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INSIGHT

Potential Effects of the COVID-19 Pandemic on the Developing Brain

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By now, the COVID-19 pandemic has affected all corners of the world for over two years. Two years constitutes 4% of the life experience of a 50-year-old, or 50% of the life experience of a 4-year-old. Thus, in terms of the sheer proportion of total life experience, the pandemic has affected children much more than adults. Another major difference between children and adults is that the nervous systems of children are still developing, and thus are more subject to influence by experience and environmental factors.

Here, we focus on the effects of the pandemic on young children, in the framework of potential effects on neural circuit development and plasticity. We do not discuss the short- or long-term effects of viral infection *per se*, which have been reviewed elsewhere [1].

Brain Development and Its Regulation by Experience

Extensive studies in both humans and animal models have shown that early life experience bidirectionally impacts wiring of the brain, with rich sensory experience and rewarding social interactions promoting brain development and maturation, and on the other side, sensory deprivation and social isolation delaying or disrupting normal brain development.

Although the vast majority of the 86 billion neurons in our brains are already present at the time of birth, the synaptic connections that link them together are few and far between [2] (Fig. 1). Over the first several years of life, rapid growth of neuronal arbors and formations of synapses take place, building the intricate and precise neural network that allows us to perceive and to think, and that guides our behavior.

The development of different brain regions follows a stereotypical pattern, with subcortical regions first, followed by sensory and motor cortices, then language-related regions, and finally regions associated with higher cognitive functions [3] (Fig. 2). In each cortical region, the total synapse number first increases and then decreases. During the increasing phase, synaptogenesis and the formation of connections predominate, while during the decreasing phase, neural activity refines connections, strengthening those encoding important functions and pruning (or eliminating) rarely used ones [4]. The time window during which rapid synapse formation and pruning takes place corresponds to the sensitive period of the particular brain region [5, 6]. During the sensitive period, the anatomical and functional properties of neurons are particularly sensitive to modification by experience: enriching experience promotes synapse formation and maturation, while impoverished environments have the opposite effect [5, 6]. We draw attention to the concept of sensitive period in the context of the pandemic, because for young children with plastic brains, experience has long-lasting effects on how their brain gets wired up, and different brain regions are most sensitive at different developmental stages (Fig. 2).

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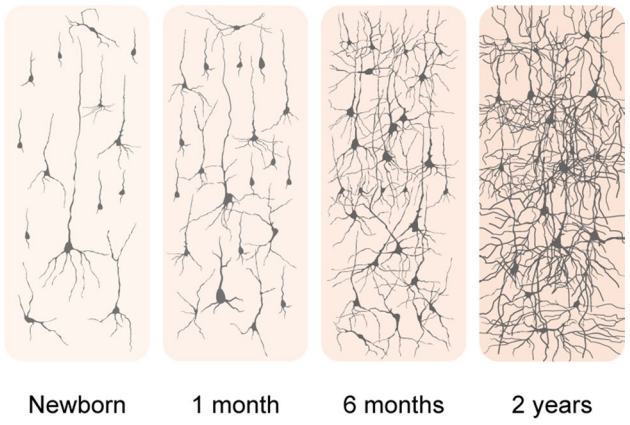

Fig. 1 Neuronal development in the human cerebral cortex during the early years. Golgi-stained sections of the middle frontal gyrus, showing a significant increase in dendrite arborization and neuronal connectivity during the first two years of postnatal life. Schematic based on literature [2].

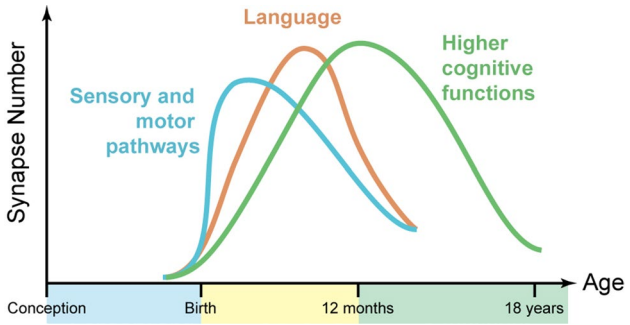

Fig. 2 Dynamic changes in synapse density during development. The time course of synaptogenesis and synapse pruning for different brain regions. Synapse number peaks during the sensitive period. Schematic based on literature [3].

