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Anxiety and Brain Imaging

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Abstract

This article is a brief review of the contribution of brain neuroimaging to the knowledge of different forms of anxiety or fears. Visualization of the amygdala has been essential in recent years. The different brain imaging techniques are discussed as well as the role of these techniques in understanding the mechanisms of action of cognitive behavioral and drug therapy. The results of these investigations proved to be the most convincing in the knowledge of post-traumatic stress, obsessive compulsive disorder and simple phobias.

Keywords: Magnetic resonance imaging; Positron emission tomoscintigraphy; Post-traumatic stress disorder; Obsessive compulsive disorder; Cognitive behavioral therapy

Introduction

Various possibilities are now available to explore the brain without having to open the skull or take unwanted samples. The only reasonable approach was the lumbar puncture of the cerebrospinal fluid and the determination of its components. This type of investigation, if it makes it possible to conclude that a meningeal infection is present, hardly reflects the complexity of cerebral neurochemistry. Initially, neuroradiology allowed us to visualize the cerebral circulation after having previously injected contrast products into the carotid arteries. Secondly, it was possible with the scanner to better understand the various regions of the brain; we could see tumors or decreases in volume of certain areas. There is now an anatomical imagery, and a functional imagery. It therefore becomes possible to visualize morphological differences in certain types of pathology, but also to better understand their modifications in the face of a stressful event or an anxiety disorder. You should know that all these investigations are expensive and cannot be used in everyday medicine. In the area of anxiety, its research; in the case of Alzheimer's disease, this is an additional diagnostic element, since it is not possible to perform brain biopsies.

What is functional imaging based on? What can we visualize?

Functional imagery seeks to characterize the brain in action [1]. The traditional use of these methods is to have an individual perform a cognitive task and measure the signal produced by brain activity. Depending on the techniques and mathematical tools used, it is possible to find, with more or less precision, which region of the brain was particularly active and at what point in the cognitive task. In recent years, various neuroimaging techniques have developed, such as: - magnetic resonance imaging (MRI) which is a medical imaging technique allowing to obtain two- or three-dimensional views of the interior of the body in a non-invasive way with a relatively high contrast resolution [2] -functional magnetic resonance imaging (fMRI) which is an application of magnetic resonance imaging to visualize brain activity indirectly [3]. It is an imaging technique used to study how the brain works. It consists of recording minimal hemodynamic variations (variation in the properties of blood flow) in the local brain, when these zones are stimulated. Positron emission tomoscintigraphy (PET), called PET or PET scan, which is a medical imaging method which allows to measure in three dimensions a metabolic or molecular activity of an organ thanks emissions produced by positrons from a radioactive product injected beforehand [4]. Recently, the development of neuroimaging techniques such as high-resolution magnetic resonance (MRI), functional magnetic resonance (fMRI), positron tomography (PET), or simple photon emission tomography (SPECT) have made it possible to identify the structural and functional characteristics underlying mental disorders.

As for anxiety disorders, neuroimaging techniques have helped in diagnosis and treatment, and have helped shed light on the neurobiology of anxiety. The number of neuroimaging studies of anxiety has only increased since the 1980s [5]. Most functional neuroimaging studies have used a model that creates anxiety symptoms. This consists in exposing subjects to emotional situations called "negative", that is to say for example photos of frightening objects or in neutral or even positive situations and comparing them in anxious subjects or in volunteers healthy. The amygdala, an important brain structure in anxiety, is a group of nuclei located in the medial temporal lobe it is involved in several processes related to fear and emotions such as conditioning fear, regulating the effects of stress on memory, rewarding learning and processing emotionally and socially relevant information [6]. Besides the amygdala, other areas of the brain such as the anterior cingulate cortex and the insula have also been shown to be involved in the development and maintenance of anxiety disorders [7]. They were previously called "the network of fear". The insula is a central structure for the processing of emotions, for subjective feelings and interoceptive awareness, and the anterior cingulate cortex plays an important role in the approach and avoidance and learning of fear. In general, all regions of the fear network seem to be involved in the processing of emotions in relation to the self and therefore also play a role in anxiety. Imaging studies in almost all anxiety disorders have consistently demonstrated increased activation of the fear network during the provocation of symptoms [8].

