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Communication

Brain imaging in understanding the action of psychotropic drugs: The drugs for depression

L'imagerie au service de la compréhension de l'action des psychotropes : les antidépresseurs

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ABSTRACT

Objectives. – Brain imaging is now used to inform hypotheses relating not just to brain function but also the actions of drugs for depression. It can identify the relevant functional neuroanatomy of drug action and its relation to hot and cold cognition.
Patients. – Patients with acute major depression or in recovery from same, in comparison with healthy controls.
Results. – In the case of drugs for depression, we are limited by our understanding of the neurocognitive mechanisms involved. However, it has already been possible to show improved memory for positive descriptors for a range of drugs for depression and these are aligned in both healthy controls and patients. Brain imaging has shown corresponding early effects of drug treatment on how the amygdala responds to negative emotional stimuli. Study of cold cognition, while less developed, has attracted interest from the development of vortioxetine. Imaging studies in recovered patients and controls suggest cognitive enhancing effects of vortioxetine, which may be relevant to recovery from depression.
Conclusions. – The challenge is to develop a coherent neurocognitive theory of depression that can explain or give context to the observed patterns of symptoms and their response to treatment. Brain imaging will play an important part in this programme of work.

Mots clés :
Antidépresseur
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RÉSUMÉ

Objectifs. – L'imagerie cérébrale est maintenant utilisée pour informer les hypothèses relatives non seulement pour le fonctionnement du cerveau, mais aussi les actions de médicaments pour la dépression. Elle peut identifier la neuroanatomie fonctionnelle pertinente de l'action du médicament et de sa relation à la cognition chaude et froide.
Patients. – Les patients souffrant de dépression majeure, par rapport aux témoins sains.
Résultats. – Dans le cas des médicaments pour la dépression, nous sommes limités par notre compréhension des mécanismes neurocognitifs impliqués. Cependant, il a déjà été possible de montrer une meilleure mémoire pour descripteurs positifs pour une gamme de médicaments pour la dépression et ceux-ci sont alignés dans les deux contrôles sains et des patients. L'imagerie cérébrale a montré les effets précoces de traitement sur la façon dont l'amygdale répond à des stimuli émotionnels négatifs correspondant. L'étude de la cognition froide, certes moins développée, a suscité l'intérêt du développement de Vortioxétine. Les études d'imagerie de patients guéris et contrôles suggèrent des effets de l'amélioration cognitive de Vortioxétine, qui peuvent être utiles à la récupération de la dépression.

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Conclusions. – Le défi consiste à développer une théorie cohérente neurocognitives de la dépression qui peut expliquer ou mettre en contexte les tendances observées de symptômes et leur réponse au traitement. L'imagerie cérébrale jouera un rôle important dans ce programme de travail.

1. Introduction

Brain imaging has become a powerful adjunct to cognitive neuroscience. It is used to inform a range of hypotheses relating to brain function from simple perceptual activities through to complex decision-making. Its use in relation to the actions of psychotropic drugs and, in particular, drugs for depression, is still relatively under developed. However, its importance lies in three areas. The first is in identifying the relevant neural networks within which the primary actions of drugs appear to occur. Thus, it allows the identification of the relevant functional neuroanatomy of drug action. Secondly, it allows us to look in some detail at the candidate functions, which are or may be modulated by drugs for depression. These are usually classified along a continuum defined by the involvement of emotional processing of various kinds. The extremes of this dimension are, on the one hand, pure emotional processing or so-called 'hot cognition' and on the other, the usual classical domains of attention, memory and executive function or 'cold cognition'.

