Editorial

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Environment and Brain Development: Challenges in the Global Context

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The human brain develops over an extended period; its maturation continues through adolescence and young adulthood [1–3]. Studying trajectories of brain development in representative samples of the general population is important in order to understand exposures and stressors in the child's and adult's physical and social environment that shape human brain development [2–4]. Early environments may be particularly important in their impact on mental health, learning and behavior in human societies [2, 3]. In this context, it is important – for both theoretical and practical reasons – to measure trajectories of brain development in large population-based epidemiological studies [2, 5].

Researchers with expertise in environmental epidemiology, neuropsychology, psychiatry and developmental cognitive neuroscience contributed to a 2-day scientific debate convened in Barcelona during October 2014. The debate focused on neuroimaging and neuropsychological approaches for the assessment of brain and cognition in typically developing children and adolescents and the challenges of assessing environmental exposure for studies carried out in the general population. The ultimate goal was to generate a consensus about the importance of population-based studies that integrate information across different levels: molecular (e.g., biochemical, genetic), systems (e.g., structural and functional neuroim-

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aging and cognitive assessments) and populations (e.g., air pollution) [2]. The debate covered 3 strategic areas: (a) environmental pollution and population science, (b) measures of brain development and (c) future directions and conclusions.

Environmental Pollution and Population Science

There are about 214 chemicals that have been documented in clinical and epidemiological studies as having neurotoxic properties, mainly in adults. Only 12 of these have been properly examined with regards to their effects on human brain development; this is because most of the other chemicals have not been explored specifically in pregnant women and children, and/or we have only limited data on exposures to these chemicals at the population level. The evidence available on these 12 substances suggests that adverse impacts on brain development can happen at much lower exposures than those that affect the mature brain [3]. Nonetheless, the present documentation [3] almost certainly underestimates the real number of chemicals affecting neurodevelopment. In consequence, there is a need to develop screening methods that are validated against epidemiologic data in their prediction of neurotoxicity. It has been hypothesized that many untested neurotoxic chemicals may be responsible for a 'silent pandemic', in which early life exposures are causing multiple neurodevelopmental disorders, costing billions of dollars annually to our societies [3]. For example, ambient air pollution is not yet listed in the European Environmental Agency as a neurotoxic hazard due to the complexity in measuring a mixture of exposure components. And yet, recent findings indicate negative relationships between cognitive performance and air pollution in school age children [6]. Similar problems in relation to exposure measurements exist for other environmental chemicals, such as persistent organic compounds including organo-chlorinated and brominated compounds, or endocrine disruptors, such as phthalates and phenols, which are mixtures of different highly correlated compounds [3]. Multiple biological pathways and modes of action can help to explain the neurotoxicity of these and other environmental pollutants, from enhancing pro-inflammatory and oxidative stress mechanisms to endocrine system disruption [3]. Parallel concerns about social environments and stresses reflect their importance in brain development; it is recognized that adverse exposures, such as child maltreatment, poverty of the learning environment, and poor and inconsistent parenting, can all disrupt a child's mental health on their own and in interaction with pollutant hazards [3, 7]. Both the environment and neurodevelopment are complex, and studying the interaction of the chemical and non-chemical factors requires a multi-modal approach that takes into account several dimensions in terms of measurements, including time (longitudinal approach with repeated exams) and space (neighborhoods, personal space), as well as co-exposures within and between physical and social environments. Taking such an integrated approach is important given that some co-exposures may have opposing effects on the outcomes, some positive and others negative; for example, omega-3 fatty acids versus methylmercury (or PCBs) in seafood, or physical activity versus exposure to ambient air pollution while exercising. Finally, even a weak effect on neurodevelopment is of large concern when the exposure is ubiquitous across populations. As pointed out by Geoffrey Rose, 'the majority of cases in the population occur not in the small numbers at very high risk but in the center of the population distribution, where large numbers of people are exposed, albeit with only modest increases in risk' [8]. Thus, reducing even slight exposures of the general population to various risks present in their physical and social environments – especially during development – is likely to accrue large benefits for public health.

