



Article title: Do patients with chronic stress and patients with ADHD develop the same brain structures?

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Do patients with chronic stress and patients with ADHD develop the same brain structures?

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Abstract

Attention deficit hyperactivity disorder (ADHD hereafter) is a disorder associated with the impaired development of the child's nervous system and can be prolonged to adulthood with the symptoms such as impulsivity, inattention, issues with remembering of information.

Stress, especially chronic stress, also negatively affects brain function and causes nearly the same symptoms as ADHD. The symptoms are almost parallel. Recent research is shedding more light on the relationship between stress and ADHD. There might be a combination of genetic and environmental factors that influence ADHD onset, and, interestingly, the majority of environmental factors are related to chronic stress during pregnancy or in life.

The aim of this review is evaluating the similarities and differences between ADHD and chronic stress, and analyze the nature of alterations caused by ADHD and chronic stress.

Research findings showed that in several brain areas both ADHD and stress create similar structure alterations (mainly reduction) (Saenz et al., 2019; Blix et al., 2013). But that data is not 100% consistent and may need more research. Also, in the amygdala (Hoogman et al., 2017; Perlov et al., 2008) and in the hippocampus (Hoogman et al., 2017; Plessen et al., 2006), we see not consistent data and even have an opposite direction of data that needs further review and might explain that these brain structures both are not properly functioning but in different ways.

Introduction

ADHD

A Brief review of ADHD

Attention deficit hyperactivity disorder (ADHD) is a disorder associated with the impaired development of the child's nervous system. Most often, the disease manifests itself at the age of seven, or with the beginning of regular education (in school or preparatory group). ADHD is characterized by a child's inattention and high distraction in almost any class, excessive motor activity, impulsive behavior, and problems in social communication. ADHD is one of the most common chronic diseases in children. There are forms with a predominance of hyperactivity, with a predominance of inattention and impulsivity, or combined.

At the moment, it is known that this phenomenon does not always go away with growing up, and a large part of people suffer from it in adolescence and adulthood as well. This is a serious disorder that, if left untreated, can cause severe damage to a person's functional abilities and health, and is often accompanied by concomitant diseases, mainly in the field of behavior and mental health. Therefore, early and correct diagnosis of the disorder is essential and should be high on the list of priorities in determining national health policy (Centers for Disease Control and Prevention - CDC, 2010). There is also a theory that ADHD might be overdiagnosed both in children and adolescents that might lead to overtreatment (Kazda et.al., 2021).

Despite thousands of research articles written on ADHD, the cause has still not been established. Theories include genetic abnormalities, structural differences in the brain, nutritional supplements, etc. While these factors can be physiologically correlated with ADHD symptoms,

none have been established as a cause (Centers for Disease Control and Prevention - CDC, 2010; Faraone et al., 2015, Magnus et al., 2021).

Factors that increase the risk of ADHD include premature labor, low birth weight, poor maternal health, poverty, and maternal smoking. While it may be difficult at first glance to find a unifying relationship between these risk factors, a closer examination of all of these situations creates significant physiological and potentially psychological stress for the developing fetus and the growing baby.

ADHD is recognized to have an underlying genetic component, with an estimated high degree of heritability, and involvement of some reported candidate genes (Larsson, 2013).

Several environmental risk factors have been associated with the potential development of ADHD, and combinations of certain polymorphisms and environmental risk factors may increase the likelihood of certain ADHD symptoms.

Data from the Quebec Child Development Study revealed risk factors for pregnancy or early childhood associated with ADHD symptoms in a total of 2,057 children aged 5 months to 8 years. The study reported several early risk factors for the subsequent development of ADHD symptoms, including preterm delivery, low birth weight, and prenatal tobacco exposure (Galéra, 2011).

Risk factors for ADHD

There are some socioeconomic risk factors for ADHD:

- Non-intact family
- Single-parent household
- Maternal depression

- Lower maternal education
- Lower social class
- Households of social welfare recipients
- Young maternal age at birth of the target child (Galéra, 2011; Hjern, 2010).

Exposure to lead in the environment has been identified as a risk factor for ADHD in several studies:

In the US National Health and Nutrition Examination Survey, high blood lead concentrations in children (aged 8–15 years; n=2588) were significantly associated with ADHD (aOR 2.3; 95% CI 1.5–3.8; p=0.001; Froehlich, 2009).

Data from the New England Children's Amalgam Trial suggested that children (aged 6–10 years) with blood lead levels of 5–10 µg/dL had lower scores in tests of IQ, achievement, attention, and working memory than children with levels of 1–2 µg/dL (p=0.03; Surkan, 2007).

