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Integrating early life stress in neurological disease: advancing preventive neurology

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ABSTRACT

Background In 2021, an estimated 43% of the world's population had been diagnosed with a neurological disorder. Early life stress (ELS) is now a well-established risk factor for later-life neurological disorders. However, translation to clinical practice is hindered by oversimplification, lack of standardisation and limited knowledge of the patterns and mechanisms of disease pathogenesis.

Methods The current paper reviews existing literature relating to ELS and neurological disorders and provides an overview and clinical perspective of the gaps in knowledge and future directions required to improve clinical care for patients.

Results To develop effective preventive or restorative therapies, there will be an increasing need to understand and further define the role of ELS in the subsequent emergence of neurological disorders and to investigate the interaction of ELS with other more widely recognised genetic and environmental factors.

Conclusions We propose that additional interdisciplinary studies are needed to develop standardised scales to assess ELS and a new taxonomy and survey of ELS for future interdisciplinary studies. In addition, we suggest that further studies involving clinical cohorts have the potential to contribute to important findings that could help enhance the care of patients.

INTRODUCTION

Collectively, neurological disorders affect around 3.4 billion people worldwide, making them the leading cause of illness and disability.[1] Traditional neurology emphasises the biological aspects of brain dysfunction and, although the psychosocial history is included in the evaluation, exploring childhood adverse events is not typically included for adults. However, research into early life experiences including parenting styles, environment and sociodemographic factors is providing evidence that a significant portion of neurological dysfunction may be caused by modifiable and preventable factors experienced in early life.[2] This includes a reported association between ACE's and a greater incidence of headaches, an increased risk of functional neurological disorders, earlier onset and faster progression of neurodegenerative disease and earlier onset of multiple sclerosis.[3 4]

Many Australians have experienced adverse childhood experiences in multiple forms. The Australian Child Maltreatment Study has significantly advanced our knowledge of child maltreatment in Australia by surveying over 8500 individuals aged 16 and older.[5] Key findings include that approximately 39.4% of respondents have experienced more than one type of maltreatment and approximately 23.3% have experienced between three to five types of maltreatment. A smaller percentage, 3.5%, have experienced all five types of maltreatment: Physical abuse, sexual abuse, emotional abuse, neglect and exposure to domestic violence. The study found that experiencing multiple forms of maltreatment was associated with three to five times the odds of anxiety, depression, substance use disorder, post-traumatic stress disorder or self-harm.[6 7] The study also found that maltreatment was associated with increased hospitalisations for stroke and higher rates of health provider consultations.[8]

Social determinants of health and child maltreatment have been implicated in atypical neurobiological maturation and functional abnormalities.[9 10] Poor parenting styles have been recognised as a major contributing factor in child and adolescent mental illness.[11] While associations between early life stress (ELS) and neurological development are generally well-accepted, the mechanisms of action and patterns of these relationships require further investigation. Not all children exposed to ELS will experience deficits or similar patterns of neurological dysfunction. ELS is thought to act in concert with individual genetic factors to create individual risk and vulnerability profiles.[12]

Neurological impact

ELS alters the development of the brain's structure and function. Complex behaviours rely on the intricate coordination of brain circuits orchestrating signals at molecular, cellular, synaptic and network levels. These circuits underpin critical cognitive functions and disruptions can precipitate neurological disorders, often resulting from interplays between genetic predispositions and environmental impacts during vital developmental windows.[13] Genetic programming in presynaptic and postsynaptic neurons sets the blueprint of brain circuits, yet these circuits remain immature throughout development. The maturation timeline varies across different circuits; sensory circuits develop earlier than those responsible for higher cognitive functions. Significantly, circuits central to executive functions, particularly those in the prefrontal cortex, are among the last to mature. Early life experiences and stress are paramount in shaping these developmental pathways. Exposure to stress during sensitive periods can significantly

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affect brain circuits' typical maturation and functionality leading to enduring alterations in brain structure and function.[10] Such changes can result in cognitive, behavioural and emotional challenges in later life.

