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Klingberg Lab
Stockholm Brain Institute
Aging Research Center

Program

Thursday 1 September

08:00 Registration / coffee & tea

09:00 Welcome & introduction by Torkel Klingberg

Topic 1: Typical and atypical brain development across the lifespan

Chair: Brad Schlaggar

09:15 Jay Giedd
Child and adolescent brain development: New views from neuroimaging

10:00 Tomáš Paus
Social cues and the adolescent brain

10:45 Fika (Swedish coffee break)

11:00 Sarah Durston
Brain development in neurodevelopmental disorders

11:45 Patrick de Zeeuw (replacing Hugo Schnack)
Prenatal exposure to cigarette smoke or alcohol affects the volume of cerebellum in ADHD

Lunch

Topic 2: Cognitive development and brain function across the lifespan

Chair: Tomáš Paus
Co-chair: Tim Ziermans

13:00 Brad Schlaggar
Insights into typical and atypical development of the brain's functional network architecture

13:45 Andria Shimi
How does attentional control constrain visual short-term memory? Developmental and neural mechanisms

14:05 Eveline Crone
Learning from feedback across development

14:45 Fika

15:00 Ulman Lindenberger
Cognitive development from childhood to old age: Individual differences, mechanisms, and plasticity

15:45 Iroise Dumontheil
Effect of genetic polymorphisms of the dopamine system on brain and behaviour during development

16:05 Lars Nyberg
Relating 20-years of change in episodic memory to life-style, genetic and neural factors

16:45-18:00 Poster session & Meet the experts

19:30 Speakers dinner (bus departs at 18:15 from Nobel Forum)

Friday 2 September

09:00 Coffee & tea

Topic 3: Neuroplasticity in healthy individuals: "Boosting the healthy brain"

Chair: Torkel Klingberg

09:30 Torkel Klingberg
Training and development of working memory

10:15 Silvia Bunge
Intensive reasoning training alters patterns of brain connectivity at rest

11:00 Fika

11:15 Lars Bäckman
The role of dopamine in cognitive plasticity

12:00 Martin Lövdén
Spatial navigation experience shapes adult brain development in interaction with the BDNF gene

Lunch

Topic 4: Neuroplasticity in specific populations: "Boosting the vulnerable brain"

Chair: Lars Bäckman

13:30 Art Kramer
A tale of two training strategies: Boosting cognition & brain function

14:15 Rumana Chowdhury
Non-linear relationship between successful long-term memory and levodopa in healthy older adults

14:35 Barbro Johansson
Multisensory interaction in stroke rehabilitation

15:20 Fika

15:35 Sven Bölte
Facial affect recognition in autism: Can we animate the amygdala and the fusiform gyrus?

15:55 Michael Merzenich
Brain plasticity based therapeutics

16:40 Concluding remarks & goodbye

Abstracts

Oral Presentations – Thursday 1 September

09.15 Jay Giedd, MD, PhD

Child Psychiatry Branch, National Institute of Mental Health, NIH, Bethesda, USA

Child and adolescent brain development: New views from neuroimaging

Since 1991 my team at the Child Psychiatry Branch of the National Institute of Mental Health has used brain imaging, genetics, and psychological assessments to explore the neurobiology of cognitive/emotional/behavioral development in health and illness. The study design is for subjects from ages 3 to 30 years to be evaluated longitudinally at approximately 2-year intervals. As of July 2011 the data set comprises over 8000 scans from over 3000 subjects – ¼ from typically developing singletons, ¼ from typically developing MZ or DZ twins, and ½ from 20+ clinical populations including ADHD, Autism, and Childhood Onset Schizophrenia. Structural MRI data demonstrates roughly linear increases in white matter during the first three decades of life. Cortical and subcortical gray matter volumes generally follow an inverted U shaped developmental trajectory with peak size occurring at different ages in different regions. Particularly late to stabilize to adult cortical thickness is the dorsolateral prefrontal cortex, an area involved in neural circuitry subserving impulse control, decision-making, and long term planning. Functional MRI studies indicate a greater integration of brain components and a diffuse to focal activation pattern with increasing age. During adolescence there is a changing balance between earlier puberty related maturation of limbic structures and later maturing frontal regions. Twin studies show that heritability of brain morphometry varies substantially by age and region. Male brain measures are more variable and females, as a group, have earlier peak sizes of gray matter. The relative contributions of the X and Y chromosomes vs hormones is evaluated by studies of people with sex chromosome variations (i.e. XO, XXX, XXY, XYY, XXYY, XXXXX, and XXXXY) and of people with anomalous hormone profiles (i.e. Congenital Adrenal Hyperplasia, Cushing Syndrome, Familial Male Precocious Puberty, and Androgen Insensitivity Syndrome). The effects of specific genes and the impact of psychopathology on brain developmental trajectories will also be discussed.

10.00 Tomáš Paus, MD, PhD

Rotman Research Institute, Baycrest Centre, Toronto, Ontario, Canada

Social cues and the adolescent brain

No abstract available.

11.00 Sarah Durston, PhD

NICHE lab, Rudolf Magnus Institute, University Medical Center Utrecht, the Netherlands

Brain development in neurodevelopmental disorders

Brain development is an important parameter to investigate in neurodevelopmental disorders, such as ADHD and autism. Anatomical MRI studies have shown that brain changes in these

disorders are not fixed, but rather that the developmental trajectories of the brain may be most informative, and may relate to risk factors (such as risk genes) and even outcome (e.g., Shaw et al., 2007). In this presentation, I will discuss recent work using anatomical MRI and DTI in both cross-sectional and longitudinal designs to investigate developmental brain changes in neurodevelopmental disorders.
In ADHD, we investigated the relationship between IQ and brain development. Our results suggest that there may be multiple brain phenotypes associated with ADHD, where ADHD combined with high IQ is characterized by small, more global reductions in brain volume that are stable over development, whereas ADHD with low IQ is associated more with a delay of cortical development (De Zeeuw et al., submitted).
In autism, we have previously shown changes in the developmental trajectory of striatum that related to repetitive behaviour (Langen et al., 2009). I will be presenting new results from a longitudinal study, showing that it is the developmental changes in particular that relate to this behaviour (Langen et al., "Boosting the Brain" symposium, 2011).

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De Zeeuw P, Schnack HG, Van Belle J, Weusten J, Van Dijk S, Langen M, Brouwer RM, Van Engeland H, Durston S: Differential brain development with low and high IQ in Attention-Deficit/Hyperactivity Disorder. Submitted.