Low-level lead exposure was associated with higher ADHD scores in a study of 246 African American inner-city children at age 7.5 years (Chiodo, 2004).

The etiology of ADHD may be the result of complex interactions between genetic and environmental factors and may explain the individual differences observed in response to environmental risk factors. Combinations of certain polymorphisms and environmental risk factors may increase the risk of ADHD symptoms.

Long-term studies have shown that ADHD symptoms persist into adulthood (Biederman, 1998; Hill & Schoener, 1996). Epidemiological studies have shown that ADHD prevalence rates are higher than expected (Barkley, 2002), and indicate high comorbidity with other mental disorders (Hornig, 1998). ADHD in adults is associated with an increased risk of substance abuse, anxiety,

and mood disorders (Biederman et al., 1993), as well as the destructive family environment which can harm the development of the offspring (Biederman, 2002).

Functional neuroimaging studies have revealed insufficient or excessive activation of certain brain networks in adults with ADHD compared to adults without ADHD, in particular:

1. Excessive activation (reduced suppression) of the network in default mode during the execution of the task.
2. Insufficient activation of the fronto-striatal and fronto-parietal contours and other frontal areas of the brain.
3. Insufficient activation of the systems involved in executive functions and attention (ADHD institute, 2021).

An adult ADHD diagnosis can be made if a person has difficulties to:

1. Follow the instructions.
2. Remember the information.
3. Concentrate.
4. Organize tasks.
5. Finish the job on time.

These symptoms can vary from mild to severe and change over time. They can cause problems in many areas of life - at home, at work, or at school. Treatment and learning about how to manage ADHD can help. Most people learn to adapt. And adults with ADHD can build strengths and be successful.

Problems in people with ADHD in adults

If you have ADHD, you might have problems with (Mayo clinic Adult ADHD symptoms):

- Anxiety
- Chronic boredom
- Chronic delay and forgetfulness
- Depression
- Problems concentrating when reading
- Anger control issues
- Problems at work
- Impulsiveness
- Low tolerance for disappointment

ADHD subtypes

There are three main subtypes of ADHD:

1. ADHD-inattentive

Inattentive ADHD - commonly known as ADHD - accounts for about 33% of all ADHD in adults. ADHD, or inattentive ADHD is characterized by difficulty staying focused and concentrating on daily tasks. People can easily be distracted by irrelevant sights and sounds, switch between activities or get bored quickly.

2. ADHD-hyperactive and impulsive

Hyperactive and impulsive ADHD accounts for 7% of all ADHD in adults. The underlying symptoms are related to impulsivity and hyperactivity, while inattention can be secondary and not so serious.

3. ADHD-combined

Combined ADHD accounts for about 60% of all adult ADHD and, as the name suggests, is a combination of inattention and hyperactivity/impulsivity.

Theoretical models of ADHD

1) Pennington and Ozonoff (1996), among the first to develop a theoretical model of the etiology of ADHD, postulated that attention problems and impulsive behaviors observed in people with ADHD result from a deficit in executive functions (Pennington, B. F. & Ozonoff, 1996).

2) Barkley's Executive Deficit Model (1997). This model argues that the central deficit in ADHD is due to response inhibition (often referred to as "behavioral inhibition" by Barkley). Barkley suggested that response inhibition consists of three interrelated processes: (i) the ability to suppress an automatic response or a reaction that may cause immediate reinforcement ("pre-potential response"), (ii) the ability to delay the answer. or suspend a response that has already been initiated and (iii) the ability to stay focused on the response in question and not be distracted by competing stimuli ("interference control"). According to Barkley, the disruption of reaction inhibition directly disrupts four executive processes: working memory, the ability to hold information in consciousness and manipulate it; self-regulation, the ability to control one's emotions, motivation and arousal to achieve goals; the internalization of the word, an interior monologue allowing reasoning and a; and recreate, analyze and synthesize verbal and behavioral information to understand and reproduce increasingly complex language and behavior (Barkley, 1997).

3) Diamond (2005) suggested that inattentive portrayal is a disturbance in working memory, while the combined type arises from response inhibition problems.

4) Another popular theory suggests that the inattentive type is associated with disturbances in the "cold" pathway of Executive function, while the hyperactive type is associated with the "hot" pathway of Executive function (Castellanos, 2006).