There is reasonable evidence that changes occur in acute episodes of major depression in both emotional processing and cold cognition. Moreover, some changes (notably in memory function) may be enduring and of functional significance [7]. The way in which hot and cold cognition fit together in regulating mood remains hypothetical. It is known that events, particularly major events, are triggers for the onset of mood episodes. These usually take the form of losses or disappointments. They are most prominent in first episodes of depression and become less obvious in subsequent recurrences [5]. It may also be true that the more minor events in the flow of daily life result in changes in mood that can accumulate and grow into mood instability. In bipolar patients mood instability results in movements of mood in both euphoric and depressive directions between mood episodes. In unipolar patients, the effect is less obvious and must primarily be to create depressive mood swings. The obvious hypothesis that springs from these descriptions is that depression may result from a greater sensitivity to everyday and more major events. Vulnerability to depression might reside in this greater sensitivity. Alternatively, it can be hypothesised that any relatively minor changes in daily mood must be regulated importantly by methods that are subsumed under the term 'cognitive control'. This is a term that has a wide variety of meanings in cognitive neuroscience. The failure to have adequate automatic or conscious regulation of one's emotions may be one of the additional factors that contribute to the risk of developing mood episodes. Whether it is either increased sensitivity or impaired cognitive control (or both) remains uncertain and relatively little studied.

If feeling either excessively happy or excessively sad about real events may be something that is subject to regulation by both automatic and conscious mechanisms, how should we conceptualise and measure them. It is tempting to identify such cognitive control with central executive function but it is by no means clear that this is appropriate. The little evidence that there is derives from findings in recovered patients with unipolar disorders and the relatives of patients with bipolar disorder, both of whom appear to share increased rates of repetitive responding in a test of executive function.

Major depressive episodes are of course defined by the recurrence of a consolation of particular symptoms. Those that refer to and invoke specific changes in emotional processing include depressed mood, diminished interest or pleasure, worthlessness or excessive guilt and recurrent thoughts of death, suicidal ideation etc. Access to the ideas and memories that are implicit in the latter items could be conditioned by a depressed mood and a bias in the accessing of emotionally valenced information. In other words, such symptoms reflect emotional bias in the processing of personally sensitive information. On the other hand, the depressive syndrome also includes items reflecting cold cognition. These include psychomotor retardation, fatigue or loss of energy and a diminished ability to think or concentrate resulting in indecisiveness. All of these symptoms are observable features of the way in which patients with depression behave. Each and all could contribute to measurable failures of cold cognition which, in turn might relate quite simply to an inability to control intolerable feelings of loss, worthlessness etc. or be a mechanism whereby behavioural efforts to change the environment are impeded or even prevented. In any case, it is clear that a full syndrome requires both elements of the cognitive spectrum and either one on its own is not a convincing episode of depression.

Given this provisional understanding of the neurocognitive mechanisms that underlie depression, the locus for the actions that may be the basis for the efficacy of effective treatments is likely to be elusive. In consequence, the findings that exist to this point are indicative but not definitive. Brain imaging has provided an important part of the necessary preliminary understanding.

2. Emotional processing as a target for drugs for depression

The discovery of effective medicines for treating depression was initially by guided serendipity. Thus, the objective of most observational treatment studies has been dominated by a primary effect on the symptoms of depression. It is an important conceptual step to try to move beyond symptoms to study the cognitive mechanisms described previously. There is now a substantial body of work with drugs for depression that is based on the observation of their neurocognitive effects in healthy volunteers. Thus, we have a reasonable descriptive knowledge, at the level of behaviour, of the consistencies in how drugs for depression affect automatic processing or negative biases independent of the effects of depression per se. Such biases can be estimated either in the perception of social expressions on the faces of volunteers or the access to self-reference adjectives in recall or recognition tasks. Negative bias is expressed in the increased sensitivity to negative facial expressions on the one hand and negative words or descriptors on the other. The most consistent observed effect has been to increase positive bias in self-referent memory. Thus, for example, treatment with citalopram or reboxetine has a similar effect demonstrable in healthy volunteers taking either drug for one week [1]. Obviously, this effect could be the basis for the correction of prevailing negative bias in depressed patients. Indeed, a single dose of reboxetine was subsequently shown to correct and indeed to normalise the negative bias in patients being treated for major depression [3]. Moreover, this correction weakly predicted the subsequent change in symptoms at six weeks.