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Review

Brain imaging findings in children and adolescents with mental disorders: A cross-sectional review

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ABSTRACT

Background: While brain imaging studies of juvenile patients has expanded in recent years to investigate the cerebral neurophysiologic correlates of psychiatric disorders, this research field remains scarce. The aim of the present review was to cluster the main mental disorders according to the differential brain location of the imaging findings recently reported in children and adolescents reports. A second objective was to describe the worldwide distribution and the main directions of the recent magnetic resonance imaging (MRI) and positron tomography (PET) studies in these patients.
Methods: A survey of 423 MRI and PET articles published between 2005 and 2008 was performed. A principal component analysis (PCA), then an activation likelihood estimate (ALE) meta-analysis, were applied on brain regional information retrieved from articles in order to cluster the various disorders with respect to the cerebral structures where alterations were reported. Furthermore, descriptive analysis characterized the literature production.
Results: Two hundred and seventy-four articles involving children and adolescent patients were analyzed. Both the PCA and ALE methods clustered, three groups of diagnosed psychiatric disorders, according to the brain structural and functional locations: one group of affective disorders characterized by abnormalities of the frontal-limbic regions; a group of mental disorders with "cognition deficits" mainly related to cortex abnormalities; and one psychomotor condition associated with abnormalities in the basal ganglia. The descriptive analysis indicates a focus on attention deficit hyperactivity disorders and autism spectrum disorders, a general steady rise in the number of annual reports, and lead of US research.
Conclusion: This cross-sectional review of child and adolescent mental disorders based on neuroimaging findings suggests overlaps of brain locations that allow to cluster the diagnosed disorders into three sets with respectively marked affective, cognitive, and psychomotor phenomenology. Furthermore, the brain imaging research effort was unequally distributed across disorders, and did not reflect their prevalence.

1. Introduction

While the majority of mental disorders have onset during childhood or adolescence, brain imaging techniques have generally been applied in adult patients. Studies in adults suggest involvement of various neuroanatomical and/or functional regional deviations in mental disorders. Brain imaging reports in juvenile patients subsequently suggested that some regional brain changes are also present in children or adolescents at onset, or even before, onset of psychiatric conditions [23,24,79,86,95,98]. The observation that brain abnormalities might be present early in life has lead to an increasing development of neuroimaging studies in children and adolescents in recent years.

Consequently, several reviews and meta-analyses have aimed at summarising the main findings related to juvenile subjects [3,41,79,88,94,95,106,117]. However, these reviews have generally focused on only one disorder, thus, there is no outline of recent neuroimaging studies of child and adolescent psychiatric conditions, neither as regards the similarities or differences of brain imaging features across disorders, during childhood or adolescence, nor as regards the worldwide distribution and representativity of the research effort.

Abbreviations: ALE, activation likelihood estimation; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; PCA, principle component analysis; PET, positron emission tomography scan; sMRI, structural magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MNI, Montreal Neurological Institute; NIMH, National Institutes of Mental Health.

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The aim of the present review was to determine, which regional brain abnormalities were reported for each mental disorder and to pool them on that basis. To this end, we analysed all neuroimaging reports related to child and adolescent psychiatric disorders published between 2005 and 2008, a period during which a large number of studies were produced (more than 400 articles). Brain imaging includes several techniques, which provide anatomical (with sMRI and DTI), functional (with fMRI and PET) and metabolic (with MRS) data. Two other techniques, magnetoencephalography and electroencephalography, which measure the electric variations of the brain were not included in the present analysis because their spatial resolution is lower than MRI. As the present review was focussed on describing the locations of findings, but not their pathophysiology, we pooled the observations from all studies whatever the technique used by cerebral region and by disorder. Then, by means of PCA, and meta-analysis using the ALE method, we plotted the reported location of cerebral alterations and mental disorders, in search of overlaps.

A second objective was to provide the worldwide distribution and the main directions of these recent neuroimaging reports. Indeed, among the previous reviews, none has reported the geographical distribution of investigations, so the respective contribution of European, American, Asian, or other teams is unknown. Because brain imaging mental disorders in juveniles is a relatively new field, it is worthwhile assessing the contribution of each country in order to determine if the neuroimaging findings arise from homogeneously distributed regions. A further lack of information concerns the identification of the DSM IV mental disorders investigated – are neuroimaging studies focused on a subset of disorders or are all disorders investigated equally? – and the respective contribution of the various imaging techniques. Therefore, we carried out a descriptive analysis to characterise these reports by extracting the following information from articles published between 2005 and 2008: geographical distribution, annual progression, nature of the mental disorders and imaging techniques.