Stress

A Brief review of Stress

Science has shown that many people around the world experience stress regardless of their age, race, religion, skin color, profession, academic background, or environment (Esia-Donkoh, 2011). A study by Anspo, Hamrik, and Rosato (2003) showed that stress manifests itself in different forms and affects different personality types at different ages and in different areas of life. Environmental and personal stressful events are called stressors. The perception and response to stressors vary from person to person. Stress is an integral part of life, it is inevitable.

The concept of stress was formulated by Hans Selye in 1936. He defined stress as the body's response to demands, which includes physiological responses known as general adaptation syndrome (OSA). Stress is broadly defined as an actual or anticipated threat of well-being or disruption of organism homeostasis (McEwen, 2007). Yusoff (2010) defines stress as “an emotional disorder or changes caused by stressors”. Stress levels can range from mild to severe depending on the individual. There are two categories of stress: eustress and distress. Eustress is positive stress that motivates a person to keep working. This beneficial stress stimulates and facilitates learning and work, and the ideal level of such stress can increase the ability to learn and work (Yusoff, 2010). Distress, on the other hand, is negative stress that occurs when favorable stress becomes too strong to handle. Such negative stress impedes learning and work and should be stopped and avoided in the future.

In the 70s of the XX century, it was discovered that the hypothalamus and pituitary gland form a single functional complex, called the hypothalamus-pituitary system (or Hypothalamic-pituitary-adrenal axis, the HPA). The activity of the pituitary gland is controlled by the hypothalamus by special adenohypophyseal substances that activate or inhibit the secretion of hormones in the anterior lobe of the pituitary gland.

The body has a direct connection between the individual endocrine glands: the corticotropin-activating factor of the hypothalamus stimulates the formation and secretion of ACTH in the pituitary gland, which activates the synthesis of glucocorticoid hormones in the adrenal cortex. Summarizing the relationship of the hypothalamus, pituitary gland, and adrenal glands, we can say that in the body the neuroendocrine reactions of these organs proceed in the following sequence: hypothalamus - anterior pituitary gland - adrenal cortex (Chen, 2016).

Thus, the stimulating effect of various external stimuli (normal physiological) on the pituitary-adrenal cortex system is carried out with the participation of the hypothalamus and other parts of the central nervous system.

Usually, negative feedback mechanisms controlled by glucocorticoids at different levels of the HPA axis serve to normalize glucocorticoids secretion and restore homeostasis; however, depending on the type, duration, and intensity of the stress stimulus, hypersecretion of glucocorticoids can persist and become a potential threat to health (McEwen, 2007).

An increase in the functional activity of the hypothalamic-pituitary-adrenal system is a kind of trigger mechanism for a complex restructuring of the body during the development of a stress state arising under the influence of various unfavorable environmental factors (Kapoor. 2006).

The body's response to stress in the form of increased secretion of ACTH, adrenaline, norepinephrine, and glucocorticoid hormones in response to irritation is a necessary prerequisite

for further activation of specialized defense mechanisms -behavior, immunity, inflammation- by the central nervous system, which are subtle and different reactions to stressors (Veldhuis, 1982).

Stress Types

Stress may be acute and chronic. Short-term (acute) stress and long-term (chronic) stress have different effects on human health. Acute stress tends to come on quickly and unexpectedly. Its extreme is a shock. Changes in the structure and function of the brain make our cognitive system trigger stress-coping mechanisms (Kivimaki, 2015). The body transiently starts producing catecholamines and corticosteroids to perfect mobility and responsiveness. That's why acute stress is often useful to the body. If a person fails to cope with the situation of shock and he constantly returns to it, recalling what he has experienced, then acute stress becomes chronic. Long-term or so-called chronic stress carries more serious consequences for the body, this can manifest as insomnia, gastrointestinal disorders, anxiety, and depression (McEwen et al., 2015; Chen and Baram, 2016; McEwen and Morrison, 2013). Some investigations show the effect of chronic stress on an increased risk of cardiovascular disease, mental illness, and cancer (Sotiropoulos, 2008). Chronic stress can come without a stage of acute stress when there are seemingly insignificant constantly acting factors – a tense relationship with someone, dissatisfaction with any situation, and other factors of constant action.

Trauma can have long-term effects that impair physical, psychological, and emotional well-being. It can also lead to mental illness, including acute stress disorder and post-traumatic stress disorder (PTSD).

Acute Stress Disorder (ASD) is a trauma and stress-related disorder characterized by obsessive memories, negative mood, dissociation, avoidance, and/or hyperarousal in the first month following a potentially traumatic event. ASD was added to the Manual of Diagnosis and

Statistics of Mental Disorders (DSM-IV) in 1994 to describe and classify symptoms occurring early in the post-traumatic period and to identify those at risk of developing post-traumatic stress disorder. -traumatic (PTSD) (World Health Organization, 1992).

