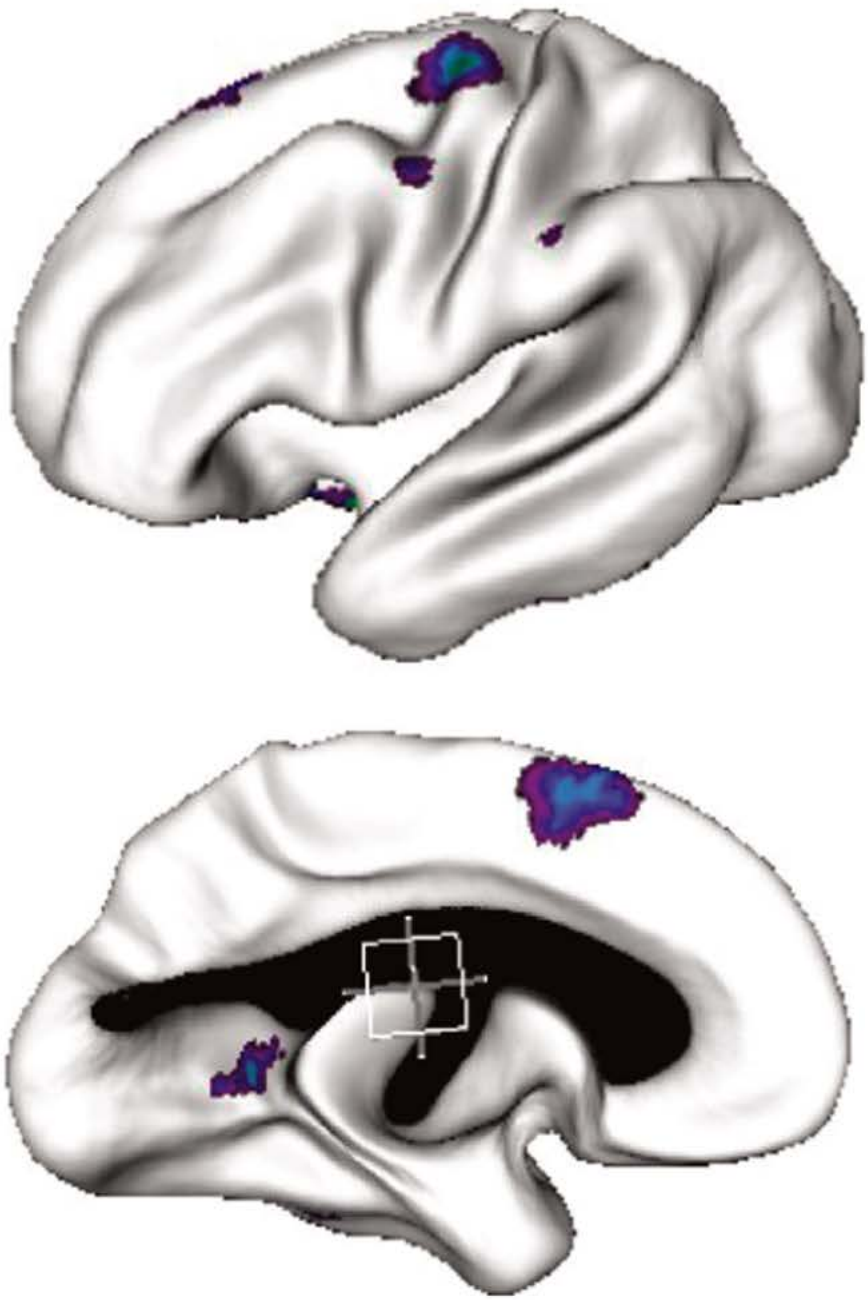


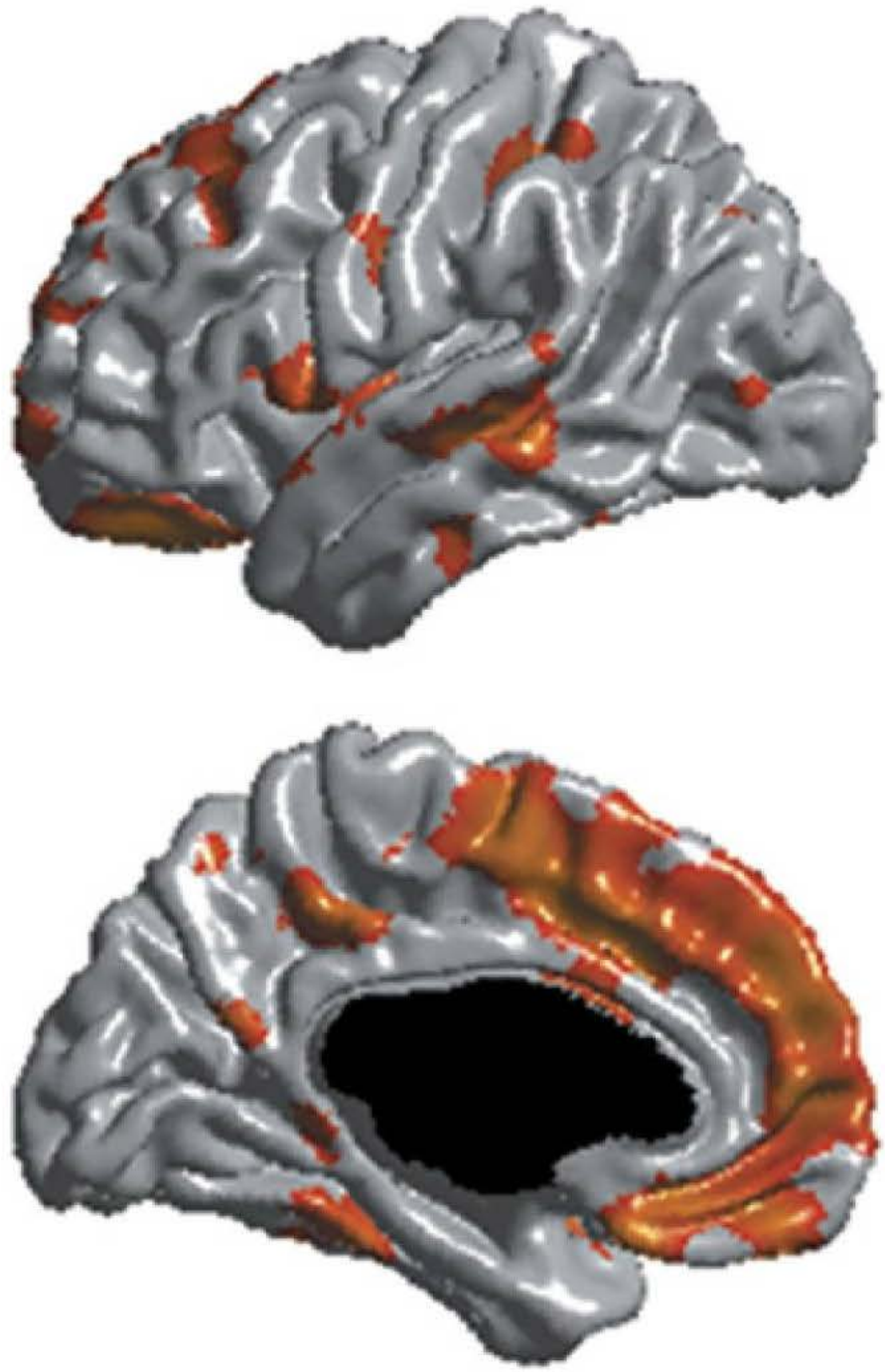

...
Socks
Countries
Colors
Animals
2000 ms
Blue
Countries
Colors
Animals
2000 ms
What was the last word in each of the categories:
Countries
Colors
Animals



(A) ADHD on cortical thickness

(B) CBCL * age interactions on cortical thickness

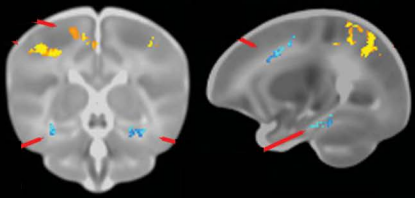




Shaw et al. (2006)

