AROUSAL MODULATION IN ADHD

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is known to be one of the neurodevelopmental disorders with a high frequency in paediatric population, associated with a high degree of risky behaviour in adolescence and chronicity throughout adulthood if not treated correctly. One of the most plausible hypotheses that answer both questions about pathogenic mechanisms and pharmacology is the „Low arousal theory”. In this article we shall review studies that link arousal modulation to ADHD.

Keywords: ADHD pathogenic mechanism, arousal theory.

INTRODUCTION

Nowadays, attention Deficit Hyperactivity Disorder is one of the most frequent psychiatric entities observed in child and adolescent psychiatry. An epidemiology study published by Froehlich et al in 2007 found a prevalence of 8.6% in the American population aged 8 to 15 years old [1]. From a developmental point of view, with age, hyperactivity and impulsivity tend to wear off while inattention is persistent throughout adulthood with a prevalence of 4.4% among adults aged 18 to 44 years [2].

This alarming data is the reason why researchers are trying to think about some ethiopathogenic hypothesis behind this disorder. There are many theories taken into consideration by scientists and one of them is modification of arousal in ADHD.

Arousal is defined as a physiological and psychological state of being awake or reactive to stimuli. It involves the activation of the Reticular Activating System in the brain stem, the Autonomic Nervous System and the Endocrine System, leading to increased heart rate and blood pressure and a condition of sensory alertness, mobility and readiness to respond.

Arousal is important in regulating consciousness, attention, and information processing. It is crucial for motivating certain behaviours, such as mobility, the pursuit of nutrition, the fight-or-flight response and sexual activity. It is also very important in emotion, and has been included as a part of many influential theories such as the James-Lange theory of emotion.

According to Hans Eysenck, differences in baseline arousal level lead people to be either extraverts or introverts [3]. Later research suggests it is most likely that extroverts and introverts have different arousability. Their baseline arousal level is the same, but the response to stimulation is different which means they have different potentials for arousal.

The Yerkes-Dodson Law states that there is a relationship between arousal and task performance, essentially arguing that there is an optimal level of arousal for performance, and too little or too much arousal can adversely affect task performance.

One interpretation of the Yerkes-Dodson Law is the Easterbrook Cue-Utilization hypothesis.
Easterbrook states that an increase of arousal leads to a decrease in number of cues that can be utilized. However, many sport psychology researchers have challenged this relationship, and the current trend is a shift toward a more multidimensional view of arousal-anxiety and its effects on performance.

In 2003, Arent and Landers published “Arousal, anxiety, and performance: A re-examination of the inverted-U hypothesis” study. As predicted by the Inverted-U-hypothesis, optimal performance on the simple task was seen at 60 to 70 % of maximum arousal. Furthermore, for the simple task used in this study, only somatic anxiety accounted for significant variance in performance beyond that accounted for by arousal alone. These findings support predictions of the Inverted-U hypothesis and raise doubts about the utility of theories that rely on differentiation of cognitive and somatic anxiety to predict performance on simple tasks that are not cognitively loaded.

On the other hand, a study published by Mumford et. al. states that „The intercorrelation matrix of all variables - gymnastic ability, pulse rate, palmar sweating, state and trait anxiety, and gymnastic performance - revealed limited relationships between gymnastic performance and arousal/anxiety measures. As expected, gymnastic ability was the best correlate of gymnastic performance”[5].

Many theories concerning the implication of arousal in different psychopathologies such as Autistic Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Mood Disorders or Anxiety Disorders as well as in everyday normal life have been proposed and studied.

For many years, high arousal has been regarded as an unpleasant and unwanted state. With an anxious patient we are most likely to try and reduce arousal, in order to make them feel better. One may accomplish this by using different techniques for inducing relaxation. But now, after years of research and controversy, scientists have come to the conclusion that high arousal is not necessarily bad. As Svebak and Stoyva concluded in their paper: „In a broad segment of human behaviour, especially in the areas of sports and entertainment, people seem clearly to be looking not for low arousal but for its opposite. People seek out high arousal and enjoy it!” [6].

At the time they wrote The Theory of Psychological Reversals, a motivational theory had been developed to explain the relation between arousal and hedonic state. According to this theory, there are people who prefer to function in a hyperaroused state, called paratelic and people who function mostly in the so called telic mode defined by low arousal. It is also well known that, for the normal individual, both high and low arousal can be good and desirable in terms of the activity that person performs.

Arousal states strongly influence behavioural decisions. In general, arousal promotes activity and enhances responsiveness to sensory stimuli. Earlier work has emphasized the nonspecific effects of arousal on multiple classes of behaviours. However, contemporary work indicates that arousal has quite specific effects on behaviour. Neural substrates for both general and specific effects of arousal have been identified.

Based on the scope of their actions, we can distinguish two major classes of arousal elements: localized versus general. Actions of localized arousal elements are often limited to one class of behaviour, and may thereby mediate specific effects of arousal. In contrast, general arousal elements may influence multiple classes of behaviours, and mediate both specific and nonspecific effects of arousal. One common way in which general arousal elements influence multiple behaviours is by acting on localized arousal elements of distinct networks. Often, effects on distinct networks have different time courses that may facilitate formation of specific behavioural sequences. Jing’s review from 2009 highlights prominent roles of serotonergic systems in arousal. The studies also indicate that the serotonergic elements can act as either localized or general arousal elements [7].