MRI scans in individuals who have experienced ELS have shown atypical volume and activation in the prefrontal cortex, amygdala and hippocampus—areas involved in emotion regulation, memory and cognitive functions.[14–16] The mechanisms of these neurological changes are thought to involve chronic inflammation and hormonal imbalances that accelerate neurodegeneration.[17 18] These alterations can predispose individuals to neurological deficits and psychiatric disorders, influencing later responses to stress and predicting symptomatology.[19 20] Children who experience maltreatment often show cognitive impairments such as difficulties in attention, executive function and memory.[9 21] These issues can persist into adulthood affecting educational achievement, employment and daily functioning.[22] Additionally, there is growing evidence that ELS increases the risk of and influences disease onset and progression in Alzheimer's disease.[23] Increased deposition of tau is linked to increased stress levels and poor sleep function, both of which are impacted by ELS. The risk of developing other neurodegenerative diseases like Parkinson's is also increased in individuals who have experienced ELS and there is a particular association with an increase in the severity of non-motor symptoms.[24]

Current gaps in research and practice

Given the profound impacts of ELS, neurological interventions must leverage an understanding of how ELS affects individuals presenting with neurological disorders. Clinical assessment and management must be informed by improved knowledge of how ELS influences clinical presentation. For example, windows of sensitivity to ELS have been observed but are poorly understood.[25 26] These windows of sensitivity are particular ages estimated to be around 0–24 months, 3–5 years and 9–13 years at which children are considered to be more vulnerable to the impacts of ELS due to observed effects on brain structure and function at defined timepoints.[25 27] Mapping the perinatal and early childhood critical windows of vulnerability and the differential impacts of adversity subtypes would improve our understanding of the mechanisms behind these relationships. Not all individuals who experience ELS will develop dysfunctional coping mechanisms, psychiatric disorders or neurological diseases. Resilience factors such as social support and innate personality traits may limit or ameliorate the impacts of ELS in some cases. Knowledge of potentially modifiable resilience factors could precipitate innovative strategies for disease prevention and treatment.[27] An improved understanding of vulnerability and resilience factors may: Assist in screening and identification of ELS-related disorders; impact policy relating to child protection and; inform improved education resources for parents.

Implementing a survey of ELS in clinical and research settings will offer deeper insights into how early adversities influence neurological health. Moreover, the insights from such a survey can guide personalised treatment plans that consider an individual's history of ELS, thereby enhancing the management and outcomes of neurological diseases. The survey is a simple way to gain insight into the human experience and its contribution to neurological disorders. There are currently a number of tools that aim to quantify childhood adversity including the Childhood Trauma Questionnaire (CTQ).[28] The CTQ is, at the time of publication, one of the most widely used and psychometrically robust measures for ELS.[29] However, among the large number of ELS surveys and screening tools currently in use, there is little consistency or standardisation. The CTQ and other ELS tools are also complex and often timely assessments for clinicians to administer in the context of busy clinics and briefer tools are lacking rigorous validation testing. Personal questions are also unlikely to be answered honestly without rapport which requires continuity of care and repetitious screening. Implementing screening into clinical practice would require consideration of which measure or questions would be used, who would conduct screening, when screening should occur, and in what setting. Determining how screening or survey results would be used to inform clinical practice would also depend on an improved understanding of the mechanisms of the impact of ELS on neurological development.

For neurologists, understanding the impact of ELS on brain development is not merely academic; it's critical for crafting interventions that foster optimal neurological development and prevent disorders stemming from disrupted neural circuitry. This insight is essential for developing preventative strategies and therapeutic approaches that address the root causes of neurological disturbances ensuring better outcomes for those affected by ELS. Engaging with this topic could revolutionise our approach to neurological care, moving from reactive to proactive care and emphasising the importance of early intervention and holistic management to safeguard brain health across the lifespan.

An improved understanding of the neurological impacts of ELS would allow for the development of take-home brain health strategies for patients to enact themselves. Patient education in this area would empower patients to maintain or improve their brain health, enhance treatment response and alter disease trajectory; improving quality of life despite many having a potentially 'incurable' neurological disease. Based on past and emerging research in brain health, proactive strategies for treating ELS-related disorders may include nutrition, exercise, cognitive training, mind-body techniques, emotion regulation, resilience-building and coping skills training and patient education. Through education, workshops and community support, patients should be encouraged to take an active role in their brain health and overall well-being. We can only go so far with longitudinal studies. There is a need to go beyond the laboratory and longitudinal studies to work further which is based on assessments of patients in the clinic. Such an approach will also need to rely on the history obtained from families and carers of patients.