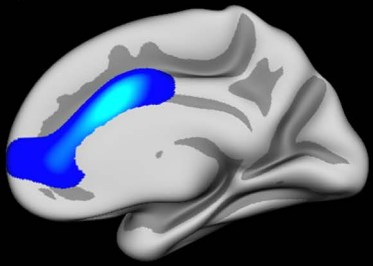
Ducharme et al. (2012)

(A) APOE e4 on gray matter in neonates



Knickmeyer et al. (2013)

(B) Relationship between self-regulation and cortical area



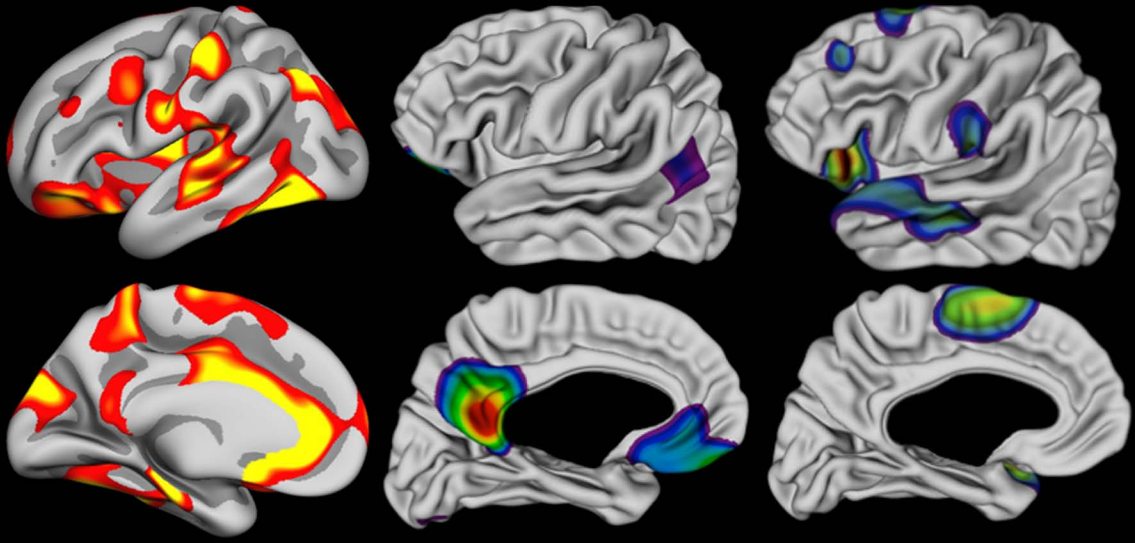
Fjell et al. (2012)

(C) Effects of birth weight on cortical area

Singletons

Singletons

MZ twins



Walhovd et al. (2012)

Raznahan et al. (2012)