Acute stress disorder lasts more than 2 days and is accompanied by dissociative symptoms that dominate the clinical picture of the disorder. The main diagnostic criterion requires the presence of 9 of 14 symptoms (in each specific cluster), including intrusion symptoms [i.e., recurrent distressful dreams, recurring distressful memories of trauma, intense or prolonged distress when confronted with something reminiscent of the trauma, and psychological reactions anything reminiscent of trauma]; dissociation symptoms i.e., derealization, emotional numbness, and inability to remember certain aspects of the trauma (usually dissociative amnesia); avoidance symptoms (i.e. avoidance of internal or external stimuli that evoke memories of the traumatic event); and arousal symptoms (i.e. irritable or aggressive behavior, increased start reflexes, sleep disturbances, hypervigilance, and trouble concentrating). Symptoms can last from three days to four weeks after exposure to the traumatic event and lead to clinically significant distress and impairment. Acute stress disorder is considered as a precursor to PTSD, and if the disorder lasts more than 4 weeks, PTSD is diagnosed (American Psychiatric Association, 1994).

A diagnosis of PTSD requires symptoms to be present for more than one month, to result in clinically significant distress or dysfunction, and not to be associated with chemical exposure or disability. In response to the trauma, individuals with PTSD re-experience nightmares, flashbacks, or intrusive and unwanted memories of the event. People with PTSD will often avoid people, places, or activities that remind them of the event to try to avoid re-experiencing the event.

Stress-related exhaustion disorder (ED) is a clinical condition characterized by psychological and physical symptoms of exhaustion developed in response to long-term psychosocial stress [Grossi

et al., 2015]. Stress-related exhaustion disorder has been associated with impaired cognitive performance, most consistently demonstrated in the domains of executive function, working memory, attention, and processing speed (Ellbin et al., 2018; Jonsdottir et al., 2013; Krabbe et al., 2017, Oosterholt et al., 2012, Öhman et al., 2007). Impaired cognitive performance (Eskildsen et al., 2016; Jonsdottir et al., 2017) and elevated levels of subjective cognitive complaints (Eskildsen et al., 2016) can persist for several years post-rehabilitation, indicating that cognitive deficits can be a significantly debilitating and long-lasting symptom that constitute an important interventional target.

Burnout syndrome was first described by Freudenberger (1974) while working as a clinical psychologist at the New York-based Alternative Medicine agency. Freudenberger (1974) observed that some of the volunteers, including the author, in response to the daily struggle to care for their patients, mainly drug addicts, have developed a set of symptoms. Based on his field observations, Freudenberger (1974, 1975) characterized burnout as a slowly developing syndrome including, among other signs and symptoms, fatigue, physical weakness, and predisposition to disease, sleep disturbances, weight changes, irritability, and frustration, periods of crying, cynical and suspicious attitude, psychological rigidity and professional inefficiency. The most famous description of the burnout syndrome, according to A. Langle: personnel and a decrease in personal achievements, which may arise among specialists involved in different types of people and helping professions” (Länge, 2003; p. 3). Clinical observations suggest that patients with chronic burnout have certain cognitive impairments to watch out for when evaluating symptoms and treatment regimens for this disorder.

How stress affects the brain

Stress can affect the functioning of the brain and the whole body. When stressed, the hormone cortisol is released. Stress causes an overabundance of the hormone cortisol, impaired

concentration, and memory. Memory loss after stress can occur even with one strong experience and affects the functioning of all body systems. Because of this, the work of the cardiovascular and nervous system is disrupted, which can lead to a deterioration in well-being, problems with sleep, and malfunction of the gastrointestinal tract (Shields, 2016).

Stress negatively affects brain function and causes the same symptoms as ADHD. The symptoms are almost parallel. In fact, one could say that the differences are simply the difference in how a symptom is expressed in an adult and a child.

Symptoms of ADHD	Symptoms of stress
Difficulty sustaining attention	Inability to concentrate
Not listening when spoken to	
Difficulty organizing	Difficulty Organizing
Forgetfulness	Memory problems
Speaks without thinking	Poor judgment
Impulsivity	Short temper

Table 1: Comparison of symptoms of ADHD and stress (Grosswald, 2013)

Recent research is shedding more light on the relationship between stress and ADHD. Vance and al. have demonstrated dysfunction of the right prefrontal regions of the brain in children with

ADHD (Silk, 2009). This region is responsible for developing coping strategies that affect the ability to cope with stress. Early stressful experiences are thought to influence the response levels of the HPA axis and the autonomic nervous system.