Reduced Physical Activity and More Time Using Electronic Devices

Over the past two to three years, children in most parts of the world experienced disruptions to their daily routine, including lockdown, not being able to go to school/kindergarten/nursery, attending curriculum online, and conducting daily activities indoors. Not being able to go to school or to go outdoors, as well as limited access to sports facilities and extracurricular activities, typically means reduced physical activity. Exercise, or physical activity in general, helps to maintain physical health and mental well-being. In adults, lack of exercise mostly affects body weight and/or mood. Young children need to learn new motor skills, from crawling and walking, to riding a bicycle and playing ball. The motor cortex is highly plastic during the first few years of life [3], when motor skills are acquired most easily, following a typical developmental trajectory [7, 8]. A delay of a few months in learning any particular skill can be caught up. However, if reduced motor learning occurs over an extended period of time, it may lead to general developmental delay. We note that all brain regions are highly interconnected. The motor system works together with the sensory system to perceive, and to execute the decisions of higher cognitive regions. Thus, a delay in motor cortex development likely indirectly affects the development of other brain regions.

Concurrent with reduced physical activity, not going to school typically also means more time spent using electronic gadgets. Unavoidably, online classes are delivered through computers or other electronic devices. If/when parents have to work from home, children may be allowed to play on phones or pads to entertain themselves. While online learning can be a more effective teaching tool in some contexts and for some children, it may not suit everyone. In an in-person class, learning is multimodal. In online classes, the view is typically restricted, sound may not always be optimal, somatosensory or olfactory inputs are limited or nonexistent, and motor learning is very limited. For children who rely more on these modalities, learning may be less effective.

Changes in routines, not going to school, less physical activity, and more time using electronic gadgets may also lead to altered sleep patterns. Given the importance of sleep to neural circuit formation and maturation, less sleep or less regular sleep may negatively impact brain development.

Reduced Social Interaction Opportunities

Not going to school/kindergarten/nursery, as well as fewer extracurricular activities, typically means fewer opportunities for social interaction. The development of social skills, like all other skills, follows a typical developmental trajectory [7, 8], has sensitive periods [5, 6], and benefits from both opportunities to observe others and to practice skills. At one year of age, children begin to show interest in other children; between two and three years, they start chasing each other, learn to play cooperatively, and learn to negotiate solutions to conflicts. Reduced social interaction time with peers means fewer opportunities to engage with other children and to develop social skills through practice. In older children, in order to learn a team sport, such as basketball or soccer, one needs to interact with others in highly dynamic situations and to make rapid decisions as the game progresses. While learning to play any particular sport is not essential, being able to work with others in a team is an important social skill. Staying at home and social distancing also means that children interact with unfamiliar adults less frequently. This also reduces their opportunities to watch how different individuals interact with each other. In the real world, one needs to interact with different people in

diverse situations. These skills need to be developed over time, through cycles of observation and practice.

Routine Changes and Alterations in Household Dynamics

The pandemic has changed everyone's routine at some point in the past couple of years. For children whose parents travel extensively or work late hours, the pandemic may mean that they actually spend more time with their parents. Parents may be stressed about working from home and taking care of the children at the same time [9]. Some children may sense the stress and become anxious themselves, while others may enjoy and benefit from more quality time with their parents. For children whose parents are essential workers, school closure may mean that they receive less care than usual for some time during the pandemic.

Changes of routine and uncertainties are stressful for most people. Extensive research in humans and animal models have shown that stress significantly affects brain development, but how each person responds to stress is highly individual [11, 12]. Most youngsters can overcome mild stress, and the experience likely aids their overall growth and development [13–15], making them more resilient to future challenges (Fig. 3). As the German philosopher Friedrich Nietzsche wrote: "what doesn't kill me, makes me stronger". However, if/when stress is beyond one's coping abilities, negative consequences follow [11, 12] (Fig. 3). How sensitive each child is to stress is highly individual, and is influenced by genetic factors, family and community environments, and developmental timing [14]. Extended stress during early development may have detrimental effects on brain development, and is a significant risk factor for psychiatric disorders later in life [11, 12] (Fig. 4).

