1. Gore2008 (truncated)

http://emedicine.medscape.com/article/288154-overview

Posttraumatic Stress Disorder

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2008

Practice Essentials

PTSD is defined as a pathological anxiety that usually occurs after an individual experiences or witnesses severe trauma that constitutes a threat to the physical integrity or life of the individual or of another person.

Essential update: PTSD linked to increased prevalence of myocardial ischemia

In a prospective study, myocardial ischemia, detected by exercise treadmill testing, was observed in 43 (10%) of the 433 outpatients without PTSD and 40 (17%) of the 233 outpatients with PTSD (*P* = .006). The relationship between PTSD and myocardial ischemia remained significant after adjustment for potential confounders, including age, sex, and prior cardiovascular disease. Additionally, the researchers found that patients with more severe symptoms were also significantly more likely to have myocardial ischemia.[1, 2, 3]

Signs and symptoms

Symptoms of posttraumatic stress disorder (PTSD) include the following:

- Persistent reexperiencing of a traumatic event
- Resultant numbness, avoidance, and hyperarousal[4]
- Avoidance
- Negative thoughts and mood or feelings

Symptoms should be present for a minimum of 1 month following the initial traumatic event.

In addition, the patient's general appearance may be affected by PTSD. Individuals may appear disheveled and have poor personal hygiene. Individuals with chronic PTSD may present with somatic complaints and, possibly, general medical conditions. Special attention should be paid to the patient's sleep hygiene.

Diagnosis

Currently, diagnosis of PTSD is based on 8 criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5).[5]

The first DSM criterion has 4 components, as follows:

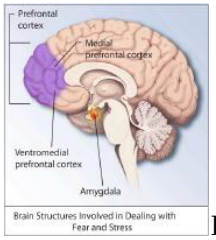
- Directly experiencing the traumatic event(s)
- Witnessing, in person, the event(s) as it occurred to others
- Learning that the traumatic event(s) occurred to a close family member or friend
- Experiencing repeated or extreme exposure to aversive details of the traumatic event(s); this does not apply to exposure through media such as television, movies, or pictures

- Alpha1 blockers (eg, prazosin; off-label use): For nightmares and sleep disturbances
- Alpha2 agonists (eg, clonidine; off-label use): For hyperarousal, and possibly nightmares

The following medications have also been used in PTSD:

- Monoamine oxidase inhibitors
- Tricyclic antidepressants
- Eszopiclone: To improve overall PTSD severity and sleep[6]
- Low-dose glucocorticoids: For decreasing recall of traumatic memories[7]

Image library



Brain structures involved in dealing with fear and stress.

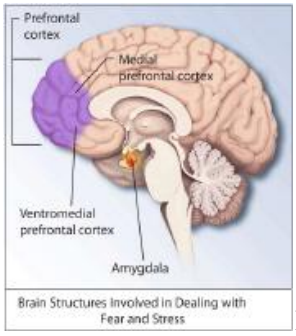
Background

Formerly in the "Anxiety Disorders" chapter, PTSD is now included in a new chapter of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* titled "Trauma- and Stressor-Related Disorders." Furthermore, a fourth diagnostic cluster (in addition to Criteria B, C, and D) capturing behavioral symptoms has been added. The 6 diagnostic criteria included in *DSM-IV-TR* were maintained, with minor revisions, and 2 additional criteria have been added: (1) negative alterations in cognition and mood associated with the traumatic event, beginning or worsening after the event, and (2) the disturbance is not attributed to the direct physiologic effects of a substance or another medical condition.[5]

The individual initially responds with intense fear, helplessness, or horror. The person later develops a response to the event that is characterized by persistently reexperiencing the event, with resultant symptoms of numbness, avoidance, and hyperarousal.[4] These symptoms result in clinically significant distress or functional impairment. To meet the full criteria for PTSD, these symptoms should be present for a minimum of 1 month following the initial traumatic event.

The events experienced may be natural disasters, violent personal assaults, war, severe automobile accidents, or the diagnosis of a life-threatening condition. For children, a developmentally inappropriate sexual experience may be considered a traumatic event, even though it may not have actually involved violence or physical injury.

Brain structures associated with the body’s reaction to fear and stress can be seen in the image below.



Brain structures involved in dealing with fear and stress.

- Play therapy
- Art therapy
- Anxiety management
- Eye movement desensitization and reprocessing (EMDR)
- Hypnosis
- Relaxation techniques

Medications may be required to control the physiologic symptoms, which can enable the patient to tolerate and work through the highly emotional material in psychotherapy. The principal agents used include the following:

- Selective serotonin reuptake inhibitors (SSRIs; eg, sertraline, paroxetine, fluoxetine): May relieve all 3 symptom clusters
- Benzodiazepines (eg, lorazepam, diazepam): For anxiety and other symptomatic relief
- Beta-blockers (eg, propranolol): For hyperarousal-related symptoms
- Anticonvulsants (eg, carbamazepine, lamotrigine; off-label use): For impulsivity and emotional lability
- Atypical antipsychotics (eg, risperidone, olanzapine; off-label use): For patients who do not respond to antidepressants
- Alpha1 blockers (eg, prazosin; off-label use): For nightmares and sleep disturbances
- Alpha2 agonists (eg, clonidine; off-label use): For hyperarousal, and possibly nightmares

The following medications have also been used in PTSD:

- Monoamine oxidase inhibitors
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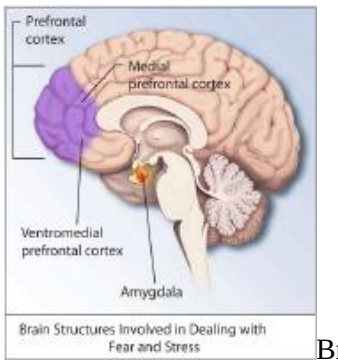
Image library



Brain structures involved in dealing with fear and stress.

Etiology

When PTSD occurs, symptoms of PTSD usually begin within 3 months of the traumatic event. However, a delay of months or years may occur before symptoms appear.

Physiologic factors

The amygdala is a key brain structure implicated in PTSD. Research has shown that exposure to traumatic stimuli can lead to fear conditioning, with resultant activation of the amygdala and associated structures, such

as the hypothalamus, locus ceruleus, periaqueductal gray, and parabrachial nucleus. This activation and the accompanying autonomic neurotransmitter and endocrine activity produce many of the symptoms of PTSD.

The orbitoprefrontal cortex exerts an inhibiting effect on this activation. The hippocampus also may have a modulating effect on the amygdala. However, in people who develop PTSD, the orbitoprefrontal cortex appears to be less capable of inhibiting this activation, possibly due to stress-induced atrophy of specific nuclei in this region.[12, 13]

Risk factors

As mentioned, PTSD is caused by experiencing, witnessing, or being confronted with an event involving serious injury, death, or threat to the physical integrity of an individual, along with a response involving helplessness and/or intense fear or horror. In various studies, a direct relationship has been observed between the severity of the trauma and the risk of developing PTSD.[7]

When these events involve an individual with a physiologic vulnerability based on genetic (inherited) contributions and other personal characteristics, PTSD results. These personal characteristics include prior exposure to trauma, childhood adversity (eg, separation from parents), and preexisting anxiety or depression.

