A Systematic Review - The Effects of Stress in the ADHD Brain

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Background and Aim: Stress is a known risk factor for psychopathologies, whereas evidence is lacking regarding the specific consequences of stress on the neural basis of ADHD (1-3). A systematic review (SR) of all available literature was thus performed to clarify the role of stress in the association between alterations in brain structure, connectivity, and function in ADHD.

Methods: The SR was conducted according to the PRISMA guidelines and registered in the International PROSPERO under the identifier CRD42023379809 (4,5). Screening 25,026 non-duplicate articles retrieved from PubMed and CINAHL using keywords within three categories (ADHD, neuroimaging, stress exposure) published prior to 22nd of December 2022 yielded 20 eligible studies for inclusion (**Figure 1**). A narrative synthesis of the evidence was established with respect to stress exposure, neuroimaging and ADHD outcomes in studies, all of which were also critically appraised with regard to risk of bias, overall quality, and strength of the evidence (6-8).

Results: The majority of the 20 studies of high (n = 11) and medium (n = 9) quality failed to yield high strength evidence due to small sample sizes and lack of statistical approaches to clearly determine whether neural alterations may be the direct mediators of stress in ADHD. Nevertheless, several structural and functional stress-associated alterations in the brain were directly and indirectly associated with ADHD outcomes (see **Table 1**). Exposure to early life trauma, institutionalization, prenatal maternal risk factors, environmental pollution, low birth weight (BW) and low socioeconomic status (SES) were associated with structural neural alterations, impaired brain function or connectivity via the use of functional (fMRI), MRI, and EEG.

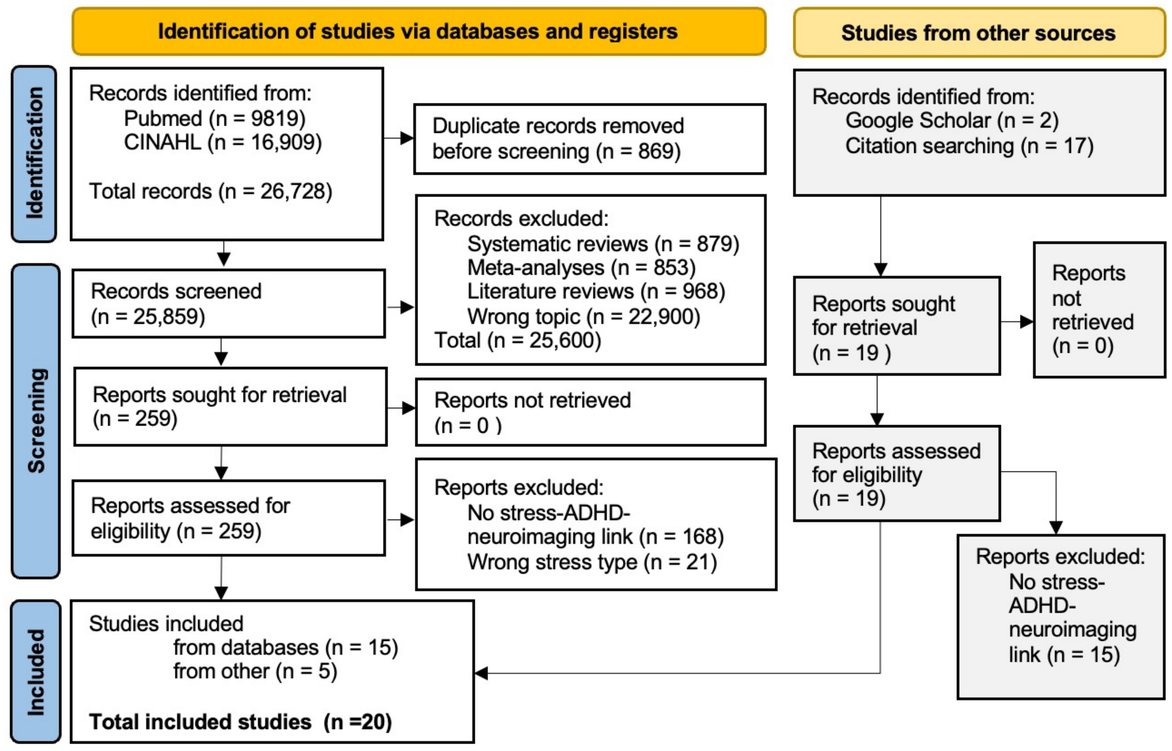

Figure 1: PRISMA flowchart of the literature search, screening, and selection processes for qualitative analysis.

