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RESEARCH HIGHLIGHT

Mapping Underlying Maturational Changes in Human Brain

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Human brain development is a complex process that continues between birth and maturity, and monitoring the underlying maturational changes at these stages is crucial for our understanding of typical development as well as neurodevelopmental disorders. During the critical periods of brain development, on one hand, many human capacities originate, but on the other hand, a brain undergoing rapid plastic changes may also be vulnerable to neuropsychiatric disorders [1–3]. Multi-modal magnetic resonance imaging (MRI) has been increasingly used for its ability to noninvasively reveal structural and functional changes in the brain. However, interpretation of the neurobiological processes underlying the findings obtained with MRI is very limited [4, 5]. Recently, in a report in *Science*, Gomez *et al*. attempted to test if, during brain maturation, the macromolecular tissue of a hominoid-specific structure, *i.e.*, face-selective regions in the fusiform gyrus, is pruned, proliferates, or remains stable, and to further understand the functional significance of these changes [6]. Most interestingly, the new findings from this study have overturned much of the traditional view by demonstrating that microstructural proliferation, rather than synaptic pruning and myelination, plays a dominant role in the development of the human face-recognition system during this stage. Here, they used quantitative MRI and estimated the macromolecular tissue volume (MTV) [7] in both children and adults, and have provided a different picture of the developmental basis of face-processing. This remarkable advance in the field of neuroimaging could open new windows into our understanding of the origin and etiology of disorders of face perception and recognition, such as prosopagnosia, Asperger syndrome, and autism [8].

This topic is of great interest in neuroscience. The basic stages and mechanisms of human brain development, especially in the postnatal period, are mainly inferred from observations in other species, or limited postmortem human brain tissues. Far from being a uniform process, human brain development continues throughout childhood and adolescence, with different regions developing at different rates. Nevertheless, the underlying age-related changes in human brain maturation at these two stages are still not fully understood. In general, neurogenesis appears to continue throughout adult life but produces only a small part of the neuronal population. Three other processes, proliferation and myelination, as well as synaptic exuberance and pruning, contribute to brain development in the postnatal stages from birth to adulthood [9]. (1) The proliferation and migration of glial precursors and differentiation of astrocytes and oligodendrocytes are largely postnatal processes, which could play an important role in the functional maturation of the human brain. (2) In terms

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of myelination, not only the formation of an insulating sheath along the axon, but also neuron-oligodendrocyte interactions have been shown to influence neuronal size and axon diameter. (3) The process of synaptic exuberance and pruning consists in the selective elimination of cells and their connections. Unfortunately, these underlying processes have not been clarified, partially because the human brain exhibits many structural and functional differences from other species, and a direct translation from animal to human could be misleading. Another hurdle is that many invasive investigation tools available to study animals cannot be applied to humans.

Recent advances in MRI technology allow tracing developmental changes in the human brain across the entire lifespan. Studies using MRI may furnish important clues about age-related biological alterations in the brain, providing opportunities to link these changes to human behavior. Numerous multimodal MRI images to date have spatial resolution adequate to describe *in vivo* changes in the developing human brain, but the nature of the underlying biological events is largely unknown [10–13]. The spatiotemporal patterns of normative changes in human brain tissues revealed by MRI thus far are consistent with the known cellular maturational changes occurring from childhood to adolescence. It is, however, often considered that the underlying changes in neuropil, neuronal size, and dendritic/axonal arborization are invisible to MRI.

Targeting functional selectivity and recognition memory, the researchers in this study used a new type of neuroimaging technique, quantitative MRI, to further investigate how the development of cognitive abilities is related to structural development of the brain. Quantitative MRI can be used to quantify many properties of the brain, such as the volume of tissue macromolecules, myelination (T1 relaxation rate), and changes in molecular composition (surface interaction rate). More importantly, these measurements are independent of the scanner hardware and imaging protocols. The developmental processes in macromolecular tissues can be predicted by the changes of MTV and T1. The prediction is rationalized as follows: proliferation increases MTV and decreases T1, while pruning leads to decreases in MTV and increases in T1. Like proliferation, increases in the myelination of axons would also result in increased MTV and decreased T1. The other biological event, potentiation, would lead to no changes in either T1 or MTV [6]. Based on the information extracted from the quantitative MRI data from children and adults, the researchers found that tissue proliferation is the mechanism influencing the observed cortical MRI changes, and mirrors improvements in the ability to recognize faces. Being curious about the underlying cellular structures, the group collaborated with colleagues in Germany, and demonstrated that the brain regions for face recognition have a unique cytoarchitecture, visibly different from that of the place-recognition region in the fusiform cortex. Moreover, the microscopic cellular structure of these regions resembled, and was indirectly compared with the face-processing regions identified by functional MRI. The results in their study showed that tissue proliferation plays a role in fine-tuning of the cortex, which was further confirmed in postmortem analysis of adult brains, and also simulations of increases in myelination. Furthermore, the changes seen in the fusiform gyrus are probably unique to humans, and may reflect the importance of facial recognition during adulthood.

To conclude, this study provides new insight into the human brain and cognitive development. Nonetheless, several related issues still need to be mentioned. First, the cross-sectional samples in this study are insufficient to map dynamic structural changes during maturation because of the difficulties in assembling comparable cohorts at different ages. In future, these limitations could be overcome by studying longitudinally acquired pre- and post-pubertal samples, in which the same children are rescanned prospectively at different ages over a long period. Recently, several life-span brain development projects have been launched around the world, including the Lifespan Human Connectome Project (http://lifespan.humanconnectome.org/), The Adolescent Brain Cognitive Development (ABCD) project (http://www.abcdstudy.org/), and the Chinese Color Nest Project (http://zuolab.psych.ac.cn/colornest.html). Second, although proliferation mainly contributes to the development of the face-processing areas, it should not be extrapolated to tell the whole story of human brain development. At each developmental stage, different brain areas could present various underlying cellular events. Recently, Chung *et al*. demonstrated in monkey prefrontal cortex that excitatory synapses on parvalbumin interneurons are pruned across adolescence [14]. Synaptic pruning has been proposed to contribute to the maturation of working memory in primate prefrontal cortical circuitry. Therefore, knowledge accumulated through these findings in animal studies, together with *in vivo* multimodal MRI mapping in the human brain, is essential to grasp the structural and cognitive development across the lifespan. Third, convergent evidence has shown that the face patch regions are specifically connected to each other, and functionally embedded in a larger-scale network of cortical and subcortical structures [15–17]. Besides, it is well known that brain function arises from the activity of neural networks beyond a local region, thus further studies are required to map the maturity of the entire face-processing system. From the perspective of brain networks, it would open up new avenues of research on normal and abnormal cognitive development. Recently, using non-invasive multimodal neuroimaging techniques, researchers have built a

new brain atlas, the human Brainnetome Atlas, which not only identifies the subdivisions of the entire human brain, but also reveals their connectivity profiles *in vivo* [18, 19]. This new brain atlas can help researchers to integrate the structure, function, and connectivity of specified functional regions. Using such a strategy, distinct sub-regions involved in different cognitive processes can be first delineated for each subject. Then, the structural and functional variations of the identified sub-regions and the white matter connecting them can be detected. Therefore, the work of Gomez *et al.* is just a starting point, and more research needs to be done to understand typical brain development as well as neurodevelopmental disorders.

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