One of the most pivotal observations in relation to the development of PTSD in adults who were traumatized as children is the association between early trauma exposure and subsequent retraumatization.[14]

Researchers have identified factors that interact to influence vulnerability to developing PTSD.[15, 16] These factors include the following:

- Characteristics of the trauma exposure itself
- Characteristics of the individual
- Posttrauma factors

Regarding characteristics of the trauma exposure itself, factors that influence the development of PTSD include the trauma's proximity and severity, as well as the duration of an individual's exposure to the trauma

Characteristics of the individual that increase vulnerability to PTSD include prior trauma exposures, family history or prior psychiatric illness, and sex (women are at greatest risk for many of the most common assertive traumas).

Posttrauma factors that influence whether PTSD develops include availability of social support, emergence of avoidance or numbing, hyperarousal, and reexperiencing symptoms.

With regard to reexperiencing symptoms, a pilot monozygotic twin study showed that patients with PTSD have impaired extinction of novel conditioned fear stimuli.[17]

Combat and PTSD

Approximately 30% of men and women who have spent time in a war zone experience PTSD.[18]

Studies conducted with veteran participants from Operation Iraqi Freedom and Operation Enduring Freedom (Afghanistan) determined a strong correlation between duration of combat exposure and PTSD. Service members from Operation Enduring Freedom (Afghanistan) reported less combat experience and, consequently, a lower incidence of mental health disorder compared with veterans of Operation Iraqi Freedom, who reported greater combat exposure.[19, 20] A study by Polusney et al suggests that combat-related PTSD is strongly associated with postconcussive symptoms and psychosocial outcomes one year after return from Iraq; however, little evidence of a long-term negative impact due to concussion and mild traumatic brain injury after accounting for PTSD.[21]

Reviews in the Neurosciences, 20, 405-427 (2009)

Evolving Concepts of Arousal: Insights from Simple Model Systems

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SYNOPSIS

Arousal states strongly influence behavioral decisions. In general, arousal promotes activity and enhances responsiveness to sensory stimuli. Earlier work has emphasized general, or non-specific, effects of arousal on multiple classes of behaviors. However, contemporary work indicates that arousal has quite specific effects on behavior. Here we review studies of arousal-related circuitry in molluscan model systems. 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 behavior, and may thereby mediate specific effects of arousal. In contrast, general arousal elements may influence multiple classes of behaviors, and mediate both specific and nonspecific effects of arousal. One common way in which general arousal elements influence multiple behaviors 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 behavioral sequences. This review highlights prominent roles of serotonergic systems in arousal that are conserved in gastropod molluscs despite extreme diversification of body forms, diet and ecological niches. The studies also indicate that the serotonergic elements can act as either localized or general arousal elements. We discuss the implications of these findings across animals.

KEY WORDS

arousal, molluscs, neural network, modulators, serotonin, feeding, defense, behavioral sequences

INTRODUCTION

Arousal phenomena are present in vertebrates and invertebrates alike, and are essential to animals' survival and well-being. Previous reviews of arousal in a variety of contexts are available /30, 33,62,84,101,125,126,133,141,161,163,168/ (see also Ann NY Acad Sci, 2008, Vol. 1129, edited by Pfaff and Kieffer). We review arousal-related work in simple model systems, with a focus on circuitry findings in gastropod molluscan model systems. Work in both vertebrates and invertebrates underscores the fact that actions of modulatory systems are central in establishing the arousal state (e.g., /81,126,168/). However, as will become apparent later in this review, circuitry studies in molluscan model systems can provide essential experimental evidence that may distinguish between alternative neural models of arousal. Furthermore, studies of possible roles of arousal elements in multiple behavioral networks suggest the need to classify neuronal elements involved in arousal as localized versus general arousal elements. We believe that such a distinction may be useful in understanding common outstanding issues in both vertebrates and invertebrates. In classifying modulatory elements, we take into account their roles in multiple neural circuits. This classification scheme differs from the

Accepted: 10 August, 2009

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Turkish Journal of Psychiatry 2011

Anxiety Sensitivity and Its Importance in Psychiatric Disorders

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SUMMARY

Anxiety sensitivity refers to the extent of beliefs that anxiety symptoms or arousal can have harmful consequences. There is growing evidence for anxiety sensitivity as a risk factor for anxiety disorders. Anxiety sensitivity is elevated in panic disorder as well as other anxiety disorders. It is thought to contribute to the maintenance and severity of anxiety symptoms. Studies have shown that anxiety sensitivity more specifically predicts the future occurrence of panic attacks. The Anxiety Sensitivity Index (ASI), which measures the construct of anxiety sensitivity, has three subscales, namely, the ASI-Physical subscale, ASI-Social subscale and ASI-Mental Incapacitation Concerns subscale. The dimension reflecting "*fear of physical sensations*" of anxiety sensitivity is the most predictive one of panic attacks and panic disorder. Research on the ASI has demonstrated that persons diagnosed with post-traumatic stress disorder, generalized anxiety disorder, obsessive-compulsive disorder, and social anxiety disorder all had ASI scores higher than normal controls. Depression was speculated to hold a positive correlation to high anxiety sensitivity scores. The relationships between anxiety sensitivity, alcohol and substance use disorders are still unknown. There is evidence that anxiety sensitivity is related with "drinking used as a way of coping". Since anxiety sensitivity is a cognitive construct, it should be taken into consideration when evaluating patients with anxiety and psychotherapeutic formulations.

Key Words: Anxiety sensitivity, trait anxiety, psychiatric disorders.

INTRODUCTION

The cognitive models of anxiety disorders have been developed in the last two decades. Spesific cognitive mechanisms are suggested to play a role in the etiology of anxiety disorders and/or their persistence. One of these disorders, Anxiety Sensitivity (AS) was, for the first time, defined by Reiss and McNally in 1985. In our article, the definition of AS, its relation with other anxiety concepts, sex differences, evaluation and the importance of AS in psychiatric disorders will be discussed. All of the publications between 1985-2010, which include the key words, "anxiety sensitivity" and "anxiety sensitivity index" in the database of PubMed have been scanned. Additionally, the reference sections of the accessed articles have also been researched. The articles dealing with the definition of AS, its scaling, and relationship with psychiatric disorders have been evaluated.

