AJNR

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AJNR Am J Neuroradiol 2012, 33 (11) 2033-2037
doi: https://doi.org/10.3174/ajnr.A2800
http://www.ajnr.org/content/33/11/2033

REVIEW ARTICLE

Functional and Structural MR Imaging in Neuropsychiatric Disorders, Part 2: Application in Schizophrenia and Autism

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SUMMARY: During the past decade, the application of advanced MR imaging techniques in neuropsychiatric disorders has seen a rapid increase. Disease-specific alterations in brain function can be assessed by fMRI. Structural GM and WM properties are increasingly investigated by DTI and voxel-based approaches like VBM. These methods provide neurobiologic correlates for brain architecture and function, evaluation tools for therapeutic approaches, and potential early markers for diagnosis. Having provided insight into principles of functional and structural imaging and delineated common findings in mild cognitive impairment and Alzheimer disease in Part 1 of this review, we will now focus on autism and schizophrenia as common psychiatric disorders covering different stages of the life span. This review concludes by summarizing current applications, limitations, and future prospects in the field of MR imaging–based neuroimaging.

ABBREVIATIONS: ACC = anterior cingulate cortex; ASD = autism spectrum disorders; BOLD = blood oxygen level–dependent; DMN = default mode network; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; FA = fractional anisotropy; GM = gray matter; HFA = high-functioning autism; ICD = International Classification of Diseases; RSN = resting-state network; rsfMRI = resting-state fMRI; VBM = voxel-based morphometry

The past years have seen significant gains in the areas of functional and structural neuroimaging, particularly in their application to the field of neuropsychiatric disorders.

MR imaging–based methods such as fMRI, DTI, and VBM provide neurobiologic correlates of neuropsychiatric disorders in vivo and potential early markers of disease for improved diagnosis. However, we still need to tune the available neuroimaging markers to provide individually applicable markers of disease to predict the risk of asymptomatic or oligosymptomatic subjects developing a specific neuropsychiatric disease. This is most relevant for the design and conduction of future primary or secondary prevention trials of neurodegenerative disorders such as Alzheimer disease or genetically determined disorders the course of which, however, can be dramatically improved through early intervention, such as schizophrenia or ASD. To date, the clinical application of MR imaging in neuropsychiatric diseases is mostly limited to the exclusion of macroscopic abnormalities. Part 1 delineated the methodologic basis and main findings in mild cognitive impairment and Alzheimer disease; this part summarizes major findings gained by applying these techniques to schizophrenia and ASD. We conclude with a discussion of the scope, limitations, and future prospects of functional and structural MR imaging techniques in neuropsychiatric disorders.

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Indicates open access to non-subscribers at www.ajnr.org

Indicates article with supplemental on-line tables.

http://dx.doi.org/10.3174/ajnr.A2800

Schizophrenia

Schizophrenia is a chronic mental disorder characterized by severe perturbations in cognition, affect, and behavior. Delusions and hallucinations, predominantly auditory in type, are typical symptoms of schizophrenia, but not obligatory. With a lifetime prevalence of approximately 1%, schizophrenia is a relatively common disorder[1] that affects most patients in adolescence and early adulthood. This early age of onset and the often severe symptoms account for the profound consequences of the disease for the social and occupational status and the well-being of patients and their families. Clinical and genetic studies have accumulated evidenced for the concept of prodromal stages of psychosis,[2] which may offer the chance of early intervention and even prevention of the full manifestation of schizophrenia.[3] However, we still lack sensitive and specific biomarkers that may be useful in increasing the accuracy of the presently available preclinical criteria of schizophrenia for future intervention trials. Here, structural and functional imaging may gain an important role in the near future. Imaging studies have described findings in individuals with a (genetic) risk for schizophrenia, relatives of patients with schizophrenia, and patients with first-episode schizophrenia and chronic schizophrenia. In this review, we will concentrate on residual or recurrent schizophrenia because most studies have focused on these stages and the findings obtained in these subjects will set the basis for the neuronal network changes that may occur in prodromal stages of schizophrenia.

Brain Function

Alterations of task-induced brain activation have been described in schizophrenia. Two core findings across studies are a decrease of frontal activations, referred to as hypofrontality, and an increased activation of midline structures such as the ACC, interpreted as resting-state activations that persist inappropriately into task conditions.[4-6] Consistently, a meta-

analysis of 41 executive-function studies in schizophrenia revealed reduced activation in the left dorsolateral prefrontal cortex, rostral/dorsal ACC, left thalamus, and inferior/posterior cortical areas. Increased activation was observed in several midline cortical areas.[7]

Investigation of functional connectivity by means of rsfMRI showed decreased connectivity between the bilateral auditory cortex regions in patients with auditory hallucinations.[8] Reduced resting-state connectivity between the left temporoparietal junction and the bilateral ACC and amygdala was found to correlate with the severity of auditory-verbal hallucinations.[9] Reduced connectivity is furthermore reported between cognitive control networks,[10] within the DMN,[11] and between the retrosplenial cortex and both the temporal lobe and the DMN[12] as well as among the bilateral posterior cingulate cortex, extrastriate cortex, medial prefrontal cortex, and parahippocampal gyrus.[13] Although reduced connectivity seems the leading finding in schizophrenia, there are resting-state MR imaging studies reporting not only reduced but also increased connectivity between components or subsystems of the DMN.[14-16] For a comprehensive review of both task-dependent as well as task-independent functional connectivity in schizophrenia, also see a recent review by Pettersson-Yeo et al.[17] The diagnostic use of these changes in first-episode or even prodromal stages of schizophrenia is still unexplored.