Brain Imaging and Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is the anxiety disorder that has been studied the most by brain imaging. PTSD is in DSM 5 is an anxiety disorder that some people suffer from after witnessing, or after experiencing, an event that caused or threatened to cause severe trauma or death. PTSD usually manifests at least two months after the stressful event, with or without experiencing a stressful event again [9]. Brain imaging is one tool that has helped to better understand the role of the amygdala in PTSD and that of the median frontal and anterior cingulate cortices. These areas of the brain are hyperactive and hypoactive, respectively. The hippocampus shows reduced activity. This hyperactivity of the amygdala has been shown to induce a brain response that is characteristic of fear, while the decrease in activity in the frontal regions contributes to reducing or even stopping fear [10]. The hippocampus is also an important area in the expression of PTSD, indeed, it is he who deciphers the information, and so if the hippocampus has a decrease in activity, particularly pejorative information will be poorly recognized.

In addition to these functional disturbances, structural changes have been shown in the hippocampus, the amygdala and the medial prefrontal cortex in PTSD [11]. Fortunately, however, not all subjects who have experienced a traumatic event do not develop PTSD. It is not known whether these functional or structural abnormalities are contingent on PTSD or whether they participate in the development of the disorder. The results of the various studies carried out so far are contradictory. However, there is a bidirectional relationship updated during the studies carried out. Indeed, the reduction in hippocampal volume seems to be a predisposing factor for the development of PTSD but also to be a consequence of this anxiety disorder. This reduction in volume could be corrected, as the disorder progresses, perhaps through treatment, be it behavioral or medication. On the other hand, if we compare the right amygdala of patients with PTSD versus non-traumatized controls, this brain area is activated in patients and not in controls, when emotionally images are presented to them [12].

Brain Imaging and Obsessive-Compulsive Disorder

In DSM-5, published by the American Psychiatric Association in May 2013, obsessive-compulsive disorder (OCD) was removed from the chapter on anxiety disorders to form a new specific category, obsessive-compulsive and related disorders in order to highlight the common features of these disorders that distinguish them from other anxiety disorders. OCD is characterized by the presence of recurring and continuously disturbing thoughts and images (obsessions), mainly followed by repetitive behaviors (compulsions) to reduce anxiety. Constraints usually include washing your hands or other parts of the body, repeatedly checking for acts of daily living. According to a widely accepted model, the primary pathology of OCD is located in the striatum, in particular the caudate nucleus with hyperactivity in the orbitofrontal and anterior cingulate cortex [13]. The fact that OCD has been removed from the classification of anxiety disorders anxiety disorder is justified by the fact that the role of the amygdala in this pathology is clearly limited. On the other hand, the anxiety symptoms that can be observed in patients with OCD are related to the hyperactivity of the cingulate cortex [14]. The researchers set out to find cortical excitement. They were thus able to show that there was an activation of the areas of the frontal cortex in patients compared to healthy volunteers.

However, hyperactivation of the amygdala in patients has been observed with the onset of OCD symptoms during aversive stimuli [15]. The appearance of intrusive thoughts is associated with orbitofrontal hyperactivity, while hyperactivity in the anterior cingulate cortex would be reflected by non-specific anxiety that results from these thoughts [16]. Compulsions are born to activate the striatum in order to obtain an activity of the thalamus which aims to neutralize intrusive thoughts. Studies of patients with anxiety disorders have consistently demonstrated the activity of the "fear network" during the provocation of symptoms [17]. The symptoms of anxiety are believed to be due to a pathologically overactive amygdala and insufficient negative regulation of the frontal brain regions. However, at least in OCD, there appears to be a network of distinctly activated regions in this disorder. Other research is likely to identify more specific regions involved in the development and maintenance of each anxiety disorder.