The Definition of Anxiety Sensitivity

AS accounts for the main baseline of the "fear expectation model". According to this model, the processes of "AS" and "anxiety expectation" play a role at the root of the motivation for avoiding an incident or situation that causes fear in humans. AS is characterized as *the fear that the sensations and symptoms relative to anxiety have harmful physical and/or social consequences.* The expectation of anxiety, on the other hand, *is the expectation that one will experience an anxiety or fear in "a particular situation".*

The concept of AS partly overlaps with the *anxiety of expectation* in panic disorder (PD) in a clinical sense. Yet, the anxiety of expectation, different from AS, is acquired in the wake of panic attacks and is the concern about the inevitable recurrence of a panic attack. AS, on the other hand, is a basic fear that is permanently existent in one's nature. When experienc-

Received: 24.04.2010 - **Accepted:** 22.02.2011
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Br. J. soc. clin. Psychol. (1976), **15**, pp. 267–274
Printed in Great Britain

Vigilance and Arousal in Depressive States

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An experiment was performed to investigate predictions of vigilance performance among depressive patients, based on the assumptions that vigilance would vary in a predictable manner with level of arousal, and that levels of arousal among diagnostic categories of depressive patients are well known. It was found that psychotic depressives, presumed to be hypo-aroused relative to normals, exhibited poor signal detection performances and committed few false positive errors relative to normals. This was consistent with predictions. Neurotic depressives, presumed to be hyper-aroused relative to normals, detected fewer signals than did normals, but also made more false positive errors than normals. Again this was consistent with predictions.

A measure of arousal in experimental subjects, namely barbiturate tolerance, was found to directly relate to the false positive error rate in all subjects. The relationship between arousal and total signal detection rate was significantly curvilinear, and an 'inverted *U*' (quadratic) function provided the best fit. This justified the conclusion that vigilance performance is a function of at least that component of arousal measured by barbiturate tolerance.

Of the numerous theories of vigilance, that one which views signal detection performance during a long, monotonous watch as being an arousal dependent phenomonon, has received considerable experimental support. In a review of the evidence Davies & Tune (1970) concluded that 'a progressive decline in the detection rate [in a vigilance task] is accompanied by changes in one or more physiological measures from which a progressive decrease in the level of arousal can be inferred'. More recently Coles & Gale (1971) have shown that some electrodermal indices of arousal act as predictors of vigilance performance; the higher the arousal level, the more vigilant the subject. Krupski, Raskin & Bakan (1971) have demonstrated that inefficient vigilance performance (commission of errors) was associated with low electrodermal arousal. Some 'adequate' level of arousal would appear then, to be a prerequisite to efficient vigilance performance.

Welford (1962) has further argued that the relationship between signal detection performance and arousal follows an 'inverted *U*' function. At low levels of arousal the central nervous system (CNS) is relatively inert, such that only the strongest signals secure a response. Thus few signals in any presentation are detected. A moderate increase in arousal raises the neurophysiological sensitivity of the CNS and increases the probability of detecting incoming stimulation. This improves the signal detection rate. However, further increases in arousal not only increase CNS sensitivity, but also result in random cell firing. Thus the CNS becomes 'noisy' and signal detection performance again deteriorates. Welford (1962) suggests that impairment of vigilance performance at high levels of arousal results from 'action becoming unduly vigorous, impetuous and ill-controlled'.

If the preceding assumptions concerning vigilance performance and arousal are correct, then groups of subjects about whom levels of arousal are known, would be

ORIGINAL ARTICLE

Hypofunction of Right Temporoparietal Cortex During Emotional Arousal in Depression

Stephan Moratti, PhD; Gabriel Rubio, MD; Pablo Campo, PhD; Andreas Keil, PhD; Tomas Ortiz, MD, PhD

Context: Neuropsychological models of depression highlight temporoparietal hypofunction associated with low emotional arousal in major depressive disorder (MDD). These models were derived from indirect measures such as neuropsychological tests and electroencephalography alpha band power.

Objective: To determine if high-arousing stimuli directly modulated activity in attention and arousal–related sensory brain regions in patients with MDD.

Design: Between-group comparison (patients with MDD vs healthy control subjects) of neuromagnetic oscillatory activity driven by flickering emotional and neutral pictures (steady-state visual evoked fields [ssVEFs]).

Setting: Center of magnetoencephalography at a public university and public ambulatory mental health service.

Participants: Fifteen female low-anxious patients with MDD and 15 female controls. The groups were matched with respect to age and handedness.

Intervention: Magnetoencephalographic recordings and self-report ratings.

Main Outcome Measures: Modulation of current source strengths obtained by frequency domain minimum norm source localization of ssVEFs.

Results: Controls and patients with MDD showed enhanced current source strengths at ssVEF frequency in occipital and parietal cortex for high-arousing emotional pictures ($P<.05$ for permutation statistics). While this arousal modulation in controls was pronounced in the right temporoparietal cortex, weak arousal modulation characterized that brain region in patients with MDD ($F_{1,28}=7.2$, $P<.05$ for interaction group by quadratic contrast).

Conclusions: Although emotional pictures engaged the dorsal visual stream to a greater extent than neutral pictures in both study groups, only controls showed strong arousal modulation in the right temporoparietal cortex. Because the right temporoparietal cortex is associated with the arousal dimension of emotion, subjects with depression may have difficulties in activating arousal-related brain areas, whereas basic stimulus processing related to activation of the dorsal visual stream is intact.

Arch Gen Psychiatry. 2008;65(5):532-541

Author Affiliations: Center of Magnetoencephalography Dr Perez Modrego, University Complutense of Madrid (Drs Moratti, Campo, and Ortiz), and Servicios de Salud Mental Retiro (Dr Rubio), Madrid, Spain; and Department of Psychology, University of Florida, Gainesville (Dr Keil).

PATIENTS WITH DEPRESSION ARE characterized by high levels of anhedonia, blunted affect,[1] and low emotional arousal.[2] Therefore, depression is regarded as an affective disorder implicating disturbed processing of emotional information (eg, reflected by abnormal startle modulation during emotional stimulation[3] and by reduced facial expression[4]).

In emotion research, the concept of motivated attention[5-7] emphasizes that affective stimuli activate action dispositions, which can be described in terms of hedonic valence (appetitive vs defensive) and emotional arousal (intensity).[8] High-arousing emotional stimuli drive motive systems that guide attention processes (eg, reflected by increased orienting responses).[5,8] These facilitatory processes are believed to be mediated by subcortical circuits, including the amygdala[8-11] and the cortical attention networks,[7,12-14] exerting top-down influences on sensory systems during processing of emotional stimuli.[13]

It has previously been shown that high-arousing affective pictures generate greater steady-state visual evoked potentials (ssVEPs) or steady-state visual evoked fields (ssVEFs) than neutral low-arousing pictures in occipital and right parietal cortical networks, indicating involvement of higher-order attentional mechanisms in the processing of emotional stimuli.[12,15] Steady-state VEFs are the neuromagnetic counterpart of ssVEPs that can be recorded using electroencephalography (EEG) and are evoked by intensity-modulated stimuli at a certain frequency

6. Wikipedia (truncated)

http://www.thefullwiki.org/Arousal

Arousal

View Full Essay Arousal is a physiological and psychological state of being awake. 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.

