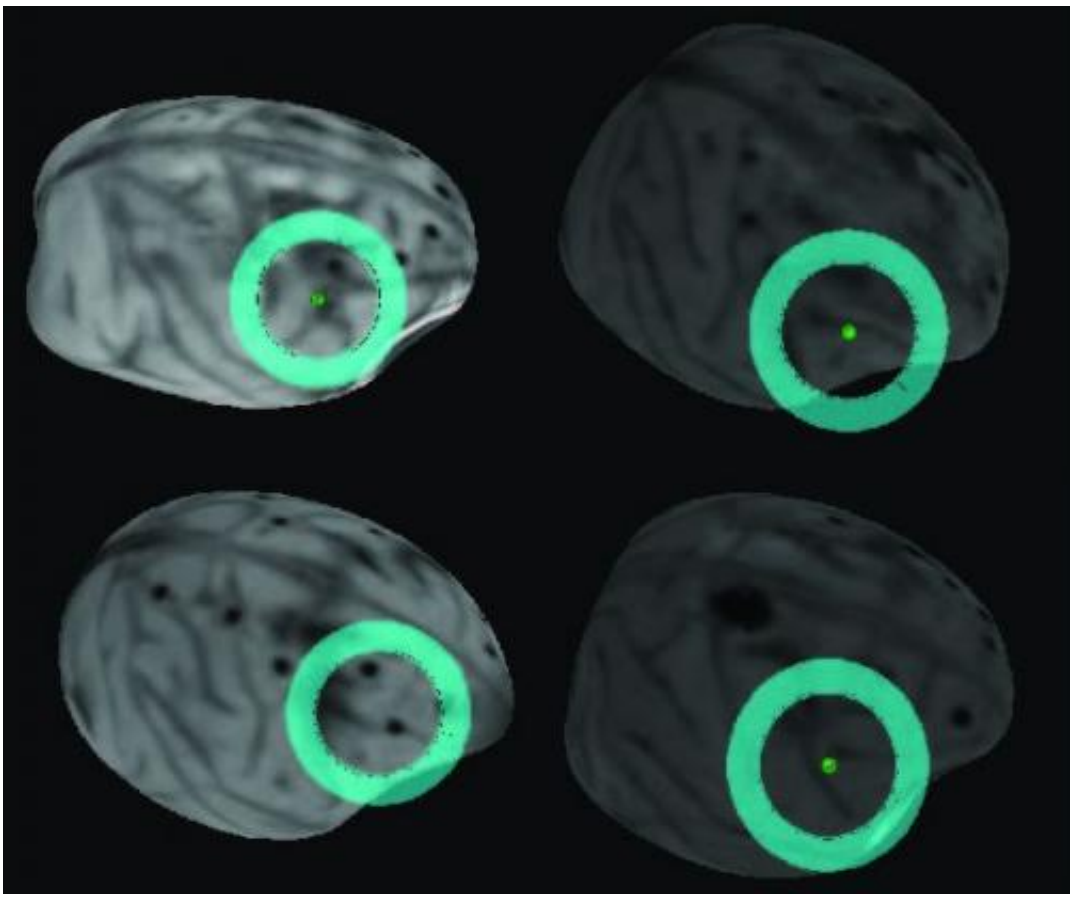
Medical Xpress

Childhood's end: ADHD, autism and schizophrenia tied to stronger inhibitory interactions in adolescent prefrontal cortex

March 14 2014, by Stuart Mason Dambrot



Images of the monkey brain around the time of puberty, with the prefrontal cortex highlighted. Credit: Courtesy of Xin Zhou

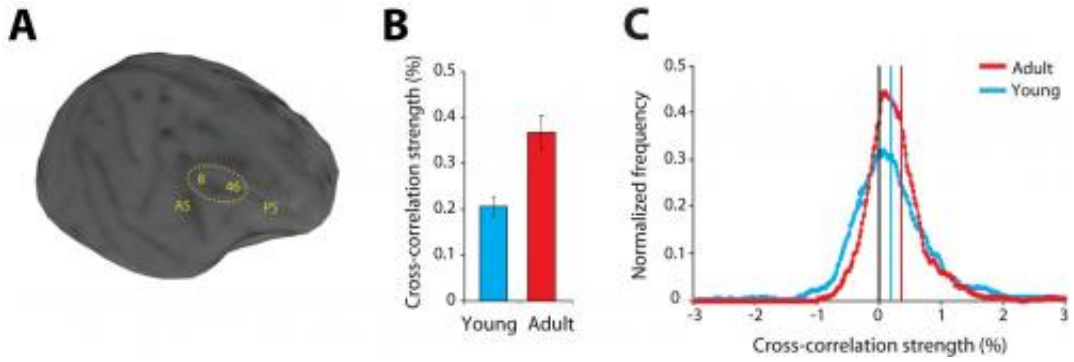
(Medical Xpress)—Key cognitive functions such as *working memory*

(which combines temporary storage and manipulation of information) and *executive function* (a set of mental processes that helps connect past experience with present action) are associated with the brain's prefrontal cortex. Unlike other brain regions, the prefrontal cortex does not mature until early adulthood, with the most pronounced changes being seen between its peripubertal (onset of puberty) and postpubertal developmental states. Moreover, this maturation period is correlated with cognitive maturation – but the physical neuronal changes during this transition have remained for the most part unknown. Recently, however, scientists at the Wake Forest School of Medicine in Winston-Salem, NC recorded and compared prefrontal cortical activity peripubertal and adult monkeys.

The researchers found that compared with adults, peripubertal monkeys showed lower connectivity due to stronger inhibitory interactions, suggesting that intrinsic (or resting state) inhibitory connections – that is, inhibitory neural connections that are active in the absence of any particular task – decline with maturation. The scientists then concluded that prefrontal intrinsic connectivity changes are a possible substrate for cognitive maturation.