Vulnerable Individuals

The above issues likely affect all children to some extent. However, some vulnerable groups may be significantly more affected. First and foremost, are those who have lost loved ones, especially close family members, due to the pandemic. Losing loved ones is a traumatic experience for everyone. This is especially the case if the person is the main caregiver or a close family member of the child.

Families with fewer financial resources are also more affected by the pandemic. If parents are essential workers, but children cannot go to school, then childcare becomes an issue, especially for families with limited means. Taking classes at home also requires various electronic tools and good internet connections. In a household with multiple children, the number of electronic tools or separate spaces

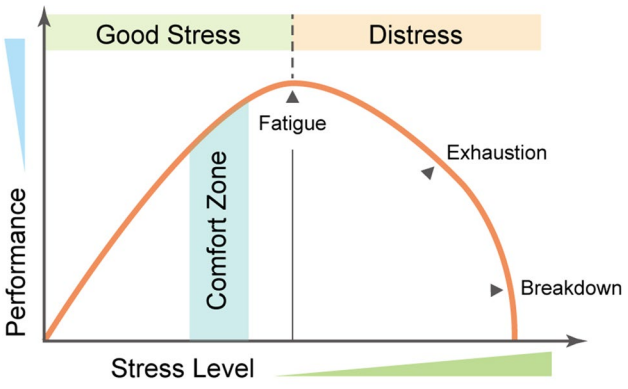

Fig. 3 The stress response curve. The curve shows that as the level of stress increases, performance initially increases. In an area called the Comfort Zone, the stress level is manageable and facilitates good performance. As stress begins to be perceived as overwhelming or excessive, the person reaches a fatigue point where the performance starts to decline, ending in exhaustion and breakdown. Schematic based on literature [13].

to take classes at the same time may be limiting [16]. Over extended periods, these differences will likely accumulate [16].

Last, but not least, are children with learning disabilities. Moving from multimodal teaching in a classroom to mostly visual- and audio-dependent teaching online may be adaptable for children with preferences in these modalities of learning; however, for children who prefer sensory-motor interactions and hands-on learning, disruption is likely to be significant. Moving online also means fewer social interactions between peers and with teachers. Children with autism spectrum disorder (ASD) have reduced social interactions and repetitive behaviors [2]. They face major challenges during the pandemic, including, but not limited to, changes of routines and reduced social learning opportunities [1]. Children with attention deficit and hyperactivity disorder (ADHD) or intellectual disability also face many challenges [1]. In children with learning disabilities, adapting to new routines and new ways of teaching is likely much more challenging than for typically developing children.

Looking into the Future: Optimism and Caution

Data on the effects of the pandemic on child development is just beginning to emerge [17]. Evidence thus far suggests that children are reaching developmental milestones more slowly, as compared to historical controls, independent of SAR-CoV2 infections. Vertical transmission of SAR-CoV2 infection is rare. However, a recent report associated birth during the pandemic with neurodevelopmental delays at 6 months of age, independent of maternal infection [10]. There is also evidence for increased levels