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.

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 (see Masters and Johnson's human sexual response cycle, where it is known as the arousal phase). 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. Later research suggest 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.[1]

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-Utilisation hypothesis. Easterbrook states that an increase of arousal leads to a decrease in number of cues that can be utilised. (Easterbrooke, 1959).

Biological Psychology, 2010, 83(3):191-200

Sympathetic arousal moderates self-reported physiological arousal symptoms at baseline and physiological flexibility in response to a stressor in generalized anxiety disorder.

Fisher AJ,
Granger DA,
Newman MG

Abstract

Compared to controls, individuals with generalized anxiety disorder (GAD) often fail to exhibit expected changes in physiological arousal in response to laboratory stressors. Nevertheless, individuals with GAD often report significant subjective arousal. We sought to assess the degree of sympathetic arousal in individuals with GAD and controls and the impact such arousal had on self-reported physiological arousal and response to an emotional challenge. Degree of baseline sympathetic arousal moderated the self-report of physiological arousal in non-comorbid GAD at baseline such that within this group, higher levels of sympathetic arousal predicted reports of heightened physiological arousal compared to controls. Overall, individuals with GAD exhibited no significant changes in arousal in response to the emotional challenge. However, basal sympathetic arousal moderated degree of change such that non-comorbid GAD participants low in baseline sympathetic arousal exhibited changes in arousal similar to controls in response to the stressor. That basal sympathetic arousal moderated both self-reported arousal at baseline and sympathetic response to a stressor suggests important physiological heterogeneity in GAD, wherein only those individuals with heightened tonic sympathetic arousal report accompanying symptoms and display diminished sympathetic reactivity.

8. Liotti1992

Brain Cogn. 1992, Mar; 18(2) : 138-51.

Right hemisphere sensitivity to arousal and depression

Liotti M, Tucker DM

Department of Psychology, University of Oregon

Abstract

Several lines of evidence show impaired right hemisphere function in depression. Lateralized simple reaction time tasks show impaired left visual field responses both in normals experiencing a depressed mood and in patients with mild unipolar depression. One interpretation for these findings is that depression impairs right hemisphere function by interfering with right hemisphere arousal and vigilance mechanisms.In order to test this hypothesis, subjects receiving either depression or relaxation mood suggestions performed an uncued reaction time task that has been shown to be sensitive to right posterior brain damage. Level of alertness was varied by contrasting uncued blocks with blocks in which targets were preceded by a warning tone. The results showed the predicted slowing of left visual field responses in the depressed mood, but only in women. The effect was significant only for the uncued blocks. The left visual field impairment was significantly larger during depression than in the relaxation state, but a smaller left visual field slowing was present in women in the relaxed state as well. These results may be consistent with the notion that depression interferes with right hemisphere function in part by influencingright hemisphere arousal mechanisms.

ELSEVIER

Journal of Affective Disorders 61 (2000) 161–176

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Anxiolytic action on the behavioural inhibition system implies multiple types of arousal contribute to anxiety

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[b]*Department of Psychology, Institute of Psychiatry, Maudsley Hospital, London, UK*

Abstract

According to ''The Neuropsychology of Anxiety'' [Gray, J.A., 1982, The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-hippocampal System, Oxford University Press, Oxford; Gray, J.A., McNaughton, N., 2000, The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-hippocampal System, 2nd ed., Oxford University Press, Oxford], anxiolytic drugs of all types act on a behavioural inhibition system, the most important neural component of which is the septo-hippocampal system. Anxiolytics affect septo-hippocampal function by impairing the subcortical control of hippocampal 'theta' activity — the principle response of the septo-hippocampal system to arousal. Our recent experiments show that there are multiple systems controlling theta activity and that anxiolytics act on several, but not all, of these systems. This pattern of results implies that there are many different types of arousal, only some of which appear to contribute to the generation of anxiety in normal subjects and to the etiology of pathological anxiety.

Keywords: Anxiety; Arousal; Generalized anxiety disorder; Behavioural inhibition system; Anxiolytic; Septo-hippocampal system; Hippocampus; Theta activity; Theta rhythm

1. Introduction

Gray (1982) published a ''Neuropsychology of Anxiety'' which had as its key suppositions that:

1. the neural and behavioural actions of anxiolytic drugs in other animals can provide us with keys to the nature of anxiety in people;
2. the behavioural actions of the anxiolytics drugs are best described as impairment of the 'Behavioural Inhibition System' (BIS) depicted in Fig. 1;
3. the most important common neural actions of the anxiolytic drugs are to impair the control of 'theta activity' in the septo-hippocampal system (SHS);
4. changes in septo-hippocampal function, and especially theta activity, can underlie both normal and pathological changes in anxiety.

An updated ''Neuropsychology of Anxiety'' (Gray and McNaughton, 2000) retains all of the above

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0165-0327/00/$ – see front matter
PII: S0165-0327(00)00344-X

10. Arent2003 (truncated)

Research Quarterly for Exercise and Sport

Vol. 74, No. 4, pp. 436–444

Arousal, Anxiety, and Performance: A Reexamination of the Inverted-U Hypothesis

Shawn M. Arent and Daniel M. Landers

Until recently, the traditional Inverted-U hypothesis had been the primary model used by sport psychologists to describe the arousal-performance relationship. 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 the current study, 104 college-age participants performed a simple response time task while riding a bicycle ergometer. Participants were randomly assigned to one of eight arousal groups (between 20 and 90% of heart rate reserve) and were told they were competing for a cash prize. Prior to the task, the Competitive State Anxiety Inventory-2 and Sport Anxiety Scale (SAS) were administered to assess the influence of cognitive and somatic anxiety. As hypothesized, regression analysis revealed a significant quadratic trend for arousal and reaction time. This accounted for 13.2% of the variance, F change (1, 101) = 15.10, p < .001, in performance beyond that accounted for by the nonsignificant linear trend. As predicted by the Inverted-U hypothesis, optimal performance on the simple task was seen at 60 and 70% of maximum arousal. Furthermore, for the simple task used in this study, only somatic anxiety as measured by the SAS 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 theories that rely on differentiation of cognitive and somatic anxiety to predict performance on simple tasks that are not cognitively loaded.