Brain Structure

Besides the reported functional alterations in frontal connectivity, schizophrenia is known to be characterized by mainly left-sided frontal GM volume reduction.[18,19] Further regions of decreased GM as detected by VBM include the limbic and paralimbic cortices as well as the thalamus.[19,20] VBM studies furthermore revealed WM reductions in schizophrenia. A recent meta-analysis of 17 VBM studies found 4 clusters of consistently reduced WM in schizophrenia compared with healthy controls, which are the bilateral frontal cortices and the bilateral internal capsules.[21]

Apart from a few exceptions, most DTI studies in schizophrenia have found fractional FA-value reduction in various brain regions.[22,23] A recent meta-analysis of 15 DTI studies in schizophrenia counted FA reductions in 112 coordinates and no FA increase. Overall, significant reductions in studies were consistent in 2 regions: the left frontal deep WM and the left temporal deep WM.[24] The first region is located within WM tracts connecting the frontal lobe, the thalamus, and the cingulate gyrus. The second region is traversed by WM tracts connecting the frontal lobe, insula, hippocampus-amygdala, and temporal and occipital lobes. Likewise impaired anatomic connections are likely to be accompanied by functional alterations, though to date, evidence about the mutual interaction and temporal sequence of functional and structural changes is still lacking.

Multimodal approaches, investigating WM and GM or structure and function at the same time, might help to elucidate these relationships. A recent study by Pomarol-Clotet at al,[25] combining fMRI, VBM, and DTI, found largely overlapping sites of pathologic alterations. Reduced task-induced deactivation of a medial frontal area, including the ACC, was accompanied by GM volume loss in the medial frontal cortex, including the ACC. DTI analysis revealed reduced FA values in the anterior portion of the corpus callosum, and a seed-based tractography showed diminished anatomic connectivity between the anterior corpus callosum and a medial frontal area largely overlapping with regions of decreased task-induced deactivation and decreased GM volume.[25] A study applying rsfMRI and DTI tractography to investigate alterations in functional and anatomic connectivity in schizophrenia also found convergent results. Reduced functional connectivity of the bilateral hippocampus to regions including the posterior cingulate cortex and the gyrus parahippocampalis was accompanied by significantly reduced FA values in the fornix body.[13] However, other multimodal approaches combining GM VBM and task-dependent fMRI[26] or rsfMRI[27] did not report such convergent findings.

ASD

ASD are relatively common neurodevelopmental disorders, affecting approximately 1 per 150 children.[28] ASD are characterized by 3 core symptoms, namely impaired social reciprocity, communication difficulties, and repetitive stereotyped behaviors. Motor function, attention, and other cognitive domains may also be affected.[29] Individuals with learning impairment are subcategorized in the group of low-functioning autism. Individuals without learning impairment but delayed phrase-speech acquisition can be attributed to the group of HFA, whereas individuals who display phrase speech before 36 months are categorized in the group of Asperger syndrome according to criteria of the ICD-10 of the World Health Organization, 1992.[30,31] Treatment of ASD despite the severe impact on families is still limited to supportive, behavioral, and symptomatic approaches. No treatments of underlying disease mechanisms are available. In vivo imaging may offer more insight into the neurobiologic basis of the symptoms and their relation to underlying genetic risk factors, eventually paving the way for primary or secondary preventive trials in ASD.

Brain Structure

ASD is known to display early alterations in WM development.[32] Overproportional brain growth[29] accompanied by mainly frontally increased FA values in young children[32] is followed by WM[31,33] and GM[34,35] volume reduction and FA value decrease in older children, adolescents, and adults with ASD compared to healthy controls.[36-40]

For example, Brito et al[41] found reduced FA values within the corpus callosum, the right corticospinal tract, and the internal capsule and in both pedunculi cerebri of school-aged children with autism. A recent whole-brain study in 13 adult patients with Asperger syndrome revealed reduced FA values within 13 largely bilateral clusters, including the internal capsule; the frontal, parietal, temporal, and occipital lobes; the cingulate gyrus; and the corpus callosum.[42] Although decreased FA values seem to be the leading finding in ASD, several studies reported mixed findings of increased and decreased FA values[36,43] and other studies demonstrated that normal FA values do not exclude structural alterations. A tractography study of the main limbic pathway in 24 subjects with Asperger syndrome showed an increase in the number of

streamlines (representing the tract volume), without detecting any differences in FA values within that same region.[44]

Brain Function

Task-dependent fMRI studies showed alterations in memory,[45] recognition of face expression,[46] selective attention,[47] cognitive control and executive function,[48] self- and other reflection,[49] self-representation,[50] and motor-response inhibition[51] in patients with ASD. Final conclusions were not yet derived from these studies because of the heterogeneity of paradigms as well as the diagnostic entities and age groups included. rsfMRI studies in patients with ASD have suggested that the disease is characterized by alterations in resting-state connectivity. Because of the predominantly reported decrease of connectivity between various brain regions,[52-55] ASD is referred to as a (frontal) disconnectivity disorder. However, increased connectivity, especially within seed regions of the DMN, has been reported and correlated with poorer verbal and nonverbal communication[54] and more restricted and repetitive behaviors[55] in patients with ASD compared with healthy controls.