Young children exposed to chronic stress may become too accustomed to fearful states, getting used to higher levels of adrenaline or their tolerance. Chronic acute stress disrupts the body's ability to return to non-stressful norms, resulting in a chronic increase in cortisol, a biochemical marker of stress. In children with ADHD, high cortisol levels impair executive function, self-regulation, and knowledge of letters (Blair, 2005).

There might be a combination of genetic and environmental factors that influence ADHD onset, and, interestingly, the majority of environmental factors are related to chronic stress during pregnancy or in life (ADHD institute).

	Genetic factors	Socioeconomic risk factors
Children and adolescents	Polymorphisms in dopaminergic genes	Maternal smoking Alcohol use Stress during pregnancy
	Polymorphisms in dopaminergic genes	Inconsistent parenting Child self-blame for marital conflict
	Polymorphisms in serotonergic genes	Adverse childhood environment Psychosocial distress

Adults	Polymorphisms in dopaminergic genes	Stressful life events
	Polymorphisms in serotonergic genes	The burden of life events

Table 2: Genetic and environmental risk factors that might increase the probability of ADHD symptoms (ADHD institute, 2021).

Hypothesis and Objectives

Significant similarities in symptoms of ADHD and chronic stress and the fact that in the combination of genetic and socioeconomic risk factors, the majority of these factors are related to stress raised interest in the review of what brain alterations both ADHD and chronic stress caused in the brain that might be visible by fMRI method.

Therefore, the objectives for this review are:

- 1) Evaluate the similarities and differences between ADHD and chronic stress.
- 2) Analyze the nature of alterations caused by ADHD and Chronic stress.

Taking into consideration the prevalence of chronic stress conditions (additionally triggered by Covid-19 situation), a literature review about discoveries about brain alterations in chronic stress

and how similar or different they are to ADHD might be useful to raising awareness and establishing factors in diagnosis and treatment of ADHD and chronic stress consequences (i.e., burnout).

The review will be limited to several main structures as data from neuroimaging, neuropsychological and neurochemical research showed that the main areas that contribute to ADHD pathophysiology are prefrontal cortex structures, anterior cingulate cortex, amygdala, hippocampus, and striatum structures (Bush et al., 2008)

Material and Methods

A narrative literature review was conducted on research results that have the fMRI results of ADHD impact on the brain and changes that chronic stress causes in the same areas.

MRI methods (Magnetic Resonance Imaging) were selected for this review as it produces high-quality images of the brain in vivo and allows to differentiate between grey and white matter and works with cortical and subcortical structures that are relevant to the nature of the research of ADHD and Chronic stress.

Search methods in selecting available literature

PubMed and ScienceDirect databases that include topics with neuroscience, mental health, neuropsychology, with the focus on reviews, include scientific and review material on the

selected topics of ADHD and Stress. PubMed was selected as the primary database (as shows more relevant and better filtered results), and ScienceDirect as the secondary one.

Keywords: ADHD, Adult ADHD, ADHD FMRI, Chronic stress, Chronic stress FMRI, ADHD and Stress. The search had boolean condition AND so the connected sources can be reviewed too.

Initially “Review” and “10 years” filters were applied and then additional literature from those reviews was considered. A database search was done using all words that were relevant and then the most relevant results were shown and considered for further review.

Results per keywords (review + 10 years filters on)	Number of articles from PubMed Central	Number of articles from Science Direct
ADHD	3,508	4,029
Adult ADHD	945	3,154
ADHD FMRI	135	833
Chronic stress	10,717	64,704
Chronic stress fMRI	165	1,986
ADHD Stress	286	2,475
ADHD Stress fMRI	8	1,661

Table 3: Search results from PubMed and ScienceDirect databases using relevant keywords (PubMed, 2021; ScienceDirect, 2021)

Identification of relevant articles also used the selection by year, a higher number of citations. Additionally, the ones that were cited in relevant works were screened too.

60 articles and publications were reviewed from search in the ADHD field and 119 in the Stress field. Then the number was reduced to 61 ones considering the most relevant ones and after applying the exclusion criteria.

Inclusion and exclusion criteria

Inclusion criteria:

- Research papers with ADHD brain structure review
- Research papers with chronic stress brain structure review
- Literature reviews or original research works
- fMRI research method

Exclusion criteria:

Reviews and publications based on these methods were considered irrelevant and excluded from this review.