Key words: activation, exercise intensity, reaction time

Until recently, the traditional Inverted-U hypothesis had been the primary model used by sport psychologists to describe the arousal-performance relationship. This hypothesis is based on work by Yerkes and Dodson (1908), which focused on the decision-making abilities of mice when presented with varying intensities of a stressor. According to the basic tenets derived from this research, optimum performance should be seen at levels of moderate arousal. As arousal approaches extremes (a comatose state on one end and panic attack on the other), performance will decline accordingly. The end result is a curvilinear relationship between arousal and performance that resembles an inverted-U. Modification of this hypothesis for application to sport has also suggested that this relationship is dynamic (Landers & Arent, 2001; Mahoney, 1979). That is, the curvilinear function can shift to the left or right depending on individual characteristics (i.e., high skilled or low skilled, extroverted or introverted) and the type of task (i.e., simple or complex). This inverted-U relationship has been demonstrated across numerous studies in the psychological and motor performance literature (e.g., Anderson, 1990; Babin, 1966; Levitt & Gutin, 1971; Martens & Landers, 1970; Wood & Hokanson, 1965). Other investigators, however, have questioned the lack of clear support for the inverted-U relationship (Hockey, Coles, & Gaillard, 1986; Jones, 1995; Neiss, 1988). Despite of a number of criticisms, even the most ardent critics have, at times, used the inverted-U hypothesis to support their findings (Hockey et al., 1986) or have stated, "...as a correlational rather than causal hypothesis, it can be said to be supported by the totality of evidence..." (Neiss, 1988, p. 355).

The criticisms of the inverted-U hypothesis have been conceptual and methodological. Investigators (Anderson,

Submitted: November 12, 2001
Accepted: March 2, 2003

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11. Psychology site

http://psychology.about.com/od/mindex/g/mania.htm

Definition: Mania is a state of excessive or abnormally high arousal, mood and energy levels. Mania is often association with bipolar disorder, which was known as manic-depressive disorder in the past. People with bipolar disorder experience cycling periods of mania with alternating periods of major depression.

The symptoms and severity of mania can vary. Some experience only mild symptoms known as hypomania, in which they tend to need less sleep, have elevated energy levels and show an increased metabolism. In more severe cases of mania, people may sometimes display psychotic symptoms that can include delusions and hallucinations.

Journal of Consulting and Clinical Psychology
1975, Vol. 43, No. 4, 504–510

Effect of Irrational Beliefs on Emotional Arousal

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This article studied the relationship between the tendency to hold certain irrational beliefs and the likelihood of becoming emotionally aroused in various types of situations. The first experiment was correlational and found a positive relationship between irrational beliefs and paper-and-pencil measures of interpersonal, examination, and public speaking anxiety. The second experiment focused on one specific irrational belief—the overriding importance of social approval—and investigated the likelihood of emotional arousal occurring among individuals who ascribed to this belief. When asked to imagine themselves in social situations that might be interpreted as involving rejection by others, subjects holding this belief reported feeling significantly more anxious and angry than those who did not. Both the theoretical and practical implications of these findings are discussed.

Psychodynamic theorists have long recognized the importance of cognitive and symbolic activities as a determinant of emotional arousal. Although the general psychodynamic paradigm has come under heavy criticism by social learning theorists, such criticism is due less to the emphasis on cognitive factors than to the highly inferential and nonverifiable constructs employed in such attempts to understand human behavior. In fact, numerous social learning theorists (Bandura, 1969; Dollard & Miller, 1950; Mowrer, 1960; Rotter, 1954; Staats & Staats, 1963) have placed great emphasis on the importance of cognitive processes as a significant determinant of emotional arousal. The acknowledgment by social learning theorists that cognition may mediate emotion does not necessarily negate the possibility that emotional arousal may occur without the existence of any mediating processes. Thus, Bandura (1969) has suggested that emotional behavior in humans may be divided into two types:

> The overall evidence would seem to indicate that emotional behavior may be controlled by two different stimulus sources. One is the emotional arousal self-generated by symbolic activities in the form of emotion-provoking thoughts about frightening or pleasurable events. The second is the response evoked directly by conditioned aversive stimuli (p. 364).

The ability of symbolic activities or covert verbalizations to elicit emotional reactivity has been confirmed in a number of studies. Rimm and Litvak (1969) found that subjects reading affectively toned sentences (e.g., "I might get injured or crippled"), as compared with neutral sentences, showed significantly greater emotional arousal, as measured by respiration rate and depth. In related studies, heart rate, and respiration (May & Johnson, 1973), and galvanic skin conductance (Russell & Brandsma, 1974) were found to change as a function of the affective nature of internally evoked thoughts. Using verbal report as well as performance in a variety of different tasks, including writing speed, decision time, reaction time, a word association test, and spontaneous verbalizations, Velten (1968) obtained changes as a function of the type of emotionally toned statements (depressive, elated, or neutral) read by subjects.

Although these studies clearly point out the influence of covert statements on emotional arousal, little research has been carried out to determine the way in which people vary in their covert verbalizations and the consequences these self-statements have for emotional arousal. In this regard, some of the writings of Ellis (1962) seem relevant; he hypothesized that the maladaptive emotional

This research was supported in part by Grant MH24327 from the National Institute of Mental Health.

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CHAPTER 17

Attention Deficit Hyperactivity Disorder and Its Treatment

Attention deficit hyperactivity disorder (ADHD) is an area of psychopharmacology that is changing rapidly. A myriad of new drugs, especially in new drug-delivery technologies, is entering clinical practice. ADHD is also increasingly being seen not just as a disorder of attention, nor just as a disorder of children. Paradigm shifts are altering the landscape for treatment options across the full range of ADHD symptoms, now reaching into treatment of comorbidities and being refined for the important differences involved in treating adults.

This chapter provides a brief overview of the psychopharmacology of ADHD. This includes a short discussion of the symptoms and treatments for ADHD, but information on the full clinical descriptions and formal criteria for how to diagnose and rate ADHD and its symptoms should be obtained by consulting standard reference sources. The discussion here emphasizes the links between various brain circuits and their neurotransmitters with the various symptoms and comorbidities of ADHD. The goal of this chapter is to acquaint the reader with ideas about the clinical and biological aspects of attention, impulsivity, hyperactivity, underarousal, overarousal, and stress. This chapter also covers some of the special aspects involved in treating adults, such as the impact of the frequent comorbidities of

norepinephrine neurons, shown at the bottom of the figure. Deficient arousal mechanisms, as shown in the brain in Figure 17-7, can be increased to normal levels of activation, as shown in the brain in Figure 17-8, following successful treatment with stimulants, with the norepinephrine transporter (NET) inhibitor atomoxetine, with the oral sustained-release formulation of the alpha 2A selective adrenergic agonist guanfacine ER, or with the wake-promoting agent modafinil (Figure 17-8).