Table 1: Results table summarizing the main neurological alterations associated with six types of stress exposure and ADHD outcomes in a total of 13,830 subjects within 20 studies.

Type of Stress Exposure	Nr. of Studies	Main Findings
Early life trauma	6	***Strong evidence (n=1):*** altered brain activity (which was associated with both exposure to early familial trauma (EFA) and increased ADHD symptoms) during a reward processing task did not mediate the association between EFA and ADHD in adults (9). ***Medium strength evidence (n=3):*** trauma-exposed children showed ADHD-associated volumetric increases within the internal capsule and the inferior temporal gyrus (ITG) (10). In comparison to trauma-exposed children without ADHD, trauma-exposed children with ADHD showed increased axonal density in the Corpus Callosum (CC) (11). In comparison to children with ADHD without trauma, trauma-exposed children with ADHD showed disrupted WM connectivity within the CC, internal capsule, right-sided corona radiata, cingulum, and superior longitudinal fasciculus (12). ***Failed to provide strong evidence (n=2):*** presence of externalizing disorders was not associated with hippocampal atrophy (13) and altered activity within the hippocampus and amygdala (14) in children with early life trauma.
Institutionalization	5	***Strong evidence (n=5):*** structural neural alterations (decreased total brain volume and decreased cortical thickness of the ITG, insula, precuneus, lateral orbitofrontal cortex, supramarginal gyrus (SMG), fusiform gyrus, inferior parietal cortex, superior temporal gyrus and sulcus, and lingual gyrus) (15,16) and functional alterations (altered baseline EEG activity, decreased peak amplitude of EEG P700 signal in response to negative faces, altered EEG error monitoring signal) mediated the association between institutionalization and ADHD symptoms in children (17-19).
Prenatal maternal risk factors	3	***Medium strength evidence (n=2):*** decreased cerebellar volume was associated with clinical ADHD in children exposed to prenatal smoking and alcohol (20) and decreased activity and atrophy of the anterior cingulate cortex, inferior frontal gyrus, and SMG in children exposed to prenatal smoking was associated with increased ADHD symptoms (21). ***Weak evidence (n=1):*** mediation by decreased volumes of the cingulate cortex, precuneus, and the superior medial prefrontal cortex on the association between exposure to the condition of severe nausea and vomiting in pregnancy (SNVP) and psychiatric problems (22).
Environmental pollution	3	***Medium strength evidence (n=1):*** exposure to Persistent Organic Pollutants (POPs) was associated with decreased inhibitory control and decreased activation of the right inferior frontal cortex and the right anterior insula (23). These changes were separately associated with increased ADHD symptoms (24). ***Failed to provide evidence (n=2):*** pre- and postnatal exposure to Polycyclic Aromatic Hydrocarbons (PAHs) was not associated with ADHD outcomes, though exposure was associated with decreased volumes within the prefrontal, lateral and temporal lobes, and the caudate (25,26).
Low birth weight (BW)	2	***Medium strength evidence (n=1):*** decreased caudate volume mediated the association between being born with low BW and impaired inhibitory control (21). ***Weak evidence (n=1):*** low BW children with ADHD showed white matter damage within the external and internal capsule, CC, and the inferior and middle fascicles in comparison to low BW children without ADHD (22).
Low socioeconomic status (SES)	1	***Strong evidence (n=1):*** decreased volumes of the left and right cerebellum, and the right caudate, mediated the association between growing up in low SES environment and clinical ADHD (23).

Conclusion: This SR was the first to summarize evidence of how exposure to stress may contribute to the common neurological alterations within ADHD patients in comparison to individuals with typical neurodevelopment (24). Future studies are necessary to confirm findings, provide further evidence, establish causality and investigate biological mechanisms at play within the complex relationship between stress, ADHD, and the brain. Raising awareness of the effects of stress could lead to earlier identification of at-risk individuals, improved ADHD prevention and intervention strategies. Findings may also by highly useful as targets within novel ADHD treatments such as fMRI neurofeedback (25).

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