Langen M, Nederveen H, Bos D, Noordermeer S, van Engeland H, Durston S: Altered development of striatal structures is involved in autistic behaviour. "Boosting the brain" symposium, Stockholm, September 2011.

Langen M, Schnack HG, Nederveen H, Bos D, Lahuis BE, de Jonge MV, van Engeland H, Durston S: Changes in the developmental trajectories of striatum in autism. Biol Psychiatry. 2009;66(4):327-333.

Shaw P, Gornick M, Lerch J, Addington A, Seal J, Greenstein D, Sharp W, Evans A, Giedd JN, Castellanos FX, Rapoport JL. Polymorphisms of the dopamine D4 receptor, clinical outcome, and cortical structure in attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2007;64(8):921-931.

11.45 Hugo Schnack, PhD

Department of Psychiatry, Rudolf Magnus Instute of Neuroscience, Utrecht, the Netherlands

Human cortical surface development and intelligence: a longitudinal MRI study in over 1000 scans

Schnack, Hugo G.[1]; van Haren, N.E.M.[1]; Brouwer, R.M.[1]; Durston, S.[1]; Evans, A.C.[2]; Boomsma, D.I.[3]; Kahn, R.S.[1]; Hulshoff Pol, H.E.[1]

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[3] Free University, Amsterdam, the Netherlands

There is considerable cortical expansion during development in humans that is strikingly nonuniform.[1] This is evident from volum changes and cortical thickness changes and from cortical surface expansion.[1,2,3,4] However, at which point in time during development local cortical surfaces have reached their maximum expansion and to which extent local cortical expansion is associated with intelligence is not known. We mapped local surface area change between 9-65 years in more than 500 healthy individuals scanned twice using structural Magnetic Resonance Imaging at 2-5 year interval.2 We find that a few cortical regions reach their maximum surface area before the age of 10 years. However, most parts of the cortex surface reach their maximum in early adulthood, before age 25. Some parts of the cortex even increase in surface area until later in adult life, up to age 40, eg, the left insula. Moreover, we find that the surface of the left hemisphere matures approximately 2 years later than the right, but much larger discrepancies are found, eg, in language associated areas. The cortical surface reaches its maximum area earlier in higher intelligent

individuals compared to those with lower intelligence (IQ). Patterns of cortical surface area development are also associated with intelligence: At the age of 10, the corical area change rate shows a wide regional variety in associations (both negative and positive), suggesting that different parts develop at different speeds and/or different ages in relation to IQ. In adulthood, the associations are negative in most regions. Our findings suggest that cortical surface expansion in humans is present in childhood, adolescence and adulthood, and is associated with cognitive functioning.

References:

1. Hill et al, *PNAS* (2010)
2. Brans et al, *J Neurosci* (2010)
3. Hedman et al, *Hum Brain Mapp, in press*
4. Shaw et al, *Nature* (2006)

13.00 Bradley Schlaggar, MD, PhD

Washington University School of Medicine & St. Louis Children's Hospital, USA

Insights into typical and atypical development of the brain's functional network architecture

A full understanding of the development of the brain's functional network architecture requires not only an understanding of developmental changes in neural processing in individual brain regions but also an understanding of changes in inter-regional interactions. Resting state functional connectivity MRI (rs-fcMRI) is increasingly being used to study functional interactions between brain regions in both adults and children. In this presentation we will briefly review methods used to study functional interactions and networks with rs-fcMRI and how these methods have been used to define developmental changes in network functional connectivity. The implementation of multivariate pattern analysis methods using support vector machine classification and regression has allowed us to make predictions about the maturity of the brain’s functional network architecture in individuals. The implications of these approaches for understanding atypical development of the brain's functional network architecture will be discussed.

13.45 Andria Shimi, MA, MSc

Attention, Brain and Cognitive Development Group, Dept. of Experimental Psychology, University of Oxford, UK

How does attentional control constrain visual short-term memory? Developmental and neural mechanisms

Scerif, G.[1]; **Shimi, Andria[1];** Astle, D.[2]; Nobre, A.C.[3,4]

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[3] Brain and Cognition Lab, Department of Experimental Psychology, University of Oxford, UK
[4] Oxford Centre for Human Brain Activity, University of Oxford, UK

Visual short-term memory (VSTM) is limited in capacity, and differentially so over the lifespan. The neurodevelopmental mechanisms by which attentional control constrains the limits of VSTM remain poorly understood, but assessing how participants of different ages orient attention to mnemonic contents can elucidate this interplay. In a series of complementary experiments, we asked: 1) whether, and if so, how, attentional orienting facilitates encoding

into and maintenance in VSTM; 2) whether attentional constraints on VSTM are also influenced by the nature of the to-be-remembered items; and 3) about the neural mechanisms through which we orient attention in preparation of encoding as well as during VSTM maintenance. Our basic paradigm required participants to encode an array of items, followed by a probe stimulus whose presence in the array had to be reported. Memory arrays could be either preceded or followed by attentional cues. We targeted 6-7-year-olds, 10-11-year-olds and adults across experiments and measured event-related potentials locked to attentional cues and target items. Although age groups differed in their basic memory ability in the absence of attentional cues, performance was significantly improved by orienting their attention in service of memory and, during maintenance, differentially more so for older participants. In addition, all groups were influenced by the semantic and perceptual relatedness of the to-be-remembered items, suggesting that the nature of the representations on which attentional control operates is also critical to attentional benefits in VSTM. Thirdly, electrophysiological markers locked to attentional orienting cues and target stimuli indicated both similarities and differences in the mechanisms through which younger and older participants orient attention to representations in memory. Collectively, these studies elucidate how attentional control boosts encoding and maintenance in VSTM and throw light onto the mechanisms driving improvements in VSTM limits from childhood into adulthood.