Changes in brain circuitry in ADHD before and after treatment are also shown in Figure 17-9. ADHD patients generally cannot activate prefrontal cortex areas appropriately in response to cognitive tasks of attention and executive functioning. Some studies show that ADHD patients not only fail to activate the dorsal ACC in response to the Stroop test but also actually recruit brain areas that normally do not participate in this function (shown in purple in Figure 17-9, top), a process that gets the job done, but inefficiently, slowly, and with errors. When treated with agents that increase the activation of D1 dopamine receptors and/or alpha 2A adrenergic receptors in prefrontal cortex, these individuals can now activate the appropriate brain area, and perform the task accurately (Figure 17-9, bottom). A very similar phenomenon is observed in prefrontal cortex of narcolepsy patients after they are given stimulants to improve their cognitive performance (see discussion in Chapter 16 and Figure 16-31). Arousal networks are thus also linked robustly to the neurobiological basis of sleep/wake disorders and their treatments (discussed extensively in Chapter 16 and also illustrated in Figures 16-1 through 16-5).

Note in Figure 17-8 that after treatment, not only are ADHD symptoms relieved but tonic firing rates of dopamine and norepinephrine neurons are increased. Tonic versus phasic firing rates for dopamine neurons is introduced in Chapter 16 and illustrated in Figure 16-32. The normal rate of tonic firing of DA and NE neurons is hypothetically linked to being normally aroused and having efficient information processing in the prefrontal cortex and thus normal levels of attention, motor activity, and impulse control (see Figure 17-8, bottom).

When arousal mechanisms are low, not only are the tonic firing rates low in arousal neurons utilizing NE and DA (Figure 17-7 at the bottom) but pyramidal neurons in the prefrontal cortex are "out of tune" and unable to distinguish important neuronal signals from unimportant "noise" (Figure 17-10 on the left). When prefrontal pyramidal neurons are out of tune in ADHD, 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; they may move or act impulsively, without thought. Increasing prefrontal arousal mechanisms by enhancing the activity of DA and NE can improve signal-to-noise detection in prefrontal cortex (middle of Figure 17-10) and relieve ADHD symptoms. DA acting at D1 receptors may diminish the level of the noise, whereas NE acting at alpha 2A adrenergic receptors may enhance the size of the signal (middle of Figure 17-10). This notion of malfunctioning prefrontal circuits that are "out of tune" rather than too high or too low is introduced in Chapter 7 and illustrated in Figures 7-25 and 7-26.

Excessive arousal and ADHD

There is also the possibility of too much of a good thing. Thus, when arousal mechanisms are too high, the signal-to-noise detection deteriorates and is no better than when the arousal mechanisms are too low (compare far right-hand side of the spectrum on Figure 17-10 with the far left-hand side of the spectrum). Correspondingly, some ADHD patients with excessive arousal (Figure 17-11 on the right) can have the same symptoms as other ADHD patients with deficient arousal (Figure 17-7 on the left). In the state of excessive

the arousal mechanisms and DA and NE activity even more, so what is one to do, since available ADHD treatments all increase DA and/or NE activity?

The answer may be to give treatments that not only slowly reduce the excessive arousal over time by desensitizing postsynaptic NE and DA receptors but also steadily downregulate neuronal activity in order to return NE and DA neurons to normal phasic firing. Treatments that do this may be those that increase DA and/or NE actions tonically themselves rather than phasically. That is, most stimulants have powerful, sudden, but abrupt actions on DA and NE. Even controlled-release stimulants act only intermittently throughout a 24-hour period (i.e., during part of the day but not at night), and their biological actions seem to be dependent upon the moment-to-moment amount of occupancy of the dopamine transporter (DAT) and the norepinephrine transporter (NET); stimulants are also critically dependent upon the rate of change in their blockade of DAT and NET. For these reasons, they are useful in states of deficient arousal but might not be ideal in states of excessive arousal.

On the other hand, NET inhibitors (norepinephrine reuptake inhibitors, NRIs) that block NET around the clock (Figure 17-12) seem to desensitize excessive arousal systems over time and return them to faster tonic NE and DA firing (see bottom of Figure 17-12), the same endpoint as treatments that enhance deficient arousal systems (see Figure 17-8, bottom). Selective actions on alpha 2A adrenergic receptors that are persistent may also reset the sensitivity and firing rates of overactive NE neurons over time (Figure 17-12). Such actions may concomitantly reduce comorbid symptoms that are also the product of excessive arousal in prefrontal cortex, such as anxiety, substance abuse, and mania/mixed mood states (Figure 17-12, right, improving with treatment at the middle). It may seem somewhat counterintuitive at first that agents that increase DA and or NE, even tonically, could reduce excessive DA and NE activity over time. Indeed, such treatments can make conditions such as anxiety somewhat worse before they make them better. Nevertheless, 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. Receptor desensitization by blockers of monoamine transporters is discussed in detail in Chapter 12 and illustrated in Figures 12-13 and 12-14; long-term downstream effects of chronic treatment with such agents are illustrated in Figure 12-15.

Stress, comorbidities, and simultaneous deficient and excessive arousal in ADHD

Explanations of deficient and excessive arousal in ADHD offered here have been overly simplified, as it is likely that different circuits have different states of arousal in the various areas of prefrontal cortex. Indeed, in complex cases, some circuits may be understimulated while others are simultaneously overstimulated. This state of affairs is illustrated in Figure 17-13, where the core symptoms of ADHD are represented as either underactivated or overactivated (as also shown in Figures 17-7 and 17-11). Also illustrated in Figure 17-13 are the most common symptoms and conditions that are comorbid with ADHD; these represent both states of theoretical underactivation and states of theoretical overactivation of DA and NE neurons and more specifically of D1 receptors and alpha 2A adrenergic receptors.

Experienced clinicians are well aware that such patients can be very difficult to treat. For example, in children tics generally representing excessive DA activation can be very difficult to treat simultaneously in patients with ADHD who have deficient DA activation and require stimulants. Stimulants may help the ADHD symptoms but make the tics much worse. Children and adolescents who have conduct disorders, oppositional disorders,

Psychological Review

Vol. 64, No. 5, 1957

ANXIETY AND BEHAVIORAL AROUSAL

ROBERT B. MALMO

Anxiety and behavioral arousal

Abstract

Clarification of the concepts of motivation, emotion, and anxiety is aided by 3 different approaches: (a) physiological indicants of behavioral arousal such as EMGs and EEGs, (b) experimental studies with psychiatric patients which show that anxiety should be restricted to the chronic pathological condition where the patient is physiologically overactive to every stimulating situation, and (c) the formulation of plausible hypotheses concerning the nature and etiology of anxiety. Anxiety can be produced in organisms by keeping the arousal level very high for long periods. On the basis of neurophysiological data continuous overarousal may result in damage of central inhibitory mechanisms. 42 references.