2. Methods

Neuroimaging literature reports of mental disorders in children and adolescents were included if they met the following criteria:

(i) the patient sample met international criteria for a psychiatric disorder;
(ii) neuroimaging techniques were used;
(iii) children or adolescents were the focus of the report.

Four hundred and twenty-three articles were identified in Medline databases between January, 2005 and December 31, 2008, using combinations of three keywords from the summary belonging to each of the following fields:

(i) neuropsychiatric disorders or psychotropic drugs (addiction, affective disorder, anorexia nervosa, anxiety, attention deficit hyperactivity disorder, autism, bipolar disorder, craving, dependence, depression, hyperkinetic disorder, mental retardation, mood disorder, obsessive compulsive disorder, phobia, posttraumatic stress disorder, schizophrenia, Tourette's syndrome/ alcohol, antidepressant, antipsychotic, anxiolytic, cannabis, cocaine, ecstasy, fluoxetine, inhalant induced disorder, marijuana, nicotine, smoking, and tobacco);
(ii) age (adolescents, child, and children);
(iii) neuroimaging techniques (MRI, magnetic resonance spectroscopy, neuroimaging, and PET).

In addition, we reviewed the references of selected articles to identify other possible articles that might have escaped PubMed®.

Of the total 423 articles, 149 were excluded for any of the following reasons. The article was a review or a meta-analysis, the study included subjects older of 21 years (however we did not reject studies with a longitudinal design including subjects from children to young adults), or was conducted on high risk subjects affiliated with patient probands. We also excluded all case or pilot studies. After exclusion, a total of 274 articles remained (References are on the supplementary material in the online version of this article).

The following information was retained for analysis from each article: geographic location of the research team, year of publication, neuroimaging technique used, nature of the psychiatric disorder, and regions where significant structural and/or functional and/or metabolic abnormalities were observed in patients compared to healthy subjects of same age. As we could not include all the variously reported brain regions for analysis, we considered a common terminology for cerebral areas, in order to lower the number of variables. The inspection of abstracts allowed to select a number of regions with a terminology appearing recurrently. Thus, the authors' observations were gathered into the following brain regions: frontal lobe, cingulum, amygdalae, hippocampus (hippocampus and parahippocampus), temporal lobe, parietal lobe, occipital lobe, thalamus, striatum and cerebellum. Imaging techniques were not individualised because our aim was not to elucidate if the disorder was structural or functional but only to summarise the regional distribution of the reported abnormalities whatever their nature. Thus, we compiled, by cerebral region and by disorder, the observations from all studies when they revealed that brain images were significantly different in between-group (patients versus controls) comparisons. This was performed for addiction, anorexia nervosa, anxiety disorders (generalised anxiety, obsessive-compulsive disorder and post-traumatic stress), attention deficit hyperactivity disorders, autism spectrum disorders, mood disorders (major depressive and bipolar disorders), schizophrenia and Tourette's syndrome. Only the mental retardation was excluded from this analysis, first because of its heterogeneity and second because no detail was provided on the location of alteration associated with this condition.

In order to cluster the disorders according to the locations of brain regional alteration, we performed a PCA using the R software package [78]. This statistical clustering method allows plotting of the association between items (i.e. mental disorders) and variables (i.e. cerebral regions), with the aid of a procedure extracting the main factors (graph axes F1 and F2) that reduce the dimensionality of multivariate data while preserving most of the variance therein. The output from PCA analysis consisted of score plots, which provided an indication of the differentiation of the mental disorders in terms of similarities in abnormalities locations, and a correlation plot giving an indication of correlations between variables with respect to their proximity. The PCA was performed on normalised data. Indeed, as the number of data was not the same for all disorders, to avoid a bias related to this difference, all data were reduced to unit one before PCA analysis. Thus, for each disorder, all numbers were divided by the maximum value, ranging data from 0 to 1.

Hence, in order to assess the consistency of the ACP results, we used the ALE meta-analytic technique developed by Turkeltaub et al. [103] in the subset of articles expressing the brain findings in Talairach's or MNI stereotaxic coordinates. This method combines the coordinates of foci maxima from multiple studies into an ALE map for the brain, revealing between-study consistencies that may not be immediately evident by simple visual comparison of individual reports. We individually screened all the articles for the