14.05 Eveline Crone, PhD

Brain and Development Lab, Unit Educational Psychology, Institute of Psychology, Leiden, the Netherlands

Learning from feedback across development

Learning from feedback is probably one of the most important skills for successful task adaptation. It is well known that across development, children become better able to adapt their behavior following changing task demands, but the exact characteristics of this developmental progression are net yet well understood. In a series of experiments using heart rate, event-related potential and brain imaging data, we have investigated the developmental changes in learning from feedback.
Our studies using event-related potentials and fMRI in adults have consistently shown that negative feedback elicits increased activation in a set of brain regions including the pre-SMA/dACC, dorsolateral prefrontal cortex and parietal cortex. In addition, negative feedback also elicits heart rate slowing, which indicates a combined contribution of central-autonomic regulation. I will elaborate on how these responses are differently related to different types of negative feedback, and how these neural signatures provide a starting point for understanding developmental changes in learning from feedback. These developmental changes have been characterized by (1) increased differentiation to informative value of feedback, (2) a shift in neural responses from positive to negative feedback, and (3) increased connectivity between striatum and ventral medial prefrontal cortex when processing prediction errors. Together, these studies indicate that feedback-related activation cannot be simply explained in terms of neural immaturity but differs depending on learning strategy, which may change across development.

15.00 Ulman Lindenberger, PhD

Max Planck Institute for Human Development, Berlin, Germany

Cognitive development from childhood to old age: Individual differences, mechanisms, and plasticity

This talk starts out with a broad look at cognitive development, emphasizing the need to integrate theory and evidence across timescales, domains of functioning, and levels of analysis. I then will examine the development of episodic memory from a lifespan perspective by directly comparing children's patterns of memory performance to that of older adults. Based on data from COGITO, a large-scale age-comparative adulthood intervention study, I will present evidence indicating that positive transfer of cognitive training in adulthood, which so far has been restricted to individual tests, generalizes to cognitive abilities and is maintained over time, thereby carrying greater promise for improving everyday intellectual competence in adulthood and old age. I will also point to the large heterogeneity in cognitive development, and discuss its implications for research.

15.45 Iroise Dumontheil, PhD

Institute of Cognitive Neuroscience, University College London, UK

Effect of genetic polymorphisms of the dopamine system on brain and behaviour during development

Dumontheil, Iroise [a,b]; Ziermans, T.[a]; Roggeman, C.[a]; Peyrard-Janvid, M.[c]; Matsson, H.[c]; Kere, J.[c,d]; Klingberg, T.[a]

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b. Institute of Cognitive Neuroscience, University College London, UK
c. Department of Biosciences and Nutrition at Novum, Karolinska Institutet, Sweden
d. Department of Medical Genetics, Haartman Institute, University of Helsinki, Finland

Brain activity has been proposed has a promising intermediate phenotype to study the effect of genetic polymorphisms on behaviour. Working memory (WM) is a cognitive capacity that relies on a frontoparietal network of brain regions and on the dopamine neurotransmitter system. WM capacity and brain activity increase during development and WM deficits may predispose to diverse psychopathology. How genetic polymorphisms affect typical development and may relate to problem behaviour is unknown. Longitudinal behavioural and fMRI data was collected in a large sample of typically developing children and adolescents (aged 6 to 25 years old). In a first study we focused on a specific candidate single nucleotide polymorphism (SNP) in the *COMT* gene and, using a voxel-based analysis approach, demonstrated that the effect of this polymorphism on both visuospatial WM (VSWM) capacity and VSWM activation in frontal and parietal cortex clusters changed during development, with the adult pattern of genetic effect emerging during adolescence. In a second study, we identified a frontoparietal and occipital network of brain regions which showed increased VSWM with age and a positive correlation with VSWM capacity. We tested the effect of SNPs located in six dopaminergic candidate genes (*COMT*, *DAT1*, *DBH*, *DRD4*, *DRD5*, *MAO-A*) on VSWM activity in this network. A single genetic marker downstream of the monoamine oxidase A (MAO-A) gene was identified as showing a significant effect over this large network. Higher WM capacity was associated with fewer oppositional and aggressive symptoms, while *MAO-A* polymorphism did not directly predict problem behaviour. These results suggest a mediating role of VSWM capacity and brain activity in linking *MAO-A* to problem behaviour during development. Overall, our research highlights the importance of

considering the full developmental picture when trying to understand the impact of genetic polymorphisms on the mature cognition of healthy adults or psychiatric populations.

16.05 Lars Nyberg, PhD

Departments of Radiation Sciences and Integrative Medical Biology, Umeå University, Sweden
Umeå Centre for Functional Brain Imaging

Relating 20-years change in episodic memory to life-style, genetic, and neural factors

Episodic memory performance declines with the passage of time. Little is known about inter-individual differences in rate of change. Here we used a novel statistical approach, which took into consideration influences of attrition, to identify 15-20 years changes in memory. The initial performance level relative to an individual's age group was factored into the analysis. Of about 1500 examined participants, who participated in 2-4 longitudinal sessions, a minority was found to have an initial level that fell in the highest quartile and showed minimal decline over time. In a second step, these "successful" individuals were characterized with regard to demographic, genetic, and lifestyle factors. A subset of the participants had undergone structural and functional brain imaging, which allowed examination of brain traits in relation to robust cognition over time. These results shed light on brain-cognition plasticity across the adult life span.

Oral Presentations – Friday 2 September

09.30 Torkel Klingberg, MD, PhD

Department of Neuroscience, Karolinska Institute, Stockholm, Sweden

Training and development of working memory

Impaired working memory is associated with low academic performance and with distractability and inattention in clinically defined groups, such as in ADHD, but also in the general population.
Klingberg and collaborators have developed and tested a computerized method for training working memory. Several studies have shown that working memory can be improved by this method, and that performance improves also on non-trained tasks demanding working memory and top-down attention. Moreover, improving working memory also decreases the symptoms of inattention in everyday life. This has now been confirmed by several, independent research groups. Klingberg and collegues have also shown that training of working memory increases brain activity in frontal and parietal regions, and is associated with changes in the density of dopamine D1-receptors in the cortex.
Training of working memory might thus be a non-pharmacological way to address the key cognitive function in children with low working memory capacity. Future questions concern which other cognitive functions can be trained, and how strong transfer-effects are between functions. An interesting question is also how the neural basis of training induced plasticity can guide the developmental increase in working memory capacity during childhood.

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Olesen, P, Westerberg, H, Klingberg, T (2004) Increased prefrontal and parietal brain activity after training of working memory. *Nature Neuroscience* 7 (1):75-79.