Psychological Review
Vol. 64, No. 5, 1957

ANXIETY AND BEHAVIORAL AROUSAL[1]

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During the past two decades there has been a growing interest in objective physiological studies of psychiatric patients. In this work, one of the most prominent psychological concepts has been that of anxiety. Although there is general agreement that the areas denoted by the term "anxiety" are important ones for study, there is nonetheless considerable disagreement concerning what the term means. In large measure, this semantic difficulty is part of a larger problem facing psychology today, and that is to find a way out of the confusion surrounding the concepts of motivation and emotion. Duffy has cogently argued that these concepts are second-order ones which reduce to primary factors of intensity and direction, and that along the intensity dimension, at least, the distinction between motivation and emotion is unnecessary (9, 10, 11).[3]

This is not to say that the directional aspect is not important or to deny that, in terms of direction, meaningful distinctions may be made between motivation and emotion, and indeed between different emotions. However, for present purposes it is essential to focus on the question of what these phenomena have in common rather than to consider their differences; in this paper, therefore, we shall be primarily concerned with the intensity dimension.

The main purpose of the present paper is to consider recent experimental data in an attempt to find a way out of the present confusion. I shall begin with a summary of two lines of investigation in our laboratory, dealing first with our discovery that certain physiological measures may serve as indicants of intensity or "behavioral arousal." These experiments were performed with nonpatient subjects. Second, in summarizing our investigations of pathological anxiety in psychiatric patients, I shall attempt to use the concept of behavioral arousal in an integrative way. Third, I shall draw on data from recent neurophysiological investigations to indicate possible mechanisms involved in the pathology and etiology of anxiety. Finally, on the basis of these theoretical considerations, I suggest problems requiring further experimental study.

Physiological Indicants of Behavioral Intensity

In 1951 we (31) reported finding a gradient phenomenon from electromyographic (EMG) recording during mirror tracing. Since that time the phenomenon has been observed under various conditions in our laboratory. Figure 1 presents mirror-drawing data from a study by Bartoshuk (1). Note that the

[1] This paper reviews work which was supported by the Medical Research and Development Division, Office of the Surgeon General, Department of the U. S. Army, under Contract Number DA 49-007-MD-626, by Defence Research Board Grant Number 9425-04 (Canada), and by Grant Number A.P. 29 from the National Research Council of Canada.

[2] The author is indebted to Drs. A. K. Bartoshuk, D. Bindra, F. R. Brush, D. E. Cameron, D. O. Hebb, and R. G. Stennett for criticizing earlier drafts of this paper.

[3] I do not wish to imply that this has been Duffy's only theoretical contribution. Her writings contain prior reference to a dimension of behavioral intensity (conceived as a continuum of "arousal," or "activation"); and she has previously cited evidence to support the argument that physiological measures may serve as the chief means of quantifying such a dimension or continuum.

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 all 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.

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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 [4]. 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. all states that *„The intercorelation 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 serotoninergic systems in arousal. The studies also indicate that the serotoninergic 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 pour, 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 Dl 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.

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Pediatric Social Phobia and Selective Mutism

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Background

Selective mutism is defined by the *Diagnostic and Statistical Manual of Mental Health Disorders, 5th Edition* (*DSM-5*) as "an anxiety disorder, given that a large majority of children with selective mutism are anxious."[1] Formerly, in the *Diagnostic and Statistical Manual of Mental Health Disorders, Edition IV-Text Revision* (*DSM-IV-TR*),[2] selective mutism was classified in the section "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence." The diagnostic criteria for selective mutism are largely unchanged from *DSM-IV-TR*.

Selective mutism is a disorder in which an individual is not able to speak aloud in specific situations when there is an expectation of conversational speech.[2] Communicative language is generally intact in such individuals, although selective mutism can coexist with language and communication disorders.

Selective mutism can be accompanied by other anxiety disorders such as separation anxiety disorder, social anxiety disorder (formerly called social phobia), agoraphobia, and panic disorder, as well as by shyness and anxiety; however, it can also exist without other anxiety-related disorders.[3]

Selective mutism generally occurs by age 5 years; however, usually it is not diagnosed until the child starts school. In some cases, adolescents and adults continue to experience an inability to speak in public. This inability is generally most disabling at school, as the child cannot be assertive and speak when called on by teachers. In adults, functional impairment occurs when public speaking or lecturing is required in one's vocation. Often, the child with selective mutism designates a friend or close family member to serve as an interpreter of communication and whispers into that person's ear, so that communication occurs with the designated person as intermediary.

Often, selective mutism can coexist with social phobia, also known as social anxiety, and is defined by marked and persistent fear of social or performance situations in which embarrassment may occur; exposure to the social or performance situation almost always causes an anxiety reaction such as a situationally bound or situationally predisposed panic attack.

Selective mutism can also be the precursor to agoraphobia and/or panic disorder. Agoraphobia is a specific phobia in which the individual fears being in crowded places. People with agoraphobia often become homebound. Panic disorder can result in significant disability and iatrogenically induced illness, especially in situations when invasive medical testing is done, because the severity of symptoms such as chest pain and palpitations and medical testing can intensify the severity of the panic symptoms.

The anxiety reaction is not due to psychosis; individuals are able to recognize their fears as excessive and unreasonable. However, the ability to fully comprehend that the reaction is out of proportion to the precipitant may be less complete in children and may depend on their cognitive-

developmental level of functioning due to deficits in emotional regulation. Recent studies have looked at physiological measures reflecting the severity of anxiety. Children with selective mutism were compared with children with social phobia in a study of 35 children (average age, 8 y). Those with social phobia and selective mutism had chronically higher levels of arousal as reflected by respiratory sinus arrhythmia and skin conductance levels. This may help explain why children with selective mutism may appear to others to not be overtly anxious; their silence may serve to decrease outward signs of anxiety observable by others.[4]

Studies that use physiological measures to objectively measure the severity of anxiety have shown that children with selective mutism and social anxiety as compared with children with social phobia alone have chronically higher levels of arousal (more intense anxiety) as reflected in the presence of respiratory sinus arrhythmia and skin conductance levels. Children with selective mutism may appear to others to not be overtly anxious, especially because of their silence, as their anxiety is not directly observable by others.[4]

Selective mutism significantly impairs the individual's level of functioning, as the individual is unable to complete required educational, social, and family tasks, and the emotional distress engendered in situations requiring the person to speak out loud can result in school refusal.[5]

Selective mutism is a disorder that first occurs in childhood and can continue into adolescence and adulthood. In adults with this disorder, functional impairment occurs when public speaking or lecturing are required in one's vocation. Severe social anxiety may not be evident, as the person may actually function in a relaxed manner when using nonverbal (ie, gestures, signing) communication styles.[6]

Shyness does not necessarily persist in adolescents with social anxiety disorder. A study by Burstein et al found that almost 50% of a group rated themselves shy; however, only 12% of adolescents who identified themselves as shy actually met criteria for lifetime incidence of social anxiety disorder as measured by the World Health Organization Composite International Diagnostic Interview 3.0, and 5.2% of adolescents who did not identify as having shyness had social phobia.[7]

There is significant comorbidity of social phobia with anxiety disorders, major depressive disorder, and drug use disorders, without regard to the presence or absence of shyness. Adolescents with shyness were more likely to report agoraphobia compared with the no-shyness group. Adolescents with social phobia versus adolescents with shyness had greater impairment in the areas of school/work, family relationships, and social life; however, they were no more likely to obtain professional treatment. Eighty percent of adolescents with social phobia failed to seek or to obtain professional treatment for their anxiety, and rates of prescribed medication use were systematically low across groups: 2.3% of adolescents with social phobia and 0.9% of adolescents with shyness used paroxetine.

