RDN YOUNG SCIENTIST COLLOQUIUM

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Neural basis on extinction learning, emotional behaviour and anxiety disorders

Extinction learning is an essential learning mechanism that enables constant adaptation to the ever changing environmental conditions. Most adaptive behavior in complex organisms is learned behavior driven by the availability of positive or negative reinforcers. In everyday situations we are confronted with situations in which the information we have learned is no longer valid, or relevant. Over trials of extinction, we learn that the former adaptive response is no longer effective in conducting to reinforcement and we will gradually desist to emit this behavior. While the initial process of acquisition of new knowledge is well studied, the process of extinction is far less understood, and so are its implications in emotional and anxiety related behaviors. In this symposium we present a series of studies that characterize the neural basis of extinction from different points of view, using different models and thus driving us all the way into its association with emotional behavior or its possible influence in anxiety disorders.

The neural circuit underlying extinction learning in pigeons - evidence from pharmacological studies

In the first study by **M. Gao** et al., pigeons were adopted as an animal model in an appetitive sign-tracking paradigm in order to uncover the variant and the invariant neural properties of extinction learning. The animals firstly learned to respond to two stimuli in two different contexts, and then extinguished their conditioned responses to the corresponding stimulus in the opposite contexts. Prior to extinction, related areas were locally reversibly inactivated. Finally, they were tested for both stimuli in both contexts. With this within-subject renewal design, it was discovered that extinction learning does not only engage the neural circuit of the nidopallium caudolaterale (NCL; the avian equivalent structure to the mammalian PFC), hippocampus, and amygdala, but also involves arcopallium, the avian motoric area, and the nidopallium frontolaterale (NFL), one of the avian higher visual-processing areas. Importantly, these findings suggested that the encoding of extinction memory requires the activation of NCL, amygdala, and NFL, seen from an impairment of extinction acquisition due to the pre-extinction inactivation of these areas. Whereas the consolidation and expression of extinction memory possibly involve NCL, hippocampus and arcopallium, indicated by an impaired spontaneous recovery during testing. In addition, the absence of a context-dependent renewal effect while the pre-extinction NFL inhibition reflects an involvement of the NFL in contextual encoding and context-dependent retrieval of extinction memory. This study provides new insights on the extinction network in the avian brain and its resemblance to the data obtained from various other species, which also indicates a shared neural mechanism underlying extinction learning shaped by evolution.

Spatial memory extinction differentially affects dorsal and ventral hippocampal metabolic activity and associated functional brain networks.

In the second study, by **Méndez-Couz** et. al, Wistar rats were used as subjects to study the involvement of brain regions associated with both spatial learning and associative learning in the extinction of a spatial reference memory task. To address these issues, quantitative cytochrome c oxidase histochemistry was applied as a metabolic brain mapping method. Rats were trained in a reference memory task using the Morris water maze, followed by an extinction procedure of the previously acquired memory task. Results show that rats successfully learned the spatial memory task and related learned behavior was subsequently extinguished. A control naïve group was added to ensure that brain metabolic changes were specifically related with performance in the spatial memory extinction task. Extinction of the original spatial learning task significantly modified the metabolic activity in the dorsal and ventral hippocampus, the amygdala and the mammillary bodies. Moreover, the ventral hippocampus, the lateral mammillary body and the retrosplenial cortex were differentially recruited in the spatial memory extinction task, as shown by group differences in brain metabolic networks. These findings provide new insights on the brain regions and functional brain networks underlying spatial memory, and specifically spatial memory extinction.

Neural mechanisms mediating the cortisol induced return of fear

The third study, by **Kinner** et al. seeks to elucidate the neural mechanisms mediating the cortisol induced return of fear in humans. Relapses represent a major limitation to the long-term remission of pathological fear and anxiety. Stress modulates the expression of fear memories and appears to promote the return of fear in patients with anxiety disorders. However, the underlying neuroendocrine mechanisms and their neural correlates remain unexplored in humans. In this study a pharmacological fMRI test was conducted, in order to test the acute effects of the stress hormone cortisol on fear renewal and reinstatement. A cortisol-induced return of fear was observed in men but not in women and was characterized by enhanced fear-related activation in the dorsal anterior cingulate cortex, amygdala, insula and orbitofrontal cortex. These findings illustrate that cortisol promotes fear recovery in men by strengthening key nodes of the fear network. With this study light was shed into the mechanisms underlying a stress induced return of fear in humans, which might constitute a potential risk factor for relapses following exposure therapy. Furthermore, the current data provide first evidence for a sex-specific cortisol effect on fear memory expression which might translate into different vulnerabilities for relapses in men and women.

Together, these studies present novel and congruent data that will help to broaden our knowledge about extinction, emotional behaviors and its implications in anxiety disorders, analyzing them from the neural and behavioural mechanisms to its clinical implications.