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Review

Functional neuroimaging in anorexia nervosa: A clinical approach

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ABSTRACT

Aims: To provide a review of the available literature about the functional neuroimaging of anorexia nervosa, and to summarize the possible role of neurobiological factors in its pathogenesis.
Methods: A systematic review of the literature was performed using PubMed and Medline electronic database (1950–September 2009). Eligible studies were restricted to those involving the main parameters of cerebral activity and functional neuroimaging techniques. Findings of the reviewed studies have been grouped on a diagnostic subtype basis, and their comparison has been interpreted in terms of concordance.
Results: We found a high level of concordance among available studies with regard to the presence of frontal, parietal and cingulate functional disturbances in both anorexia nervosa restricting and binge/purging subtypes. Concordance among studies conducted regardless of the anorexia nervosa subtypes suggests an alteration in temporal and parietal functions and striatal metabolism.
Conclusions: The most consistent alterations in anorexia nervosa cerebral activity seem to involve the dorsolateral prefrontal cortex, the inferior parietal lobule, the anterior cingulate cortex and the caudate nucleus. They may affect different neural systems such as the frontal visual system, the attention network, the arousal and emotional processing systems, the reward processing network, and the network for the body schema.

1. Introduction

Eating disorders (EDs) are severe psychiatric disorders characterized by pathological body shape, eating and weight concerns. The DSM-IV-TR specifies three main eating disorders: anorexia nervosa (AN), bulimia nervosa (BN) and eating disorders not otherwise specified (EDNOS) [2]. AN patients have an obsessive fear of being fat and refuse to maintain their body weight over a minimum of 85% of the expected. According to the DSM-IV [3], AN has been subdivided into two diagnostic subtypes: AN restricting type (AN-R) and AN binge/purging type (AN-BP). AN is a serious disorder with a high rate of chronic outcome [45]. Nowadays, the etiology of AN and, more comprehensively, of EDs is considered to be multi-factorial, considering that social, genetic and psychological factors appear to be involved in the onset and maintenance of these disorders [12]. In the last 20 years, different studies focused on the possible presence of cerebral structural anomalies or/and functional disturbances in AN patients [35,38,39,42,47].

1.1. Functional neuroimaging in AN: techniques and data analysis methods

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are nuclear imaging techniques allowing a 3D evaluation of neuronal activity through the use of gamma-cameras and PET scanners. SPECT has been applied in EDs mostly to measure brain perfusion or regional cerebral blood flow (rCBF) after the administration of radiopharmaceuticals labeled with a single-photon emitting radionuclide and trapped in the brain cells in proportion with local blood supply. PET has been most frequently used to measure regional cerebral glucose metabolism (rCMRG) after the administration of ^{18}F-fluorodeoxyglucose (^{18}F-FDG). ^{18}F-FDG is trapped inside brain cells (astrocytes and neurons) in proportion to local cerebral metabolism. The labeling radionuclide (^{18}F, half-life 109 min) decays emitting a nuclear positron (a positively charged nuclear electron) which annihilates with a negative electron giving out two opposite photons of 511 KeV each. These two techniques, in particular PET, can also be used to assess the spatial concentration and distribution of a precise proteic target (i.e. receptors, enzymes, transporters, etc.) by using specifically engineered radioligands [33]. The fMRI technique is based on the observation that sudden changes in rCBF (directly related to the regional neural activity) are

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spatially coupled with a local increase of cerebral blood oxygenation (i.e. of oxiemoglobin concentration) which reflects in variations of the signal intensity in an applied magnetic field (blood oxygen level-dependent contrast) (BOLD contrast) [33]. Therefore, unlike SPECT and PET techniques, fMRI can only be used in order to obtain information about the activity of a specific cerebral area (when adequately stimulated) by assessing a unique functional parameter (the BOLD signal), which is in turn strictly related to the variation of the rCBF in that particular area.

As far as the statistical analysis of data in functional neuroimaging (fNI) studies are concerned, the two most used methods to interpret functional data acquired with the above mentioned techniques are: the region/volume-of-interest (ROI/VOI) approach and the statistical parametric mapping (SPM) system [49]. The ROI/VOI technique consists in the predetermined selection of brain regions of interest directly on the scans with a manual or automatic procedure, so that the mean signal intensity within each ROI/VOI is used as a statistical parameter for group comparison and correlative analysis. A possible weakness of this technique is the intrinsic risk of underestimating small focal changes in signal intensity that may be hidden by averaging values on the whole ROI/VOI. SPM is a statistical technique designed to detect peak differences in brain activity recorded with fNI technologies on a voxel-by-voxel basis. The size of every voxel varies depending on the instrument used and some adjustments (corrections for multiple comparisons) are needed to avoid false positive findings (Type II errors) potentially caused by the comparison of a large number of voxels or by the erroneous identification of background cerebral activity as related to the task [1]. Such differences in the two main data analysis methods (ROI/VOI analysis versus SPM) make it difficult to compare all the available fNI findings in a unique quantitative meta-analysis.