Adolescent gender did not have a significant effect on the prevalence of social phobia. However, culture can cause parents to underreport anxiety; a clinically referred sample of 408 parent-youth dyads of African American adolescents versus Latino and white adolescents that used the Screen for Child Anxiety Related Emotional Disorders (SCARED) found that parents tended to significantly underreport anxiety symptoms.[8]

Pathophysiology

Serotonin pathways may be involved in the mediation of the anxious and obsessive qualities of selective mutism. This theory is reinforced by animal models of phobic behavior and by response to commonly prescribed medications such as selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, sertraline, or older heterocyclic-type antidepressants (eg, clomipramine [Anafranil]).[9]

A study of 106 children with selective mutism also included 1028 young adults who completed measures of social interactional anxiety and 920 young adults with childhood behavioral inhibition.[10] The study found a nominal significance (P = .018) for association of selective mutism with rs2710102, which, with rs6944808, was part of a common haplotype associated with selective mutism (permutation P= .022). Adjusting for sex and ancestral proportion, each copy of the rs2710102*, a risk allele in the young adults, was associated with increased odds of being more than 1 standard deviation above the mean on the Social Interactional Anxiety Scale (odds ratio = 1.33; P = .015) and Retrospective Self-Report of Inhibition (odds ratio = 1.40; P = .010).

This study is very encouraging that future genome-wide association studies might reflect an association of early onset variant of social anxiety disorder and selective mutism to a susceptibility gene, contactin-associated protein-like 2 (*CNTNAP2*), which has been found in other studies in relation to autism spectrum disorders. rs2710102 is a possible nonrisk allele for autism spectrum disorders and specific language impairment.

Behavioral inhibition is an early childhood temperament characterized by fearful responses to novelty and avoidance of social interactions. During adolescence, a subset of children with stable childhood behavioral inhibition develop social anxiety disorder and concurrently exhibit increased error monitoring.

Increased error monitoring in 7-year-olds who were characterized regarding behavioral inhibition at age 24 and 36 months prospectively predicted risk for symptoms of social phobia at age 9 years in this study of 291 children; Those high in behavioral inhibition had increased error monitoring at age 7 years, as indexed by larger (ie, more negative) error-related negativity amplitudes. In addition, early behavioral inhibition was related to later childhood social phobia symptoms at age 9 years among children with a large difference in amplitude between error-related negativity and correct-response negativity at age 7 years.

Heightened error monitoring predicts risk for later social phobia symptoms in children with high behavioral inhibition. Research assessing response monitoring in children with behavioral inhibition may refine our understanding of the mechanisms underlying risk for later anxiety disorders and the possible need for prevention efforts.[11]

Adolescents with early-life behavioral inhibition, similar to adolescents with social phobia, did not have striatal sensitivity to valence or self-reported affective sensitivity to incentive magnitude, which supported specificity in features of generalized anxiety disorder relative to social phobia or behavioral inhibition. Distinct striatal subregion responses showed a more generalized pattern of striatal response in adolescents with social phobia when compared with their healthy peers, and this pattern emerged across the caudate, putamen, and nucleus accumbens. Widespread magnitude-related incentive activations had underlied psychological states common to behavioral inhibition and social phobia, such as performance monitoring or

sensitivity to feedback and caudate hyperactivation in social phobia, and behavioral inhibition suggested anomalies in goal-based processes, which were more strongly modulated in the caudate rather than in the putamen or nucleus accumbens.[12]

Two efferent feedback pathways to the auditory periphery may play a role in monitoring self-vocalization: the middle-ear acoustic reflex (MEAR) and the medial olivocochlear bundle (MOCB) reflex. In selective mutism compared with a group of normally developing control children, a significantly higher proportion of selective mutism children had abnormal MEAR and MOCB function (58.6% and 38%, respectively) compared with controls (9.7% and 8%, respectively). The overall prevalence of abnormal MEAR and/or MOCB function was significantly higher in the selective mutism group (71%) compared with controls (16%).[13]

Epidemiology

Frequency

United States

The average age of onset of all anxiety disorders is 11 years, which reflects that anxiety disorders are common in children and adolescents.

In the National Comorbidity Survey-Replication-Adolescent Supplement, an epidemiologic sample of 10,123 adolescents in the United States, prevalence estimates for the different anxiety disorders were as follows: generalized anxiety disorder, 2.2%; social phobia, 9.1%; specific phobia, 19.3%; panic disorder, 2.3%; and separation anxiety, 7.6%.[14]

Social phobia is the third most common mental health disorder after depression.[15] Bergman et al (2002) reported that the prevalence rate of selective mutism was 0.71% but ranged from 0.08% to 1.9% depending on the population studied.[16]

Selective mutism is seen in fewer than 1% of children observed in mental health settings and is reported about 2-2.5 times more often in females than in males. The onset of selective mutism usually occurs during the preschool years, and it is generally not diagnosed until the child attends school and often can be misdiagnosed as oppositional defiant disorder because of the significant features of oppositionality and defiance that frequently accompany the child's refusal to speak especially in the school setting. With increased chronological age, a significant percentage of children "outgrow" the selective mutism however some children continue to have difficulty with public speaking and exhibit sparse language production compared with their age mates.[17]

Mortality/Morbidity

Generally, mortality does not result directly from selective mutism, except in cases of associated major depression resulting in suicide or reaction to medication treatment (sudden cardiac death with imipramine or clonidine) or adverse reaction such as newly onset suicidality following therapy with SSRIs or other antidepressants. A high morbidity rate is observed, with many missed school or workdays; the child often develops associated school refusal because of the anxiety associated with being asked to speak in class.[17]

There is a potential risk of iatrogenically induced illness in situations in which there is severe physical symptoms of panic disorder due to the likelihood that invasive medical testing might be performed if symptoms include palpitations or chest pain.[18]

Sex

Selective mutism is diagnosed more often in females than in males, with a female-to-male ratio of about 2-2.5:1.[16]

Age

Onset of selective mutism may occur as early as school age but generally occurs by mid adolescence following a childhood history of social inhibition or excessive shyness.[3]

The onset of selective mutism is often abrupt, occurring after a stressor or humiliating social experience and typically occurs when a child first attends school (either kindergarten or preschool). Over time, anxiety levels tend to increase as children do not "grow out of" selective mutism.[19] Selective mutism persists as low self-confidence, shyness, and discomfort in social situations, often persisting into adulthood when speaking in public is required.[20]

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