Towards an account of ELS and endophenotypes

The concept of an 'endophenotype' refers to heritable traits derived from a number of measures.[30] Future research examining different types of endophenotypes associated with different types of ELS may provide an integrative framework that could in turn inform further neuroimaging-based and genetic-based studies investigating the neural correlates of endophenotypes across development. A 'developmental endophenotype' which is sensitive to the effects of both internal factors (eg, epigenetics including methylation patterns) and external factors (eg, life adversity) may be useful for future investigations and facilitate the discovery of brain regions that are perturbed over the course of normal development. Developing a systematic account of a 'developmental-endophenotype' based on the contribution of social, genetic, developmental and cultural factors will undoubtedly be important as part of future longitudinal studies examining the differing types of effects of ELS across brain

development as well as the differing effects across different brain networks.

ELS, resilience and brain health: an interdisciplinary synthesis

The authors propose an integrated brain health approach to neuropsychological disorders that integrates the often-isolated disciplines that are essential for the optimal treatment of patients with neurological and/or psychiatric manifestations. Behavioural neurology and neuropsychiatry both examine the connections between brain function and behaviour but their integration within a Brain Health framework offers a more comprehensive understanding. This approach allows for a nuanced exploration of how neurological changes manifest as psychiatric symptoms and vice versa. It promotes a unified model of care that addresses both neurological and psychological aspects leading to more effective prevention and treatment strategies.

Developing new evidence-based preventative treatments for individuals with neurological disorders will require a renewed level of collaboration between clinicians and researchers to develop studies involving patients who have neurological disorders. The authors propose the strategic benefits of building and sustaining collaborative research groups of interdisciplinary experts to provide a more comprehensive approach with improved generalisability for real-world translation. Preventative neurology would advocate for integrated care that brings together neurologists, psychiatrists, psychologists and other health professionals to provide a cohesive brain health treatment plan. This collaborative approach ensures that all aspects of a patient's brain health are addressed, from the biological impacts of ELS to the psychological and social dimensions of their experience. This integrative brain health model has the potential to transform care for individuals with ELS, offering a path toward recovery and resilience.

In addition to developing a more nuanced understanding of the impact of ELS across different cognitive domains, there is also a clinical need to further identify why some individuals are resilient to the long-term consequences of ELS. It is likely that a combination of genetic, developmental and environmental factors may provide resilience to the adverse consequences of ELS as well as influencing the long-term trajectories of patients with neurological disorders. Disentangling the contribution of these different factors will be important as part of future interdisciplinary studies. This will require further work including potentially longitudinal studies across the spectrum of neurological disorders, drawing on a range of methodologies including genetic-based studies and neuroimaging findings.

CONCLUSION

Research across various fields of neuroscience has consistently demonstrated the significant effects of ELS on learning, memory and early cognitive development. To improve patient outcomes and prevent the onset of neurological disorders, it is imperative to develop innovative treatments grounded in understanding these early influences and its impact on brain health. This necessitates a new framework that merges insights from ELS with preventative neurology achievable only through enhanced clinical practice and research integration toward a brain health treatment plan. There is a critical need for interdisciplinary approaches to improve our understanding of the impact of ELS across different symptom presentations encountered in clinical practice. The development of more nuanced and integrated ELS assessments in practice will require further collaborative and interdisciplinary studies and approaches. The implementation of research-driven approaches to clinical management such as the inclusion of an ELS survey would provide greater knowledge to inform improved treatment and management strategies. At the same time, there is also a clinical need to further define why it is that in some cases, some individuals remain resilient and continue to thrive in the face of ELS. Such collaborative efforts could pave the way for novel pharmacological and non-pharmacological treatments leading to more effective strategies for managing these frequently disabling conditions, as well as enhancing the quality of life among patients with neurological disorders.

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