1.2. Aims of the current review

The aims of the present review are as follows:

- to present a critical review of the available literature on fNI in AN focusing on the interpretation of results on a diagnostic subtype basis;
- to use the relative frequency and concordance of specific fNI findings as an empirical and observational index to speculate on data drawn from the very heterogeneous literature in the field;
- to give an overview of the cerebral areas that may interact with an anomalous pattern of function in anorexic patients in order to discuss a possible role of neurobiological factors in AN pathogenesis.

2. Methods

2.1. Time-frame

A systematic review of the literature was performed using PubMed (U.S. National Library of Medicine, 1950 - September 2009) and Medline (National Center for Biotechnology Information, 1966 - September 2009) electronic data base.

2.2. Inclusion criteria

We used the key word ‘‘anorexia nervosa’’ in combination with ‘‘restricting’’, ‘‘binge/purging’’, ‘‘functional’’, ‘‘neuroimaging’’, ‘‘brain imaging’’, ‘‘technology’’, ‘‘receptor’’, ‘‘neurobiology’’ and ‘‘neurotransmission’’. We focused on studies reported in the past 15 years but also included commonly referenced and highly regarded older publications. Review articles and book chapters are cited to provide readers with more details and additional references. Eligible studies were restricted to the ones involving the most important fNI technologies (SPECT, PET and fMRI) regardless of the case group size and included the evaluation of a large variety of parameters used as indicators of cerebral function, such as: rCMRG, rCBF, serotonin (5-HT) and dopamine (DA) receptors density and serotonin transporter (5-HTT) activity.

2.3. Conceptual structure

Unlike previous reviews, we chose to examine results of this review from a clinical point of view. We especially focused on those studies comparing the two subtypes of AN, when it was possible. For this reason, all findings are presented separately for every nosographic subtype (AN-R and AN-BP) both in the outline of each study and in the graphical display of their frequency and concordance. A third group, the ‘‘not specified subtype AN’’ one (AN-NS), was created to include and compare those studies in which AN subtype was not assessed or in which it was assessed but no distinction was made in the statistical analysis.

In order to make the large amount of functional data homogeneous and comparable, we applied the following adjustments:

- each ROI/VOI and SPM-derived functional area has been assigned to only one of eight anatomically correspondent areas (frontal cortex, temporal cortex/amygdala, cingulate cortex, parietal cortex, occipital cortex, insular cortex, hypothalamus/thalamus and striatum);
- when necessary, the activity of a ROI/VOI or SPM functional partition has been equated to the activity of the whole area to which it belongs.

Because of the great number of studies, we realized that an evaluation of the results presented only as a chronological summary (Tables S1, S2 and S3, Appendix A, Supplementary data) might have been complex and confusing. Therefore we created a graphical display of fNI data to summarize their concordance on possible alterations in function or activation of specific areas (Figs. 1–3). In those figures, different findings for each area (increased, reduced or normal function/activation), distribution (left, right or overall), cerebral activity state (resting or task-activated), patient’s condition (affected or recovered) and functional parameter (perfusion/metabolism or receptor density) are reported in dedicated histograms.

3. Results

All results are grouped on a diagnostic subtype basis:

- AN-R in Table S1, Supplementary data and Fig. 1a and Fig. 2a;
- AN-BP in Table S2, Supplementary data and Fig. 1b and Fig. 2b;
- AN-NS group in Table S3, Supplementary data and Fig. 1c and Fig. 2c.

The relevance of specific fNI findings has been evaluated in terms of concordance among different studies. As a consequence, we did not consider as significant those alterations reported by only one study per area. By means of these criteria, we obtained the following results:

3.1. Anorexia nervosa restricting type (AN-R)

Overall, the frontal cortex shows an altered pattern of function in affected subjects, as indicated by the high level of concordance on the presence of a reduced function/metabolism at rest (Fig. 1a) [16,28,34,46] that tends to normalize after recovery (Fig. 2a)