- Non fMRI methods
- Research conducted on non-humans (e.g., rats)

- Acute Stress
- PTSD stress

Results

Brain Volume

ADHD

According to several MRI studies (Saenz et al., 2019) of brain volume in people with ADHD and comparing with populational norms brain volume in ADHD is altered (Valera et al., 2007). It was a consistent finding that total volume (whole brain) and grey matter are reduced (Valera et al., 2007; Nakao et al., 2011; Greven et al., 2015; Hoogman et al., 2017), but about the white matter, some studies did not show any differences (Greven et al., 2015) while some showed reduction (Valera et al., 2007) and some even recorded an increase (Narr et al., 2009). The grey matter volume was different both in general (total cortical volume) and in specific regions, for example, frontal areas and parietal and occipital lobes as also affected (Valera et al., 2007; Nakao et al., 2011; Norman et al., 2016; Silk et al., 2016). Specific regions are discussed below.

Stress

Chronic stress studies also detect a decrease in the gray matter of specific regions (with the link to those that are involved in stress processing). But in general gray and white matter volumes (as well as total intracranial volume) did not show any differences in stressed and non-stressed groups, therefore we should review changes in specific regions (Blix et al., 2013).

Cortical Thickness, Surface Area, Gyrification

Cortical thickness (the number of cells within a column) and surface area (area of white matter, where a number of radial columns is important) are associated with gyrification that provides links with the connectivity of a brain and is a folding structure of a brain (Hogstrom et al., 2012; Wierenga et al., 2014).

ADHD

Several works (Narr et al., 2009; Silk et al., 2016; Shaw et al., 2007; Almeida et al., 2010) detected differences in cortical thickness across the whole brain in ADHD and non-ADHD participants, both in children and adults, with more detailed investigations that showed cortical thinning in prefrontal, frontal, occipital and parietal regions. But these findings are not fully supported by other researchers, who did not detect differences of cortical thickness between ADHD and control groups (Ambrosino et al., 2017; Wolosin et al., 2009), and even increased cortical thickness was reported (Almeida et al., 2012).

Regarding the surface area of the group with ADHD, it was also reduced, and the main differences were in frontal, prefrontal, temporal, parietal, and left occipital lobes (Silk et al., 2016; Ambrosino et al., 2017; Wolosin et al., 2009; Shaw et al., 2007).

Gyrification (brain folding measure) abnormalities were reported in some studies (Wolosin et al., 2009, Mous et al., 2014), but were not supported by other researchers later (Shaw et al., 2007; Forde et al., 2017).

Therefore, we can observe both volume and surface differences between people with ADHD and typical ones, which might be evidence of complex abnormalities in ADHD.

Stress

When comparing cortical thickness between people with chronic occupational stress and a matched control group, stressed participants showed a significant thinning in the mesial frontal cortex with the effect of age making this thinning more significant. (Savic, 2015) Also thinning of the right prefrontal cortex and left superior temporal gyrus was detected by Savic, and those changes were more significant in females (Savic, Perski & Osika, 2018).

Anyway, there is some good news - cortical thickness was gradually normalized during recovery from PTSD (Blix et al., 2013).

But Gavelin (2020) regarding cortical thickness did not find statistically significant differences between groups with high and no mental fatigue that is also linked to chronic stress.

Amygdala

ADHD

Amygdala as part of limbic structures was suggested to be involved in the genesis of ADHD, therefore there is no surprise that several studies reported that amygdala volume was negatively affected in ADHD patient samples (Plessen et al., 2006).

Hoogman and collaborators (2017), in a large data set showed smaller volumes for the amygdala that authors linked to possibly be the cause of emotional regulation issues and that was the largest difference across subcortical structures with ($d=-0.19$).

But as reported before, those findings have not 100% replicability. Perlov and collaborators (2008), reported that they did not find any differences in the amygdala in their research but suggested that there might be an issue not in the amygdala per se, but in connectivity between the amygdala and prefrontal cortex (Perlov et al., 2008).

Stress

While Savic et al. (2015) reported significantly larger amygdala volumes, Golcar et al., (2014) and Jovanovich et al., (2011) also showed that connectivity between the amygdala and the prefrontal cortex was reduced. It was reported that the amygdala was functionally disconnected from the ACC and the mPFC (medial prefrontal cortex, Blix et al., 2013) even without major life events.

Enlarged amygdala volumes were more significant in females and for both genders, this enlargement remained even in the follow-up (Savic, Perski & Osika, 2018). Also, stressed subjects and controls had differences in functional connectivity of the amygdalae (left and right) (Golkar et al., 2014)

But results are not 100% consistent - while investigating GM volumes Blix et al found no changes in the amygdala (Blix et al., 2013).