10.15 Silvia Bunge, PhD

Department of Psychology, Helen Wills Neuroscience Institute, University of California at Berkeley, USA

Intensive reasoning training alters patterns of brain connectivity at rest

Mackey, A.P.; Miller-Singley, A.T.; **Bunge, Silvia A.**

Correlations in BOLD activity at rest have been shown to reflect a number of functionally relevant networks, including a fronto-parietal network. While networks detected at rest have often been interpreted to be stable traits, changes in these networks may reflect activity-dependent neuroplasticity. Neuroimaging studies have consistently demonstrated the involvement of a fronto-parietal network in reasoning ability. Rostrolateral prefrontal cortex (RLPFC), specifically, has been implicated in relational reasoning, or the ability to jointly consider multiple mental representations. We hypothesized that intensive relational reasoning training would lead to repeated co-activation of RLPFC and other frontoparietal regions, altering the connectivity of this network. Rather than designing an artificial training program, we chose to study individuals while they prepared for a standardized test that taxes

reasoning ability, the Law School Admissions Test (LSAT). LSAT questions involve relational integration since they require test takers to group or sequence items according to a set of complex rules. We recruited students who were taking an LSAT course that offers 70 hours of reasoning instruction (n=25), as well as age- and IQ-matched pre-law controls (n=24). Resting-state data was collected for all subjects during two scanning sessions 90 days apart. In the LSAT group, but not in the control group, we found a training-related increase in connectivity between left RLPFC and right posterior parietal cortex, and a decrease in connectivity between left RLPFC and left lateral frontal regions. No significant changes in resting-state connectivity for right RLPFC were observed in either group. These findings provide the first evidence that relational reasoning training can alter the strength and pattern of resting-state connectivity in the predominantly left-hemisphere network that supports this high-level cognitive capacity.

11.15 Lars Bäckman, PhD

Aging Research Center, Karolinska Institute, Stockholm, Sweden

The role of dopamine in cognitive plasticity

In an earlier age-comparative fMRI study, we found that training of updating letters in working memory (WM) transfers to an untrained and structurally dissimilar numerical n-back task in young adults. Transfer of learning was associated with caudate BOLD activity before training and a concomitant increase of caudate activity post training in both tasks. Although old adults showed marked training-related gains in the letter-memory criterion task, they exhibited no transfer. Striatal BOLD activity may be driven by dopamine (DA) agonism. Hence, in a recent PET extension of this work including young adults, we used the radioligand raclopride to examine whether updating training is associated with an increased release of DA. The behavioral data replicated those from the previous fMRI study regarding training and transfer effects. Critically, letter memory was linked to DA release before training and the intervention resulted in further DA release. Avenues for future inquiry in this program of research are outlined. In addition, I will review recent WM training work investigating the role of specific DA-relevant polymorphisms on the ability to benefit from training. The results suggest that a training context may be more sensitive in disclosing genetic effects on cognition than traditional single-assessment performance scores.

12.00 Martin Lövdén, PhD

Aging Research Center, Karolinska Institute, Stockholm, Sweden

Spatial navigation experience shapes adult brain development in interaction with the Brain-Derived Neurotrophic Factor (BDNF) gene.

Brain-behavior interactions are at the core of adult cognitive development, but these interactions, and the individual differences in how these interactions play out, are poorly understood. To inform this issue, I will report a series of intervention studies in which healthy younger and older men perform a spatial navigation task every other day over four months. Individuals in navigation training display navigation-related gains in performance and stable hippocampal volumes that are maintained four months after termination of training. Control groups display volume decrements consistent with longitudinal estimates of age-related decline. Cortical thickness of the medial parietal lobe display navigation-related increases in younger adults. Younger navigators also display increases in hippocampal N-acetylaspartate (NAA) as measured with magnetic resonance spectroscopy. Unlike measures of brain

volume, changes in NAA are sensitive to metabolic and functional aspects of neural and glia tissue and are unlikely to reflect changes in microvasculature. Training-induced changes in NAA were absent in carriers of the Met substitution in the Brain-Derived Neurotrophic Factor (BDNF) gene, which is known to reduce activity-dependent secretion of BDNF. Among BDNF Val homozygotes, increases in NAA were strongly related to the degree of practice-related improvement in navigation performance, and normalized to pretraining levels four months after the last training session. I conclude that changes in demands on spatial navigation can alter cortical thickness, hippocampal volume, and hippocampal NAA concentrations, confirming epidemiological studies suggesting that mental experience may have direct effects on neural integrity. BDNF genotype moderates some of these plastic changes, in line with the contention that gene-environment interactions shape the ontogeny of complex phenotypes.

13.30 Art Kramer, PhD

Beckman Institute, University of Illinois, Urbana, USA

A Tale of Two Training Strategies: Boosting Cognition & Brain Function

In recent years there has been an increasing interest in factors than can enhance cognition and brain. In many cases this interest has focused on the role of lifestyle factors, including physical activity, intellectual stimulation, social interaction and diet, as a means to improving cognition across the lifespan. In this presentation I will discuss two different projects in this general research domain, one focusing on the influence of physical activity and exercise and the other on theoretically-principled strategy-based cognitive training effects on cognitive and brain health. The fitness research will focus on randomized controlled trials of aerobic fitness training effects across the lifespan, concentrating on children and older adults. The cognitive training project will focus on the utility of different training strategies on learning, retention and transfer of new skills. In both cases behavioral and neuroimaging measures will be employed to provide insights into the mechanisms responsible for boosting cognition and the brain.

14.15 Rumana Chowdhury, BMedSci(Hons), MBBS, MRCP

Non-linear relationship between successful long-term memory and levodopa in healthy older adults

Institute of Cognitive Neuroscience, University College London, UK

Chowdhury, Rumana[1,2]; Guitart-Masip, M.[1,2]; Bunzeck, N.[3]; Medhora, J.[4]; Sasse, L.[5]; Dolan, R.[2]; Düzel, E.[1,6]

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[4] UCL School of Life and Medical Sciences, University College London, London, United Kingdom
[5] Department of Psychology, Birkbeck College London, United Kingdom
[6] Institute of Cognitive Neurology, Otto von Guericke University, Magdeburg, Germany

Episodic memory impairment is a common cognitive problem that emerges as part of the normal aging process. Dopaminergic neurons originating in the substantia nigra/ventral tegmental area (SN/VTA) decline with age. These neurons play a critical role in hippocampal

plasticity and consolidation of hippocampal-dependent memory. We hypothesised it may be possible to improve delayed episodic memory with administration of dopamine.
We administered 150mg of levodopa to 30 healthy older adults who performed an encoding task inside an MRI scanner, followed by behavioural memory recollection testing using a 'remember/know' paradigm after a short (two hours) and long (six hours) delay. Participants performed the tasks on two days (placebo versus levodopa, order counterbalanced) one week apart. The encoding task consisted of 120 images for which participants had to perform a category (indoor/outdoor) judgement with a button press, followed by either a neutral or monetary reward outcome. Participants were trained beforehand on which category was more likely to be rewarded, thus the images served as reward predicting or non-reward predicting cues.
Correct remember responses were used to index successful hippocampal-dependent memory recollection. We found that the relationship between the weight-adjusted dose of levodopa (150mg/weight(kg)) and correctly remembered non-reward-predicting images at delayed testing was explained by a significant quadratic ('inverted U-shape') regression model. The optimal dose of levodopa was approximately 2mg per kg of body weight.
Thus we have demonstrated that in healthy older adults, successful encoding leading to correct delayed recall of items can be modified in a non-linear fashion by levodopa administration.

