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Review article

Clinical neuroimaging markers of response to treatment in mood disorders

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ABSTRACT

Mood disorders (MD) are important and frequent psychiatric pathologies, and the management of the patients affected by thes conditions represent an important factor of disability and a huge problem in socialterms and an economic burden. The "in-vivo" studies can help researchers to understand the first events at the base of the development of the pathology and to identify the molecular and non-molecular targets of therapies, but theyhave strong limitations due to the fact that human brain circuitsthem selvesare difficult to be reproduced in animal models. Besides these challenges, they are difficult to be selectively studied with the modern imaging (such as Magnetic Resonance and Positron Emitted Tomography/Computed Tomography) and non-imaging (such as electroencephalography, magnetoencephalography, transcranial magnetic stimulation and evoked potentials) methods.

In comparison with other methods, the "in-vivo" imaging investigations have higher temporal and spatial resolution compared to the "in-vivo" non-imaging techniques.All these factors make difficult to fully understand the aetiology and pathophysiology of these disorders, and consequently make difficult not only in the development, but also the monitoring of the actions of therapies,which according to clinical observations have been demonstrated effective in the treatment. In this review, we will focus our attention on the actual state-of-theart of role of imaging in monitoring of treatment of MD, underlying that up to date there are still not standardized imaging markers available in clinical practice.We will analyse briefly the actual classification of MD; then we will focus on the "in vivo" imaging modalities used in research and clinical activity, the current knowledge about the neural models at the base ofMD. Finally the last part of the review focuses on analysis of the principle markers of response to the treatment according to the type of treatment used and to the imaging techniques adopted.

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1. Introduction

Mood disorders (MD) are important and frequent psychiatric pathologies, and the management of the patients affected by these conditions represent an important factor of disability and a huge problem in social terms and an economic burden.

Several epidemiological studies [1–5] have illustrated the high incidence and prevalence of these disorders all around the world. European Study of the Epidemiology of Mental Disorders (ESEMeD) recently conducted a study involving several European nations and concluded that patients who had 12 month history of mental or emotional discomforts had a 36% chance of being MD [1].

Different from other pathological conditions, such as infective or surgical diseases, due to intrinsic complexity of the human brain, and of its internal connections makes the study of the psychiatric disorders really difficult with the actual scientific instruments. Further, we cannot forget that the external environment plays a pivotal role in the development and progression of these diseases.

During the last decades many "post mortem" studies allowed to understand the gross anatomic-pathological alterations at the base of these pathologies. This included the differences in dimensions of the brain structures, number and morphology of neuronal cells, distribution of white-gray matter, and in the molecular and genetic expressions of specific molecules inside and on the surface of the cells. The highest limitation of these investigations are the fact that they are, for definition, post-mortem studies, which can give us some information about the end-stage of the illness, but with very low data about the first pathophysiological events [6].

The "in-vivo" studies can help researchers to understand the first events at the base of the development of the pathology and to identify the molecular and non-molecular targets of therapies, but they have strong limitations due to the fact that human brain circuits themselves are difficult to be reproduced in animal models. Besides these challenges, they are difficult to be selectively studied with the modern imaging (such as Magnetic Resonance and Positron Emitted Tomography/Computed Tomography) and non-imaging (such as electroencephalography, magnetoencephalography, transcranial magnetic stimulation and evoked potentials) methods [6].

All these factors make difficult to fully understand the aetiology and pathophysiology of these disorders, and consequently make difficult not only in the development, but also the monitoring of the actions of therapies, which according to clinical observations have been demonstrated effective in the treatment.

In this review, we will focus our attention on the actual state-of-the-art of role of imaging in monitoring of treatment of MD, underlying that up to date there are still not standardized imaging markers available in clinical practice; all the studies mentioned in this review are clinical studies performed on humans. We will analyse briefly the actual classification of MD; then we will focus on the "in vivo" imaging modalities used in research and clinical activity, the current knowledge about the neural models at the base of MD. The last part of the review focuses on analysis of the principle markers of response to the treatment according to the type of treatment used and to the imaging techniques adopted.

2. MD: definition and classifications

Historically, the definition and the diagnosis of psychiatric disorders have been quite difficult to assess. In the last decades, a great work has been made by the international psychiatric associations in order to standardize stable criteria for the diagnosis of MD; these criteria are based almost exclusively on clinical observations, and the pathophysiological mechanisms at the base of these conditions are still debate because of the difficulties exposed in the earlier part of this manuscript.

Nowadays, the diagnosis of psychiatric disorders is mostly made according to the data of the Diagnostic and Statistical Manual (DSM) of Mental Disorder, released at its 5th edition in 2013 (DSM-5th) [7] and largely integrated with the criteria of the International Classification of Disease released in its 10th edition (ICD-10) in 1990 by the World Health Organization (WHO).

According to the previous edition of DSM, the 4th, released in 1994 (DSM-4th) [8], the MD were grouped into a specific category of disorders in which the disturbance of the mood is the main future, and this was characterized by the appearance of different mood episodes (i.e. Major Depressive, Manic, Mixed or Hypomanic episode) at different times [8]. Both the episodes and the disorders have to satisfy specific diagnostic criteria, based on the features of the symptoms, on the exclusion of effects induced by concomitant drugs, and on the exclusion of other general medical conditions responsible of the symptoms [8]. Among the principle MD, the two main and more frequent are the Bipolar Disorder (BD), in particular type I (BD-I, the most studied) and type II (BD-II), and the Major Depressive Disorder (MDD) also known as Unipolar Disorder (UD).

The above mentioned classification was changed in the DSM-5th [8,9]: now bipolar and related disorders are grouped separately from the other depressive disorders, and they are considered pathologies with intermediate features between schizophrenia and psychotic related disorders on one side (i.e. psychoticism and disinhibition) and the "internalizing" disorders such as depressive disorders (i.e., negative affectivity) on the other side [8–10].

Despite this new updated classification, for convenience in the next paragraphs we will continue our analysis talking about "MD" as referred in the DSM-4th classification. This is because the greatest part of the studies published up to date has been published before the introduction of the new DSM-5th.

3. "In vivo" imaging studies in MD: a brief exposure of the main features and limits

Differences in anatomical structures, molecular compositions and functional activity among different regions of the Central Ner-

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