Neurobiology of anxiety

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Anxiety is one of prominent evolutionary adaptive features of living beings. On the other hand, anxiety disorder — which is any anxiety that persists to the point that it interferes with one's life — is the most common mental illness. In its various forms, ranging from very specific phobias to generalized anxiety disorder, it afflicts tens of million of people all over the world. Heritability of Generalized Anxiety Disorder is in the range of 30% to 40%.

"Normal" anxiety is one of ways subject process a threat. When the senses pick up a threat (a loud noise, a scary sight, a creepy feeling) the information takes two different routes through the brain.

First, shortcut, hot line to the fear centre - amygdala. It alerts other brain structures. The result is the fear responses: sweaty palms, rapid heartbeat, increased blood pressure and a burst of adrenaline. All this happens *before* the mind becomes conscious of it.

Second, the "high road". Only *after* the fear activation does the conscious mind employ. Some sensory information, rather than travelling directly to the amygdala, takes a more circuitous route, stopping first at the thalamus - the processing hub - and then the cortex, which analyzes the data and decides whether they require a fear response. If they do, the cortex signals amygdala and the body stays on alert.

Auditory and visual stimuli are processed first by the thalamus, which filters the incoming cues and shunts them either directly to the amygdala or to the appropriate parts of the cortex. **Olfactory and tactile stimuli** bypass the thalamus altogether, taking a shortcut directly to the amygdala. Smells and pain, therefore, often evoke stronger memories or feelings than do sights or sounds.

Amygdala is an emotional nucleus of the brain. It plays primary role in triggering fear response. Information passing amygdala get a label of emotional importance. **Bed nucleus striae terminalis** in contrast to amygdala, which triggers immediate bursts of fear, preserves the fear response and so leads to long-term distress and unease typical for anxiety.

There is a substantial difference between a fear and an anxiety. Fear is the response to concrete stimulus (real threat now and here), usually goal directed, rather phasic and intensive, while anxiety may develop without any stimulus, is rather generalized (to a potential threat in future), rather tonic, and of lower intensity. **Startle reflex** or startle reaction (SR) is the main experimental paradigm to study fear and anxiety. **Potentiation of SR with conditioned stimulus** (e.g., dental drill) serves as a model of fear. **Potentiation with context** (e.g., dentistry) is a model of anxiety. So the SR potentia-

tion is higher in the room, where shocks preceded in comparison to a neutral environment.

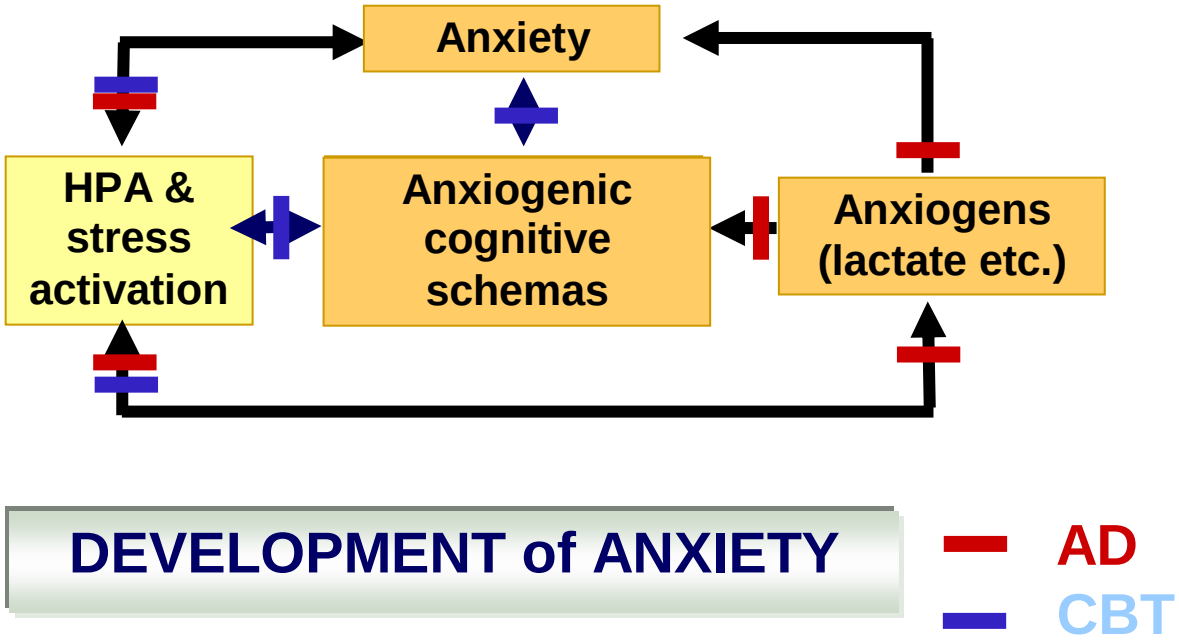
Anxiety disorders are caused by an overactive amygdala or bed nucleus striae terminalis („the accelerator“) and/or by an underactive prefrontal cortex („the brake“). Amygdalas of overanxious children are much larger than those of controls. Patients with post-traumatic stress disorder had a smaller hippocampus than normal. Signals in the amygdala appear to be more active in those with PTSD than in those without. In addition, signals to the prefrontal cortex of PTSD subjects seem to be weaker than in those without the disorder. Unlike controls, anxious patients show increase of contextual SR, with no differences in SR potentiated with stimulus, while in phobias it is the other way round.

The ability to **predict signal** of threat leads to the development of fear accompanied by general reduction of aversive states. Inability to predict that signal leads to permanent look for a threat, chronic anxiety, and generalization of aversive states. **Learning increases predictability** and decreases insecurity. First presentation of a shock is always unpredictable. Emerging anxiety generalizes to the whole context. After several repetitions a fear from stimulus occurs, while contextual anxiety decreases. To predict the signalized threat, associative learning must develop.

Experiments with **backward masking** show that autonomic reaction to threat happens even without semantic awareness. Such a reaction is “default” only to traditionally dangerous stimuli. This mechanism is evolutionary adaptive, because using the short-cut traditionally endangering stimuli release defence mechanisms faster and more effectively.

The morphology and pathophysiology of **anxiety disorders** has been intensively studied using brain imaging, behavioural models, and pharmacological interventions. Morphologically, anxiety disorders are related mainly to amygdala, bad nc. striae terminalis, prefrontal cortex, hippocampus, nc. raphe, periaquaeductal gray, lc. coeruleus, and basal ganglia. Behavioural models and psychotherapeutic approaches describe causal links within the three main domains, which contribute to the development of anxiety: **stress** (HPA activation), **cognitive schemas**, and **neurobiology of brain** (neurotransmission)(see fig.1). Current pharmacotherapeutic achievements point out the importance of **serotonin** neurotransmission (particularly 5-HT_{1A} receptors) in the regulation of mood including anxiety. The recent findings in neurobiology of anxiety help us to understand better mechanisms underlying mood disorders and to find more causal **treatment** approaches.

Fig. 1 – Development of anxiety disorders: interactions of factors (AD – antidepressants; CBT – cognitive-behavioural therapy)



Further reading:
Grillon C.: Startle reactivity and anxiety disorders: aversive conditioning, context, and neurobiology. Biol Psychiatry. 2002 Nov 15;52(10):958-75.