14.35 Barbro Johansson, MD, PhD

Wallenberg Neuroscience Center, Lund University, Lund, Sweden

Multisensory interaction in stroke rehabilitation

The brain has a large capacity for automatic simultaneous processing and integration of sensory information. After a stroke, cortical and subcortical networks are often interrupted and the capacity for automatic and simultaneous processing of incoming stimuli is reduced. Current data indicate that relearning and compensation for lost functions after stroke benefit from multisensory stimulation such as action observation, mental practice (imaging) and training in a virtual reality setting. Anatomical, imaging and psychological studies indicate that the cerebellum is involved in networks serving higher cognitive functions including action observation. Broca´s area, traditionally looked upon as an excusive language area, is now thought to represent and detect complex hierarchical dependencies regardless of modalities and use, including gestures, action and music. Singing and speaking are multimodal activities that involve integration of auditory and sensorimotor processing with both shared and distinct neural correlates. Singing is slower and engages a larger bi-hemispheric network than speaking, and it may help to engage a brain network that facilitates sound-motor mapping. Music is a multimodal stimulus and listening to music activates many brain structure related to motor functions and sensory processing. In severe aphasia, intensive melodic intonation, e.g. melodic intonation, intense training 1.5 h/d 5 days a week, and simultaneous tapping with the left hand to prime the sensorimotor and premotor cortices on the right (intact) side for articulation, can remodel the right arcuate fasciculus.
More attention should be given to stroke heterogeneity, cognitive rehabilitation, and social adjustment. Reduced attention, working memory, episodic memory and executive functions are of main importance for the long-time prognosis. Genetic polymorphism may also play a role.

15.35 Sven Bölte, PhD

Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

Facial affect recognition in autism: Can we animate the amygdala and the fusiform gyrus?

Bölte, Sven[1]; Schlitt, S.[2]; Ciaramidaro, A.[4]; Beyer, A.[2]; Hainz, D.[2,3]; Weber, B.[3]; Gapp, V.[3], Poustka, F.[2]; Walter, H.[5]

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[5] Department of Psychiatry, Charité, Berlin, Germany

Background: One of the most consistent findings in the neuroscience of autism spectrum disorders (ASD) is hypoactivation of the fusiform gyrus (FG) during facial affect processing. In addition, reduced activation of the amygdala (AMG) has been associated with emotion perception alterations in ASD.
Objective: In this study, we examined whether computer-aided basic facial affect recognition training using the «Frankfurt Test und Training of Facial Affect (FEFA)» is associated with increased activation of the FG and AMG as well as specific and generalized behavioral gains in high functioning ASD.
Method/Results: Eight FEFA training sessions lasting one hour each are applied over a period of five to six weeks by experienced clinicians. BOLD-fMRI changes in the FG and AMG are registered pre-post applying an event-related facial emotion detection paradigm. Additionally, a battery of cognitive and clinical measures is assessed at baseline, post training and follow-up. Findings in 15 trained versus 15 matched untrained participants aged 15 to 30 years (mean age: ~ 20.5 y, mean IQ: ~ 105) show enhanced BOLD-fMRI signal changes in the FG and AMG during implicit facial affect processing pre-post FEFA training. Behavioral facial affect recognition measures yield high effect size improvements for tasks being identical and similar to FEFA training material, but only minor effects for more general emotion recognition and social cognition tests as well as clinical measures.
Conclusions: In contrast to a previous pilot study (Bölte et al., 2006), the present data indicate that circumscribed behavioral gains in basic facial affect recognition are indeed correlated with robust and expected neural activation changes in the FG and AMG. Nevertheless, on the behavioral level, of a lack of sufficient generalization of acquired affect processing skills was confirmed.

15.55 Michael Merzenich, PhD

Brain Plasticity Institute, Posit Science Corporation, San Francisco, USA

Brain plasticity-based therapeutics

New studies conducted in animal models along with recent studies that more completely document neurological differences in specific clinical indications bear important implications for the designs of effective training-based strategies for delaying or preventing -- and for treating -- chronic psychiatric and neurologic illness. The influence of this rapidly evolving science on strategies directed toward addressing the neuro-behavioral deficits in schizophrenia will be described, as an example of our efforts to create a new class of medically-validated treatments for brain-based illness.

Poster presentations – Thursday 1 September

Music practice affects development of visuospatial working memory and non-verbal reasoning

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Practicing a musical instrument has previously been associated with cognitive benefits in correlational and interventional trials, but the mechanisms explaining the effect are still unclear. In this longitudinal study of child development the effect of musical practice on reasoning and working memory development was examined. Individuals (n=247) between the ages of 6 and 25 participated in neuropsychological assessment at two occasions, two years a part. Linear regression showed that musical practice affected both development of reasoning ($\beta = 0.10$, $p = 0.027$) and visuospatial ($\beta = 0.10$, $p = 0.016$) but not verbal working memory. These effects were still significant when controlling for baseline initial performance, parental education, other hobbies and were similar in magnitude across ages. Furthermore, time spent on musical practice significantly explained improvement in visuospatial working memory, whereas type of instrument played better explained reasoning improvement. This suggests that music practice positively affects reasoning and working memory development and that different mechanisms may be involved in these effects.