Prof. Christos Constantinidis discusses the paper that he, Dr. Xin Zhou and their co-authors published in *Proceedings of the National Academy of Sciences*. When comparing the functional connectivity between pairs of neurons in neuronal activity recorded from the prefrontal cortex of peripubertal and adult monkeys and evaluating the developmental stage of peripubertal rhesus monkeys with a series of morphometric, hormonal, and radiographic measures, Constantinidis tells Medical Xpress that a major challenge was to obtain neural activity from the brain of monkeys around the time of puberty. "We needed to make ourselves experts in the developmental trajectories of monkeys and conduct experiments just at the right time relative to the onset of puberty," he explains.

Furthermore, he continues, identifying changes in intrinsic connectivity between prefrontal neurons as a possible substrate for peri- and postpubertal cognitive maturation carried challenges as well. "To address a potential difference in connectivity between neurons within the prefrontal cortex – that is, intrinsic connectivity – we needed to obtain a large sample of neuronal recordings from multiple neurons simultaneously. We inferred the strength of connections using a mathematical analysis of the time course of neuronal activity in each neuron – but this indirect measure is very noisy." For this reason, their conclusions needed to be based on hundreds of recording sessions.



Intrinsic connectivity in the monkey prefrontal cortex. (A) The ellipse indicates the recording areas in the dorsolateral prefrontal cortex. AS, arcuate sulcus; PS, principal sulcus. (B) Predictor-corrected average (and SE) of cross-correlation strength for all data from the young (n = 855) and adult monkeys (n = 465). (C) Distribution of cross-correlation strengths among all pairs of neurons from young and adult monkeys. Vertical lines represent means of the distributions. Credit: Copyright © *PNAS*, doi:10.1073/pnas.1316594111

Another challenge in these experiments was encountered in conducting behavioral and neurophysiological tests. "As the monkeys performed working memory tasks," Constantinidis says, "the young monkeys were rather temperamental and impulsive, and could not focus for very long

time at the cognitive tasks we used – not unlike children of equivalent ages." The scientists therefore had to devise simplified versions of the tasks and optimize data collection to be as fast as possible."

In their paper, the scientists also acknowledge that their conclusions carry a number of caveats:

- the study relied exclusively on male monkeys
- it wasn't practical to obtain neurophysiological recordings from a greater number of animals
- while effective connectivity allows statistical comparisons at the level of neuronal populations, this represents a functional rather than anatomical measure of connectivity

Regarding their findings, Constantinidis says "When we quantified the strength of connections between neurons in the prefrontal cortex, we observed that the average overall strength of connections was lower in the young monkeys than in the adults. Considering that there are two types of connections between neurons – excitatory and inhibitory – this difference could imply that excitatory connections were weaker, or inhibitory connections were stronger. We were surprised," he adds, "to find that the latter was the case." A corollary of this observation,

Constantinidis points out, is that maturation of neuronal connections between neurons must result in a decrease in inhibitory connections as the animals mature from the adolescent to the adult stage.

"The differences in the strength of connections we observed occur at the stage in development when cognitive capacities including working memory, impulsivity and executive function, are still not fully mature," Constantinidis continues. "Our conjecture therefore is that changes in intrinsic connectivity are ultimately responsible for the maturation of these cognitive functions, at least in part. A number of neuropsychiatric

conditions – most notably, schizophrenia – also appear during the time period of transition between adolescence and adulthood. Our results raise the possibility that connections within the prefrontal cortex follow an abnormal developmental trajectory in this condition."

While their results do not speak *directly* to the treatment for ADHD, autism and schizophrenia, Constantinidis notes, they do provide some working hypotheses about the mechanisms through which treatment works. "In recent years," he illustrates, "computerized training in working memory tasks has shown promise in the treatment of conditions including ADHD and schizophrenia. We hypothesize that such training can alter the strength of connections between neurons in the prefrontal cortex."

Another recent study[1,2] finding that a microglia deficit in mice lacking a given gene impairs functional neural connectivity and thereby leads to autism-associated behavior, Constantinidis says, "is a fascinating finding, pointing that maturation of connections between the prefrontal cortex and other brain areas is also a factor in the development of social behavior, in agreement with prior human studies. Together these studies and ours outline the range of connectivity changes that occur in cognitive development."

When it comes to next steps in their research, Constantinidis notes that the researchers are currently in the process of analyzing neural activity in the prefrontal cortex in monkeys during the execution of a variety of cognitive tasks as they progress from adolescence to adulthood. "Our long term goal is to understand the critical parameters of neuronal activity that characterize mature from immature cognitive behavior, and the structural substrates that mediate them in the prefrontal cortex."

Constantinidis tells Medical Xpress that other areas of research might also benefit from their paper. "We hope our findings will guide further

research on functional and structural changes between cortical neurons. Such changes may be responsible for other types of long-term cortical reorganization as a result of normal development and experience. Moreover," he concludes, "our research may ultimately benefit clinical applications for treatment of conditions such as autism, ADHD and schizophrenia. New drugs, training in cognitive tasks and other types of interventions may be evaluated based on their potential to modify the strength of connections between neurons in the prefrontal cortex."

More information: Age-dependent changes in prefrontal intrinsic connectivity, *Proceedings of the National Academy of Sciences*, Published online before print on February 24, doi:10.1073/pnas.1316594111

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[1]Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior, *Nature Neuroscience* published online 02 February 2014, doi:10.1038/nn.3641
[2]When less is more: Microglia deficit impairs functional neural connectivity, leads to autism-associated behaviors, *Medical Xpress* February 13, 2014