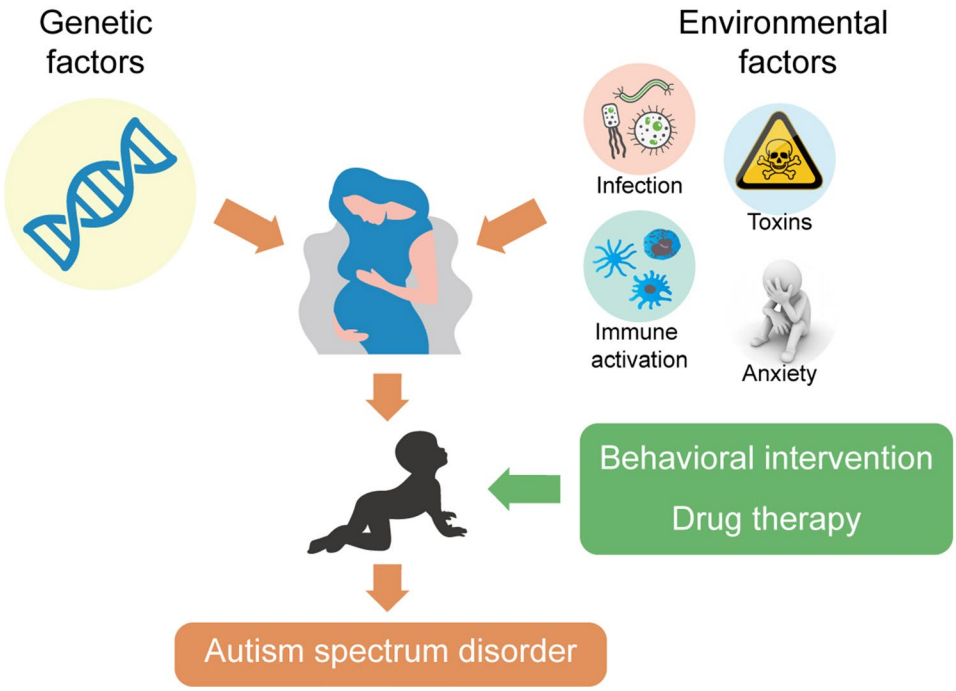

Fig. 4 The contributions of genetic and environmental factors to the etiology of autism. Genetic factors, as well as environmental factors, including but not limited to infection, toxins, immune activation, and anxiety, can increase the risk of developing autism. The ability of environmental factors to influence the progression of autism lends opportunities for behavioral intervention and drug therapy.

of anxiety and depression in children and adolescents during the pandemic [18].

How the COVID-19 pandemic, or pandemics in general, affects brain development is to be determined in future longitudinal studies. A previous study showed that babies born to individuals who experienced significant stress during the 2011 floods in Queensland, Australia, had temporary delays in the development of problem-solving and social skills at 6 months, but that significant responsiveness from parents overcame these delays by 30 months [17]. Thus, given the high level of plasticity of the developing brain, these setbacks are likely to be temporary for most children [17]. Skills not learnt during the pandemic would be picked up after a few years back in school. Similarly, the effects of anxiety and depression due to specific circumstances would not be long-lasting in most individuals.

How the pandemic affects each child depends on many factors [14]. A dimension that is constant and at the same time variable is developmental time. Each brain region has its peak sensitive period during which that brain region is most amendable to environmental influences [5, 6] (Fig. 2). If disruptions occur within this time window, then setbacks are likely to be more significant. Conversely, amendments made within the sensitive period can be highly effective (Fig. 4).

For children with ASD, ADHD, or intellectual disability, however, having fewer in-person classes or difficulties in adapting to an online curriculum, may have long lasting consequences. Children with learning disabilities typically need more instruction, more practice, or specific ways of teaching, in order to acquire knowledge that typically-developing children acquire with ease. If they do not receive these instructions and/or practice during the sensitive period, catch-up will likely be much more difficult [1]. In a recent survey, parents of ASD children reported significant service disruptions that negatively impacted children's behavior and parents' mental health, with younger children, children with more severe ASD symptoms, and children from lower-income families being most affected [19].

As a general rule, the earlier within the sensitive period, the more effective the catch-up learning; if the optimal learning window has passed, catching up to today is always better than tomorrow. For children with ASD or other learning disabilities, catch-up learning typically also mean higher intensity of instruction.

As a community, we have learnt much during the pandemic, developing many new online teaching approaches, which can be combined with traditional in-person teaching for optimal effects. Individuals for whom online learning is preferred, should continue. For others who find online learning less effective, we can further develop online tools, in combination with in-person approaches to optimize mixed teaching, in case of future lockdowns and to provide a more diverse teaching portfolio. At the community level, we will also benefit from longitudinal studies of the long-term effects of the pandemic and learn from the data acquired, using the information to build more resilient societies, with a focus on maternal, neonatal, and child health [20]. History only gives us one option, which is to look ahead and move forward.

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