The effect of dyslexia related genes on white matter structure in a normal sample during dhildhood

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Introduction: Volume and integrity of white matter correlates with reading ability, but the underlying factors contributing to this variability is unknown. In the present study, we investigated single nucleotide polymorphisms (SNPs) in three genes previously associated with dyslexia (*DYX1C1*, *DCDC2*, *KIAA0319*) and white matter density in a cohort of 76 children and young adults.
Methods: T1-weighted MR imaging was carried out in 76 healthy participants, aged 6-25 years, and repeated two years later for 69 of the participants. White matter segmentation was performed on the structural data using Voxel-Based Morphometry (VBM) and followed by an alignment technique, DARTEL. We performed a separate analysis for each of the 17 SNPs from the three dyslexia related genes to investigate if any of these polymorphisms affected white matter density. This model was corrected for the effect of age, gender, handedness and total white matter volume at the significance level of $p < 0.0029$ corrected for multiple comparisons in each SNP analysis with total corrected $p < 0.05$.
Results: We found that all three genes contained polymorphisms, *DYX1C1* (rs3743204), *DCDC2* (rs793842), and *KIAA0319* (rs6935076), that were significantly associated with white matter density in the left temporo-parietal region. The mean white matter density of each significant cluster had a significant correlation with reading scores. The correlation between polymorphism and reading was not significant.
Conclusions: The assessment of dyslexia genes effects on white matter structure showed that polymorphism of rs3743204 (*DYX1C1*), rs793842 (*DCDC2*), and rs6935076 (*KIAA0319*), have an effect on white matter density in a normal population of children and adolescents. The white matter density in these clusters significantly correlates with reading scores,

suggesting that genetic effects partly mediated through white matter development, which in turn has an effect on reading ability.

Cognitive training: An alternative rehabilitation program in Parkinson's disease, a pilot study

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Parkinson's disease (PD) is a heterogenic disease that is characterized by dopaminergic deficit in the basal ganglia which causes various motor and non motor problems for the individual. Reduced flexibility and updating in working memory is common in PD and are related to the dorsal striatum. Previous studies in healthy adults have shown that working memory training can influence the binding potential of dopaminergic neurons and can lead to an activity increase in striatum related to increased cognitive performance. Because of the central role of dopaminergic networks in PD and its connection to executive functioning we believe a period of updating training in early stages of PD could be beneficial. We performed a pilot study to investigate if training on updating was feasible in PD, if it could lead to better cognitive performance and to evaluate the effect in relation to dopamine function and brain activity on an individual level. 3 male participants underwent a 5 week long training period in cognitive updating. Dopamine function, brain activity during a working memory task, and neuropsychological assessments were performed a year apart before and after the training period for the participants and a group of 28 PD patients not participating in the intervention. Updating training was feasible and appreciated in the group. The training seems to have some effect on the trained task, and learning curves during training were similar to those seen in healthy elderly performing the same training program in a previous study. Updating training could be beneficial in PD and larger case control studies are needed to answer if a disrupted pathway can be compensated by a training intervention focusing on a task related to a target network area.

High performers are high gainers – factors influencing working memory training in children born very preterm

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Background: Children born very preterm (<32 weeks' gestational age) are at increased risk of executive dysfunction including working memory (WM) problems, which are thought to significantly contribute to academic difficulties in this population. WM training in children can increase the trained WM function and even non-trained WM domains (i.e. visual WM), fluid intelligence and reading skills. This study investigated how motivation, number of training sessions, IQ, age, and executive function influence the training gain.
Methods: Twenty-two children (7-12 years, mean IQ 101.4) born very preterm participated in 4 weeks (mean 19.4 sessions) of restorative WM training (BrainTwister, computerized adaptive verbal WM span training) and each week completed a motivation questionnaire.

Children completed neuropsychological assessment before the training to assess IQ (WISC-IV), processing speed (TMT A) and response inhibition (TAP incompatibility). A training gain score was calculated (mean WM span of last 2 training sessions minus mean span of first 2 sessions) to describe the benefit of WM training on WM span.
Results: The training gain score was positively correlated with the minimum WM span during the training (r=.478, p=.014). Motivation, number of training session, IQ, and age did not correlate significantly with the training gain score. However, response inhibition and processing speed performances before the training were found to highly influence the training gain score (response inhibition r=.490, p=.012; processing speed r=.545, p=.006).
Conclusion: Results suggest that very preterm children with higher WM span during restorative WM training benefit more from the training than those with lower WM span. Furthermore, good response inhibition and processing speed are likely to enhance the benefit of WM training in these children. The findings question the use of restorative WM training in effectively enhancing WM span in very preterm born children and other populations with executive function difficulties.

KIBRA polymorphism related to improved memory through enhanced hippocampal processing

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Several studies have linked the KIBRA rs17070145 T polymorphism to superior episodic memory in healthy humans. One study investigated the effect of KIBRA on brain activation patterns (Papassotiropoulos et al., 2006), and observed increased hippocampal activation in noncarriers of the T allele during retrieval. Noncarriers were interpreted to need more hippocampal activation to reach the same performance level as T allele carriers. Using large behavioral (N=2230) and fMRI (N=83) samples, we replicated the effect of the KIBRA T allele on episodic memory performance, but found increased hippocampal activation in T carriers during episodic retrieval. There was no evidence of compensatory brain activation in noncarriers within the hippocampal region. In the main fMRI sample, T carriers performed better than noncarriers during scanning, and importantly the difference in brain activation remained after post-hoc matching according to performance, sex and age (N=64). These findings link enhanced memory performance in KIBRA T carriers to elevated hippocampal functioning, rather than to neural compensation in noncarriers.

A developmental fMRI study on creative idea generation: indications for age-dependent ways of creative processing

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Creative idea generation involves both novelty and appropriateness, and therefore it benefits from generating ideas in a disinhibited, random way (divergent thinking), as well as combining categories in a focused and structured way (convergent thinking). Prior studies imply importance of left supramarginal gyrus (lSMG) and lateral prefrontal cortex in creative

idea generation (1, 2). Assuming that adolescence is associated with less inhibitory control and protracted development of prefrontal cortex functions involved (3), we came to two competing hypotheses: 1) creative idea generation would be enhanced in mid-adolescence based on better divergent thinking skills and less inhibitory control; 2) creative idea generation would be less well developed in mid-adolescence based on slowly developing convergent thinking skills and ability to reason in a structured way. To test these hypotheses, sixteen adults (25-30 yrs) and 24 adolescents (15-17 yrs) were presented with common objects and instructed to either think of as many a) Standard Characteristics (SC; 40 trials, control) or b) Alternative Uses (AU; 40 trials, experimental) during a15 seconds time-window, and subsequently indicated the number of solutions. Behavioral analyses revealed: a) more Standard Characteristics than Alternative Uses ($p<.001$) and; b) a trend towards more solutions for adults compared to adolescents ($p=.07$). Whole-brain fMRI analyses showed task-related activations of left lateralized frontal-parietal networks for both conditions and for both age-groups. Contrasting AU>SC revealed increased activation in lSMG in both adolescents and adults, and additional increased left dorsolateral prefronatal cortex (DLPFC) activation for adults but not adolescents. This age-group different was confirmed in a whole-brain two-sample-t-test ($p < .005$, uncorrected). Thereby, these results support the hypothesis of differentiation between creative processes and different ways of task solution depending on age. Specifically, the results show benefits for adults by reasoning in focused and structured ways, as indicated by more activation in DLPFC.