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Brain Imaging and Psychotherapeutic Interventions

Brain imaging has been used to understand psychotherapeutic interventions [18], including cognitive behavioral therapy (CBT). Exposure therapy has proven to be very effective in the treatment of anxiety disorders. Patients are systematically and repeatedly exposed to the stimulus or anxiety-provoking situation until their fear subsides. The exact neural mechanisms of this behavioral technique remain to be determined [19]. Exposure therapy seems to be quite similar to the process of extinguishing fear and could therefore also intervene on similar brain structures. Different models of neuronal functioning have been shown to be effective in successful treatments for specific phobia [20]. Indeed, patients with specific phobias generate a very high fear response, identified by the presence or anticipation of a specific object or situation. Common phobic stimuli are all animals (from mice to butterflies to dogs). But also, the fear of heights with vertigo which is only due to an alteration of the inner ear, air transport and in another area the fear of injection needles or the sight of blood. In individuals with a phobia of spiders, tonsil activity has been shown to decrease after successful exposure therapy, relative to the level of pretreatment activity [21]. On the other hand, a normalization of the activity of the insular and anterior cingulate cortex was noted. Activity in the hippocampus and anterior cingulate cortex was demonstrated to correlate with improvement in symptoms of PTSD, while activity in the amygdala and medial prefrontal cortex was associated with the severity present. Symptoms [22]. One can visualize the amygdala when presenting images of spiders in phobic subjects to spiders compared to images neutral for the subject.

This experiment can be carried out after successful or unsuccessful treatment, as well as in non-phobic control subjects [23]. D-cycloserine, which is a partial N-methyl-D-aspartate receptor agonist (NMDA), has been administered to anxious patients in combination with exposure-based therapy. It increases the effectiveness of exposure therapy, as it accelerates fear extinction processes [24]. In patients with spider phobia brain imaging shows when symptoms are induced, D-cycloserine enhances activation in regions involved in cognitive control and interoceptive integration, such as prefrontal cortex, anterior cingulate cortex [25]. Otherwise, patients with social anxiety experience behavioral changes after stress reduction therapy [26], which can be visualized by neuroimaging thus, providing the opportunity to see the structural and functional neural changes resulting from psychotherapy and can thus refine and optimize psychotherapeutic strategies [27]. Pharmacological treatments for anxiety disorders are mainly represented by selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). The effectiveness of these antidepressants can be shown by brain imaging. Citalopram decreases the response of the amygdala to aversive facial expressions, which is due to decreased activity of the prefrontal regions, the striatum, the insula and the para-limbic regions [28]. Treatment of anxiety disorders by the IRSS modifies the main characteristics of fear and anxiety at the neuronal level. Pregabalin, which was previously developed in the treatment of epilepsy, also has anxiolytic properties. Thus, in healthy non-anxious volunteers, who had received pregabalin, the amygdala filtered the induced emotions.

Oxytocin, is a polypeptide made up from nine alpha-amino acids such as cysteine (Cys), proline (Pro), asparagine (Asn), glycine (Gly), leucine (Leu), reduced stress, contributes to maternal attachment and facilitates social gatherings [29]. In patients with social anxiety, oxytocin reduces the increased activation of the amygdala in response to frightening faces. It is therefore another substance that modulates excessive activity of the amygdala when this brain area is confronted with stimuli in the context of social anxiety. These findings appear to support the fact that brain imaging may provide insight into how new pharmacological treatment options for anxiety disorders might work [30]. On the other hand, the value of brain imaging could be the prediction of response to treatment, whether it is a TBI or a drug. When the size of the cingulate cortex is smaller, it is observed in patients with PTSD, no response to behavioral therapy is observed [31]. Studies suggest that exposure-based CBT is, as is conditioned fear extinction. Thus, larger volumes of the anterior cingulate cortex would lead to better control of fear responses during exposure therapy and extinction, and therefore lead to a better response to CBT [32]. In addition, structural and functional neuroimaging studies appear to be a promising tool for revealing the neural mechanisms underlying anxiety disorders and may therefore lead to the development of more effective treatment options. They could also help to specifically assign patients to treatments that promise to be most effective for certain patients, which would lead to personalized medicine.

Conclusion

Brain imaging of the different forms of anxiety will soon be a tool that, first in difficult cases, will allow the practice of appropriate therapy. It is important to be aware that the different anxiety disorders have one thing in common, that of activating the “fear circuit” which includes the amygdala, the insula and the anterior cingulate cortex. It is possible to better assess the effectiveness or otherwise of the different treatments, whether psychotherapeutic or medicines.

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