Hippocampus

ADHD

In the largest to date meta-analysis made by Hoogman and collaborators (2017), the volume of the hippocampus was reported to be slightly smaller in ADHD cases compared to controls, but this was mainly shown in children and the effect disappeared in the adult group. Also, hippocampus data showed the highest heterogeneity across samples. This is in line with the absence of differences in hippocampus volumes in the adult group with ADHD mentioned by Perlov et al. (2008).

In the earlier data, Plessen et al (2006) showed bilateral enlargement in the ADHD group and were able to localize these changes to the head of the hippocampus.

Stress

Both animal and human studies showed that stress negatively affects the structure and functioning of the hippocampus (McEwen, 2001).

Stress is impacting several areas of the limbic system, where the hippocampus (along with the amygdala) is the most consistent stress-associated area (Dedovic, D'Aguiar & Pruessner; 2009).

Patients with chronic stress and burnout had reductions in the 5-HT(1A) receptor binding in the hippocampus (along with the anterior cingulate cortex and anterior insular cortex) (Jovanovic et al., 2011; Archer et al., 2017).

Burzynska and collaborators in their 2020 work linked physical stress and poorer memory performance with smaller volume in the hippocampus, which was not changed depending on age, education, gender, brain size. Other studies (Blix et al., 2013) detected no significant differences in the hippocampal volume in patients with chronic stress (Blix et al., 2013). That is different from the data in PTSD, where atrophy of the hippocampus was shown (Kasai et al., 2008).

Caudate and Putamen

The caudate nucleus and putamen are subcortical structures that are part of the striatum and take part in the control of voluntary movements. The caudate nucleus is also involved in reward and motivation, learning, and emotions.

ADHD

Saenz et al in their ADHD review point to the fact that volume differences (reduction) in basal ganglia were quite a consistent finding in several works (Saenz et al., 2019). Smaller volume was found for the caudate nucleus and for putamen, even though the difference was quite small (from $d=-0.10$ to 0.10) (Hoogman et al., 2017).

Stress

Patients with high mental fatigue that is related to chronic stress had significantly lower caudate and putamen volumes, compared with the low-moderate mental fatigue group (Gavelin et al., 2020). Even when groups were controlled for perceived stress and depression conditions, the difference in volumes was still significant ($p=0.004$ for caudate and $p=0.003$ for putamen). Different authors (Blix et al., 2013; Savic, 2015), also support these findings with lower volumes in those structures. Caudate volume changes were related to the perceived stress degree and motor function tests showed impaired performance. Savic and collaborators (2018) also found that reduced caudate volume was identical in males and females and in the follow-up after the stress the caudate reduction was normalized.

The group that had chronic stress in the early age that was investigated by Blix et al showed a decrease in the caudate and putamen volumes (Blix et al., 2013).

These findings are supporting the data that acute stress activates the basal ganglia and that both caudate and putamen receive input from the prefrontal cortex. Also, this might be the case for the well-known freezing symptom that is stress-related (McEwen, 2000).

ACC (anterior cingulate cortex)

ADHD

Multiple data from genetic, neuroimaging studies reported dysfunction of the anterior cingulate cortex (ACC; Bush et al., 2008). Hypofunction of ACC data is quite consistent and structural differences from the norm were also reported (Makris et al., 2010).

Makris et al (2010), investigated the volume of ACC and found a significant volume decrease in the left anterior cingulate gyrus in the treatment-naïve group, but the treated group had a volumetric decrease in the right anterior cingulate gyrus but not in the right ACC volume, that is in line with the work of Pliszka and collaborators (2006) that showed a decrease in right ACC. One more review (Bledsoe et al., 2013), showed significant cortical thinning in right rostral ACC, which was not the same with right caudal, left caudal, and left rostral ACC.

Stress

While investigating chronic stress and associated mental fatigue Gavelin et al (2020) mentioned that observation of significantly reduced volumes of the gray matter of the ACC (anterior cingulate cortex) was present (Blix et al., 2013).

Additionally, reduced gray matter volumes of the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (PFC) have been observed (Blix et al., 2013). Also, the functional neural changes that included connectivity between the ACC and motor cortex were found (Golkar et al., 2014, Jovanovic et al., 2011).

Savic, investigating chronic occupational stress showed functional disconnection o between the amygdala and the ACC (Savic, 2015). Also, the reduction of volume and density of ACC is

typical for PTSD patients compared to their twins. (Kasai et al., 2008) Hinojosa et al 2019 also mentioned that some research showed that trauma-exposed patients had diminished ACC volumes (Hinojosa et al., 2019).