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Structural and functional neural correlates of video-gaming in adolescents

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Video-game playing is a frequent recreational activity in adolescents. Previous studies have reported an involvement of the dopamine-related ventral striatum. However, structural brain correlates of frequent video-game playing have to date never been investigated. On high-resolution MRI scans of 154 14-year old adolescents, we computed voxel-based-morphometry (VBM) to explore morphometric differences between frequent and infrequent video-game players. Moreover, we assessed the Monetary Incentive Delay (MID) task during functional magnetic resonance imaging (fMRI) and the Cambridge Gambling Task (CGT) outside the scanner. We found higher left ventral striatal grey matter volume when comparing frequent against infrequent video-game players that was negatively correlated with deliberation time in the CGT. Within the same region, we found an activity difference in the MID task: frequent compared to infrequent video-game players showed enhanced activity during feedback of loss compared to no loss. This functional activity was likewise negatively correlated with deliberation time in CGT. The association between frequent video-game playing and higher left ventral striatum volume could reflect altered reward processing and represent adaptive neural plasticity. The striatal activation during loss feedback in frequent gamers may parallel recent evidence that pathological gamblers show an increased striatal dopamine release when losing money

Altered development of striatal structures is involved in autistic behaviour

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Background: Repetitive, rigid and stereotyped behaviours are core features of autism and it has been suggested that they result from differences in the anatomy of striatum. In addition, studies of brain changes in autism have indicated that the time course of brain development rather than the outcome seems to be most disturbed. However, most of the studies investigating striatal differences in autism are cross-sectional, limiting inferences on development.
Objectives: Therefore, in this study, we (1) investigate brain development, and especially development of striatal structures in autism, using a longitudinal design; (2) examine the relationship of striatal development with repetitive behaviour.
Methods: We acquired sMRI scans from 68 individuals (35 subjects with autism, 33 matched controls). Each individual was scanned twice, with a mean scan interval time of 2.4 years. Mean age was 9.9 at time 1 and 12.3 at time 2. An automated image-processing pipeline was used to determine volumes of total brain, grey and white matter, cerebellum and lateral ventricles. Striatal structures were traced manually. Multivariate analyses of variance were used to investigate differences in brain development between diagnostic groups. To examine the relationship with behaviour, correlations between changes in brain volume and measures of repetitive and stereotyped behaviour were calculated.
Results: Our results show differences in the developmental pattern for striatal structures: growth rate of these structures was increased in the autism group in comparison to controls. Effects were most robust for caudate nucleus. Results were not accounted for by overall changes in brain growth, or scan processing differences. Second, the increased rate of striatal growth was related to measurements of repetitive behaviour: faster growth was correlated with more severe behaviour.
Conclusions: These findings substantiate the involvement of striatum in the aetiology of

autism and provide further evidence of the significance of altered trajectories of brain development in this disorder.

Neural basis of learning from feedback: informative value is more important than valence

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Feedback-based learning is one of the key foundations for successful learning and refers to our ability to use feedback in subsequent behavior. Previous studies suggest that several brain areas are sensitive to feedback valence. However, negative feedback is often more informative than positive feedback, possibly confounding these findings. To disentangle brain networks sensitive to the valence and/or informative value of feedback, we used a task in which both negative and positive feedback were informative for learning.
Thirty-two healthy young adults performed the task while fMRI-images were collected. Participants were instructed to sort series of three stimuli using positive and negative feedback. Stimuli could be sorted in three locations, so that during rule-searching, both negative and positive feedback were informative for learning. After applying the correct rule for all stimuli, rule-application continued for a maximum of 12 trials, after which a new series was presented. Post-hoc, the following conditions were distinguished. During rule-searching, feedback could be (1) positive or (2) negative, which were both informative feedback conditions. During rule-application, participants either (3) correctly continued positive responses or (4) made mistakes (response/memory errors).
During rule-searching, both positive and negative feedback (informative conditions 1&2) resulted in activation in pre-supplementary motor area(pre-SMA)/anterior cingulate cortex(ACC), dorsolateral prefrontal cortex, caudate and parietal areas relative to rule-application (conditions 3&4). When contrasting positive (1) and negative (2) feedback during rule-searching, only pre-SMA/ACC and insula were more active for negative than positive feedback. Behavioral results confirm that both informative conditions are similarly used for improving performance: virtually no mistakes were made after learning from informative conditions.
This study suggests that dorsolateral prefrontal and parietal cortex areas are not primarily sensitive to feedback valence. Rather, these areas attend to the informative value of feedback, regardless of valence. Currently, we are investigating this paradigm from a strategy analysis and developmental perspective.

Neural plasticity in STS mechanisms for processing phonological components

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Contrastive use of sound characterizes the sublexical or phonological structure of speech-based languages while in signed languages contrastive use of the shape, location and movement of the signing hands serves the same function. It has been shown that

mechanisms for processing speech sounds rely on the superior temporal sulcus (STS). Using fMRI, we investigated the neural correlates of equivalent mechanisms for signed language by asking deaf native signers to monitor either the shape or the location of the hands of a deaf native signing model articulating signs and non-signs. The signs were either familiar or unfamiliar and the non-signs were phonotactically illegal combinations of individual handshapes, locations and movements: phonological features that could have been legal in other contexts. A group of non-signers performed the same task. None of the signs were semantically accessible to the non-signers. The two groups performed equally well on the task and both activated ventral visual regions or the "what" stream when monitoring for handshape and dorsal visual regions or the "where" stream when monitoring for location. This demonstrates that monitoring the shape of signing hands engages visual processing mechanisms, and monitoring the location engages spatial mechanisms, whether or not these features have phonological significance to the observer. Both tasks activated STS bilaterally in signers but not non-signers. This activity was found across all three types of material, suggesting that it related to processing phonological features of signs. These results suggest that neural plasticity during development allows STS mechanisms for processing phonological components to adapt to the sensory requirements of the mode of communication.