Measures of Brain Development

Longitudinal measures of brain development – whether neuropsychological or neuroimaging – provide insights into typical trajectories against which one can evaluate the possible impact of adverse physical or social environments. Multimodal MRI is non-invasive and provides detailed information about brain structure and function [2]. For example, a recent MRI study has identified an association between prenatal exposure to air pollutants (polycyclic aromatic hydrocarbons) and the development of brain white matter, cognition and behavior [9]. Similarly, computerized neuropsychological tests performed repeatedly over time have shown association with air pollution in school age children [6]. Moreover, the recent inclusion of computerized tests has reduced inter-observer variability during assessment, and such neuropsychological functions are recorded automatically preventing errors in the act of data collection [6]. It will be important in global health epidemiological studies to select an appropriate range of tests to assess complex cognitive functions (e.g., cognitive control or emotion regulation), as well as memory, perceptual and motor functions, with minimal cross-cultural biases. In this selection, we should go beyond WHO's recommended neurobehavioral core test battery (NCTB), which includes mostly basic cognitive functions [10]. Furthermore, such 'normative' outcome measures can be complemented by internationally standardized (behavioral) rating scales aimed at covering clinical outcome measures in order to improve our understanding of the relationship between environmental exposures and mental health. This approach relies on using a dimensional rather than a categorical approach when clinically diagnostic data are not available. The careful selection and combination of some of these measurements can make the understanding of neurodevelopment in populations feasible in a global context.

Future Directions and Conclusions

There is a need to address one of the most important emerging and newly recognized scientific challenges in global public health: the study of environment and brain development. We need tools for state-of-the-art measurements for both (environmental) exposures and (brain) outcomes to provide knowledge necessary for future interventional/prevention trials in a global context. We agree that there is some need for general 'harmonization' of neuropsychological measurements and imaging across cultures and studies. Nonetheless, we should go beyond WHO's NCTB due to (1) improved understanding of the vulnerability of the developing brain, (2) new insights into the sensitivity and validity of neuropsychological tests and (3) improved and less expensive neuropsychologic, neurophysiologic and imaging methods. Nowadays, there is enough scientific and technological expertise available to adopt common outcome assessments when building successful global consortia. The research community needs to be sensitive to contextual factors that may influence the practicality and feasibility of different approaches. These include, for example, whether or not a medical center is close to a study population and how cultural and economic differences or parental education may influence participation. Furthermore, some of the brain mapping tools (e.g., MRI) are still expensive and require major logistic efforts, including standard data capture and complex data processing protocols. Other tools (e.g., electroencephalography, event-related potentials) are more cost-effective and applicable in global context. In the future, we can benefit more from the use of new and cheaper technologies, not only from techniques and software that improve imaging and data processing but also from lighter and portable electroencephalography instruments, also due to the expanding use of smart phones and microsensor technologies to capture, for example, a child's air pollution exposure, physical activity and cognitive functioning.

If we are to understand brain development and its determinants in their full diversity, we need to strive toward global standards for assessing and characterizing normal brain maturation. Achieving a consensus on optimal assessment approaches would enhance the collaboration across studies carried out in different linguistic, cultural and economic environments. Population science targeting child neurodevelopment and mental health is relevant for framing the global burden of non-communicable disease debate. In other words, the discussion initiative tries to reach a common goal of understanding forces underlying the brain development trajectories assessed in global and diverse context. The panel discussants concluded that it is crucial to include experts in neuropsychology, neuroimaging, developmental cognitive neuroscience, environmental epidemiology and exposure sciences in international consortia assessing the global health burden.

Key Messages

- The study of neurodevelopment trajectories in a global context needs a multidisciplinary scientific approach in order to understand better human brain function and structure and its interaction with the environment.
- Mental health should not be understood as the absence of medical diagnoses but must be linked to optimal brain functioning.
- The careful selection of neuropsychological and neuroimaging measurements makes the understanding of neurodevelopment in populations feasible in a global context.
- Computer-based neuropsychological tests with low cross-cultural bias are important new tools in a global context.
- Common brain mapping approaches can be used to understand mechanistic pathways.
- Future research should take advantage of technology adding and improving measures of exposures and outcomes.
- International consortia conducting population-based studies are a key tool.

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