A study of people, suffering from chronic occupational stress showed weaker connectivity between ACC and amygdala (Golkar et al., 2014), and people with chronic stress had lesser activation of ACC in test on neutral odors (Jovanovic et al., 2011) and that the ACC grey matter volume of ACC was diminished (Blix et al., 2013).

Prefrontal and frontal structures

ADHD

Saens et al (2019, p. 1) in their review mention that “Abnormalities in the basal ganglia, prefrontal structures, and the corpus callosum have been the most consistently reported findings across studies”.

Not only cortical volume was different in ADHD groups. But in the prefrontal and other frontal areas, it was also significant. (Valera et al., 2007). Cortical thinning in frontal and prefrontal regions in children and adults was also reported by several research groups (Narr et al., 2009; Silk et al., 2016). Reduction in surface area with the largest difference in prefrontal and frontal areas has also been shown (Wolosin et al., 2009; Shaw et al., 2012).

MRI studies of children with ADHD have replicated data of reduced cerebral volumes, especially in the prefrontal cortex in its inferior part (Castellanos et al., 2001; Sowell et al., 2003),

Stress

Recently the role of frontal lobes in stress regulation was considered important in addition to hippocampus and amygdala (Dedovic et al., 2009; Lataster et al., 2011; Lucassen et al., 2014), that mean that stress impacts executive function, for example, data from (Lupien et al., 2007) that working memory that is dependent on the frontal structures is sensitive to cortisol effects even more than the hippocampus.

The stressed subjects have reduced thickness in the right prefrontal cortex as reported by Savic et al (Savic, Perski & Osika, 2018) and these differences were larger in females. Also, lower PFC thickness was correlated with the not that great ability to regulate negative emotions. Then after the follow-up, the PFC thinning was normalized. Reduced gray matter volumes of the dorsolateral prefrontal cortex (Blix et al., 2013) and reduced cortical thickness were detected in the medial PFC (Savic, 2015).

Golcar et al (2014), investigated functional neural changes that included functional connectivity between the amygdala and the PFC and that prefrontal activation was altered in the processing of working memory (Sandström et al., 2012)

Discussion

The review aimed at gathering the brain structure and volume alterations in ADHD and Stress - affected subjects with the goal of comparison of the way these conditions change the brain. The hypothesis was that both ADHD and Stress have quite similar symptoms in terms of attention,

poor organization, memory issues, and difficulty in emotion regulation, they might (or might not) share the same brain structure alterations.

In general, the majority of data showed that in ADHD and in stress conditions brain volume, thickness, and gray matter are reduced. But it can be that grey matter alteration can be both a symptom and a consequence. Here we do not have data to suggest if that is a symptom or not.

The only significant difference in direction is in amygdala volume, which is reduced in ADHD and enlarged in stressed groups. But these data are not 100% consistent, as there are research groups that report that the volume was not changed. Anyway, the amygdala is altered in both conditions and that might be the cause of issues in emotional regulation.

Consistent data in thinning and structure reduction were about Caudate and Putamen, Anterior Cingulate Cortex, and Prefrontal structures. That might explain the issues in similar symptoms in executive control, motor control, and motivation alterations.

	ADHD	Data consistency	Stress	Data consistency
Brain Volume	reduced	consistent	not changed	consistent
Cortical Thickness, Surface Area, Gyrification	thinning	not consistent	thinning	consistent
Amygdala	reduced	not consistent	enlarged	not consistent

Hippocampus	slightly reduced	not consistent	reduced	not consistent
Caudate and Putamen	reduced	consistent	slightly reduced	consistent
Anterior Cingulate cortex	reduced	consistent	reduced	consistent
Prefrontal and frontal structures	reduced	consistent	reduced	consistent

Table 4: Comparison of differences in brain structures in ADHD and Stress conditions with the consistency of data note.

Conclusions

Research findings showed that in several brain areas both ADHD and Stress create similar structure alterations (mainly reduction). But that data is not 100% consistent and may need more research. Also, in Amygdala and in the hippocampus, we have not consistent and even have an opposite direction of data that needs further review and might explain that these brain structures both are not properly functioning but in different ways.

Also, it might be interesting to review the data that ADHD might be caused both by a genetic polymorphism in dopaminergic and serotonergic genes together with stress exposure both in premature, early childhood, or being an adult. It might happen that when we have people with

chronic stress that have symptoms close to ADHD, they might have a genetic predisposition to this.

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