There are many different neural systems involved in what is collectively known as the arousal system. Four major systems originating in the brainstem, with connections extending throughout the cortex, are based on the brain's neurotransmitters, acetylcholine, norepinephrine, dopamine, and serotonin. When these systems are in action, the receiving neural areas become sensitive and responsive to incoming signals.
ADHD is described as a deficiency in information processing in the prefrontal cortex linked to under or over-stimulation of the arousal networks through deficits in the receptors for Dopamine (DA) and Norepinefrine (NA).

The key in ADHD treatment is to find the "optimal tuning of signal-to-noise ratio" [8]. It is important to know if we have a hypo or a hyper-activated brain because the pharmacological approach can vary from case to case: either by augmenting or by decreasing DA and NE.

With regard to attention deficits, in ADHD patients, studies have shown an abnormal pattern of cortical activation in other brain regions than those of control which for problem solving activate the anterior cingulate cortex. This aberrant pattern makes individuals perform, but with poor, inefficient results. Substances that increase DA or alpha 2A adrenergic receptors - stimulants, atomoxetine, guanfacine or modafinil, can be used to re-establish a normal neurotransmission. This abnormal arousal can also be found in sleep disorders – that are frequently comorbid with ADHD - and therefore treated with stimulant drugs. [8, 9]

Normal arousal means "tonic firing of DA and NE neurons" and leads to normal levels of attention. When arousal mechanisms are low, not only are the tonic firing rates low in arousal neurons utilizing NE and DA, but pyramidal neurons in the prefrontal cortex are "out of tune" and unable to distinguish important neuronal signals from unimportant "noise". These patients cannot focus on one thing more than another because all signals are the same. They cannot sustain attention because it is easy to be distracted from one signal to another and that is why they may move or act impulsively. Increasing DA may diminish the level of noise, whereas NE may enhance the size of the signal. [8]

On the other hand, some ADHD patients can present excessive arousal but have the same symptoms as ADHD patients with deficient arousal. They have a high incidence of comorbidities linked to this overstimulation by NE and DA: mood disorders, anxiety disorders, sleep disorders and substance abuse. In the case of overarousal we can observe "phasic firing of NE and DA neurons". It is believed that this is the reason for which in some ADHD patients, major neural alterations can be observed to such extent as brain atrophy due to overactivation of the HPA axis in the presence of chronic stress. Here, stimulation of DA and NE is not appropriate.

Treatments that slowly reduce overarousal in time by desensitizing postsynaptic NE and DA receptors but also steadily down regulate neuronal activity in order to return NE and DA neurons to normal phasic firing might be the answer. Norepinephrine reuptake inhibitors (NRIs) that block NET constantly around the clock desensitize overarousal systems in time and return them to faster tonic NE and DA firing with basic the same result as treatments that enhances deficient arousal systems.

It is somewhat of a paradox that agents that increase DA and NE, even in a tonic way, could reduce excessive DA and NE activity over time. That is why this treatments can "make conditions as anxiety somewhat worse before they make them better but it was observed that the therapeutic effects of such agents in the treatment of ADHD and its comorbidities increase over the first few months as NE and DA systems theoretically desensitize" [8].

The hypo or hyperarousal approach is more of a theoretical model used with an educational purpose because in real life conditions we can find that "different circuits have different states of arousal in the various areas of prefrontal cortex" and in complex cases, "some circuits maybe understimulated, while others are simultaneously overstimulated". This mixed hypo and hyperarousal can be found in patients where ADHD is comorbid with tics, conduct disorders, oppositional disorders, psychotic disorders, and affective disorders which makes the psychopharmacological approach much more difficult. Theoretically, we can use stimulants in combination with atypical antipsychotics because "atypical antipsychotics simultaneously release DA in prefrontal cortex to stimulate D1 receptors reducing ADHD symptoms, while acting in limbic areas to block D2 receptors to prevent worsening of mania or psychosis" [8].

When ADHD is comorbid with anxiety, depression or substance abuse augmenting antidepressant or anxiolytic therapies with a
tonic activator of DA and/or NE systems such as long-lasting norepinephrine reuptake inhibitors (NRIs), or alpha 2A adrenergic agonist rather than a stimulant can be an effective long-term approach. Some studies of NRIs report improvement in both ADHD and anxiety symptoms, and others report improvement in both ADHD and heavy drinking. [8, 10]

“It is interesting that ADHD is rarely the focus of treatment in adults unless it presents itself with no comorbid conditions”[8].

There is high hope in the psychiatric world that with the inclusion of Adult ADHD diagnosis in the newly published DSM-5 and the availability of the Diagnostic Interview for ADHD in Adults (DIVA) in more and more languages, this situation will change in the years to come.

“Adults with ADHD smoke as frequently as adults with schizophrenia, at about twice the rate of the normal adult population in the United States. This may be because nicotine subjectively improves ADHD symptoms, especially in patients who are not treated for their ADHD. Nicotine enhances DA release and arousal, so it is not surprising that it may be effective for ADHD symptoms”[8].

In the end, it will be of great value if longitudinal studies between patients who respond to medication and those who do not would be conducted.

REFERENCES