A psychophysiological analysis of intentional action and inhibition: Developmental comparisons

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Previous research demonstrated that response inhibition matures during childhood and, depending on task difficulty, continues to develop into adolescence. In contrast to previous studies, concerned with stimulus-driven action and inhibition, the current study focused on the development of intentional action and inhibition. Three age groups (8-10-year-olds, 11-12-year-olds, and 18-26-year-olds) performed a version of the marble task derived from Kühn et al. (2009) while their heart rate was measured continuously. In the marble task, a marble is rolling down a ramp. In the 'stimulus-driven' condition participants are instructed to stop the marble as soon as it starts rolling, whereas in the 'intentional' condition participants are instructed to freely decide whether they want to stop the rolling marble. The results showed an age-related increase in the ability to stop the rolling marble in the 'stimulus-driven' action condition. Consistent with previous findings, stimulus-driven action was associated with a brief slowing of heart rate. The results revealed that in the 'intentional' condition all age-groups were able to intentionally inhibit stopping the marble. Most interestingly, in all age-groups a pronounced slowing of heart rate was observed during both intentional action and inhibition, indicating high attentional demands for both intentional action and inhibition. Currently, we are testing the marble paradigm in a simultaneous neuroimaging and heart rate experiment to further examine the concept of intentional action and inhibition.

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Age, sex and performance influence the visuo-spatial working memory network in childhood

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Background: Working memory (WM) has been described as a core cognitive ability underpinned by a fronto-parietal network. The frontal and parietal brain regions continue to develop into adolescence. Little is known about individual factors influencing the maturing network. This study describes the influence of age, sex and performance on the visual-spatial WM network in childhood.
Methods: 39 healthy children (19 females) aged 7-12 years were recruited as part of the NEMO study. Children completed a dot location fMRI task (Klingberg et al. 2002) to detect the network and a shape location task (BASIC-MLT) to examine performance. Analyses were conducted using SPM8. Laterality indices (LI) were calculated to assess the asymmetry of activation (LI -1 right hemisphere; LI +1 left hemisphere).
Results: Main activation clusters were found in superior parietal (LI -.206), superior and middle frontal (LI -.168) regions. There were no age or sex differences in WM performance. Younger children (7-9 years) showed an extensive and bilateral fronto-parietal network while older children (10-12 years) showed a more focal and more right-sided network, with a significant group difference in parietal activation (LI -.178 and -.243, p=.033). This significant parietal activation difference was also evident between boys and girls (LIs -.071 and -.334, p=.047) and between low and high WM performers (LI -.060 and -.455, p=.014).
Conclusion: Age, sex and performance influence the maturing visual-spatial working memory network, particularly with regard to activation of the parietal region. The influence of these individual factors on the developing WM network reflects the dynamic processes in brain development at a functional level. It will be important for paediatric neuroimaging studies to acknowledge age, sex and performance related variability in the maturing visual-spatial WM network.

Dopamine, working memory and training induced plasticity

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Cognitive deficits, and particularly deficits in working memory (WM) capacity, are common features in neuropsychiatric disorders. Interventions for improving WM and related symptoms could thus be of great importance. Pharmacological interventions acting on the dopaminergic system, such as methylphenidate, are known to improve WM performance. Behavioral interventions for improving WM capacity include intensive computerized training. WM training does not only improve WM capacity, but also attention and is associated with changes in dopamine D1 receptor density. These two different means of improving WM capacity, pharmacological and behavioral, thus appear to be associated with similar biological mechanisms in the brain. We here provide novel data suggesting that polymorphisms in the

dopamine transporter gene (DAT1) influence the improvements resulting from cognitive training on both WM and fluid intelligence in a sample of pre-school aged children. These results further emphasize the role of dopamine for cognitive plasticity.

Training Attentional Control in Infancy

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We present the results of a new meta-analysis suggesting that cognitive training studies targeting younger subjects tend to report more widespread transfer of training effects, which is consistent with convergent evidence [1-4] of greater neural and behavioural plasticity earlier in development.
We then present the results of a study in which we used gaze-contingent paradigms to train 11-month-old infants on a battery of attentional control tasks. Relative to an active control group and following only a relatively short training period, post-training assessments revealed improvements in cognitive control and sustained attention, reduced saccadic reaction times and reduced latencies to disengage visual attention. Trend changes were also observed in spontaneous looking behavior during free play, but no change was found for working memory; the amount of training correlated with the degree of improvement on some measures.
These findings are, to our knowledge, the first demonstration of distal transfer following cognitive training in infancy. Given the longitudinal relationships identified between attentional control and learning in academic settings [5,6], and the causal role that disrupted attentional control may play in the development of several disorders [7], they open a number of avenues for future work.
We conclude by discussing the potential of these techniques to provide training targeted at promoting early tools for learning. We also discuss possible uses in preventative interventions for infants at high risk of going on to develop particular disorders, as identified using genetic or epidemiological factors.

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Prenatal exposure to cigarette smoke or alcohol affects the volume of cerebellum in Attention-Deficit/Hyperactivity Disorder

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Prenatal exposure to teratogenic substances, such as nicotine or alcohol, increases the risk of developing ADHD. Such exposures are thought to exert a significant influence on neural development prenatally; a period where neural plasticity is arguably at its maximum. However, studies that have examined the relationship between ADHD and prenatal smoke or alcohol exposure have typically used symptom scales as outcome measures to assess the effect of prenatal exposure, and have not investigated the neurobiological pathways involved. The present study explores the effect of prenatal exposure to cigarettes or alcohol on brain volume in children with ADHD and typically developing controls. Children with ADHD who had been exposed prenatally to either substance were individually matched to children with and without ADHD who had not been. Controls who had been exposed prenatally were also individually matched to controls who had not been exposed. For prenatal exposure to both smoking and alcohol, we found a pattern where subjects with ADHD who had been exposed had the smallest brain volumes and unexposed controls had the largest, with intermediate volumes for unexposed subjects with ADHD. This effect was most pronounced for cerebellum. A similar reduction fell short of significance for controls who had been exposed to cigarettes, but not alcohol. We conclude that the well-established increase in risk for ADHD associated with prenatal exposure to teratogenic substances appears to be mediated through neurodevelopmental effects on cerebellum.

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