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HOT TOPICS

Neuroimaging of plasticity mechanisms in the human brain: from critical periods to psychiatric conditions

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Neuropsychopharmacology (2023) 48:219–220; https://doi.org/10.1038/s41386-022-01415-0

Critical periods are windows of programmed neurodevelopmental plasticity wherein external inputs exert large and lasting impacts on the organization of neural circuits. Neural plasticity during critical periods is regulated by known biological mechanisms, which appear largely conserved across brain regions and across species [1]. Accumulating data implicate alterations in the expression of plasticity-regulating features in the etiology of youth-onset psychiatric conditions [2], suggesting the time is ripe to leverage decades of work on critical periods to mechanistically study plasticity in developmental psychiatry research. Fortunately, as highlighted below, substantial progress has been made in studying critical period associated mechanisms in humans using non-invasive neuroimaging.

Critical period plasticity is *initiated* by increases in inhibitory interneuron signaling; critical period onset can be accelerated by precocious increases in GABAergic neurotransmission [1]. Recent findings indicate that pharmacologically modulating GABA signaling alters patterns of functional connectivity in a neurotransmitter receptor-specific manner, underscoring the utility of pharmacological functional MRI for studying the inhibitory system [3]. Critical period plasticity is *sustained* in part by the refinement of glutamatergic connections, including the reorganization and unsilencing of excitatory synapses [1]. Glutamate chemical exchange saturation transfer (GluCEST) MRI [4] and positron emission tomography of synaptic vesicle glycoprotein 2A can be employed to estimate levels of glutamate and synaptic density, respectively, throughout the brain. Critical period plasticity is *reduced* by intracortical myelin growth, as myelin-derived proteins consolidate existing neural circuitry. Cortical myelination can be indirectly quantified with multiple MRI measures, for example the water-macromolecule magnetization transfer ratio, the T1-weighted to T2-weighted ratio, and the T1-based gray matter-white matter contrast (GWC).

Human neuroimaging methods can therefore be used to probe neurochemical, cellular, and functional features associated with critical period plasticity. Moreover, studies employing these methods have provided evidence that plasticity mechanisms are altered in youth with psychiatric symptoms. Attenuated development of GABAergic inhibition, as indexed by pharmacological functional MRI, was observed in older children and adolescents with heightened mood symptomatology [3]. Decreased glutamate within reward-encoding brain regions, as quantified with GluCEST imaging, was transdiagnostically associated with greater anhedonia in adolescents and young adults [4]. Altered intracortical myelination, as measured by the GWC, was linked to a more severe youth psychopathology burden [5]. Moving forward, non-invasive neuroimaging may help to discover whether disruptions in plasticity mechanisms—mechanisms illuminated by research on critical periods—represent a transdiagnostic feature of child and adolescent psychiatric conditions [2]. Evidence for transdiagnostic alterations in plasticity could inform preclinical research into plasticity-targeted treatments and aid design of Fast-Fail clinical trials that investigate the effects of treatment on neuroimaging plasticity markers. Potential investigatory approaches could include transcranial magnetic stimulation to alter synaptic inhibition and excitation, dietary enrichment with iron and sphingolipids to support myelinogenesis, short-term administration of benzodiazepines or valproate to shift the timing of plastic periods, or environmental enrichment to enhance ongoing neuroplasticity [6]. In light of data that rates of child and adolescent psychiatric symptoms and suicidality have increased across the globe in recent years, there is an urgent need to understand how we can better support youth mental and brain health during critical periods of development.

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VJS and TDS wrote the paper.

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Published online: 13 August 2022

FUNDING

VJS is supported by a National Science Foundation Graduate Research Fellowship (DGE-1845298). TDS is supported by R01MH113550, R01EB022573, R01MH120482, RF1MH116920, R37MH125829, R01MH112847, RF1MH121867, the AE foundation, and the Penn-CHOP Lifespan Brain Institute.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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