For an overview of structural and functional MR imaging findings in ASD see On-Line Tables 1 and 2, respectively.

Discussion and Conclusions

So far, neuroimaging methods have just begun to be applied to predict a neuropsychiatric disease in a single subject. Most advances in this respect have been made in the application to at-risk stages of Alzheimer disease, whereas the identification of high-risk subjects with psychosis or the individual prediction of ASD in otherwise characterized at-risk families remains a matter of future research.

One reason might be that neuropsychiatric diagnoses are predominantly grounded on clinical criteria but do not necessarily overlap specific underlying neurobiologic disorders. The question of "disease entities" (ie, the convergence of neurobiology and symptoms of a disease) has been discussed since the days of Pinel and Esquirol in the 18th century. The strong advocacy for the existence of disease entities by Kraepelin[56] has found international reception up to the ninth revision of the ICD criteria in the 1980s. Presently, the concept has been widely abandoned for a more pragmatic approach, in which, for the research criteria of ICD-11 and DSM-V, clinical criteria of psychiatric disease will be complemented by biologic markers, among these functional and structural imaging findings. Autism, for example, comprises a large spectrum ranging from low-functioning autism to HFA, with an ongoing discussion as to whether Asperger syndrome is an autonomous entity or a form of HFA. These discussions will probably only be resolved with the advent of imaging evidence if there is a characteristic endophenotype of these and other entities within the autism spectrum as described by imaging and other biologic markers.

Neuropsychiatric study populations are, furthermore, often heterogeneous in terms of duration of illness (which is likely to have an impact on brain structure) and medication. This is of high relevance particularly in the studies on schizophrenia, in which antipsychotics have been suggested to contribute to the pattern of structural and functional brain abnormalities in chronically ill patients. Only a few studies succeed in reaching sufficient sample sizes when enrolling only medication-naïve subjects. One further challenge is to control for the effects of comorbidities, which are common in psychiatric diseases but have often not been systematically addressed. For example, rates of comorbidity between autism and attention deficit/hyperactivity disorder have been reported to range between 14% and 78%.[57] To overcome some of these constraints, studies will have to include bigger sample sizes, possibly in a framework of multicenter cooperation, and apply precisely defined diagnostic inclusion and exclusion criteria.

It is also crucial to record systematically possible demographic and other behavioral and substance-related confounders. Neuroimaging measurements are sensitive to constitutional interindividual differences such as genetics, intelligence, or educational level. rsfMRI studies have, furthermore, demonstrated that sex,[58,59] age,[60] and even the method of instruction[61] influence resting-state results. Especially, functional neuroimaging measures may be affected by transient brain and body states, such as arousal, attention, sleep deprivation, sensory processing of irrelevant stimuli, or the effects of substances with impact on the central nervous system. These effects need to be taken into account and, as far as possible, be controlled for when the focus is on disease-related between-group differences.[62] For instance, including a RSN that is not expected to differ between groups can provide some confidence that reported differences in RSN connectivity between the 2 groups are meaningful and are not merely dominated by confounders such as medication differences.[63]

Pitfalls inherent in task-induced fMRI also originate from the BOLD signal intensity being only a coarse proxy of neural activity with a considerable delay between neural activation and measured hemodynamic response. One further concern in this context is that it remains unclear whether the hemodynamic signal intensity is constant throughout the task or whether, after an initial overoxygenation, a steady-state of back-to-normal oxygenation level is re-attained at some point, despite continuing neural activity. It remains, furthermore, largely unclear whether the time course of this hemodynamic response per se might be altered in disease and not (exclusively) neural activation itself. Here, the combination of fMRI with measures of neuronal activity providing high temporal resolution such as electroencephalography studies will provide more insight.[64]

Resting-state functional connectivity as a task-independent measure of brain intrinsic activity has the potential to make fMRI studies available to a wider range of patients and might thereby greatly increase the clinical utility of fMRI. It has also been argued that many pathologic entities are characterized by complex alterations in intrinsic functional connectivity, rather than by altered activation of distinct brain regions during task conditions, which cannot explain the range of cognitive and affective impairments in neuropsychiatric disorders. This assumption has initiated a shift of research attention towards intrinsic neural circuits that support sensory, cognitive, and emotional processes assessable by rsfMRI. Nonetheless, methods to extract networks of temporally coherent BOLD signals to determine functional connectivity are also applicable and increasingly used to task-condition data.

The combination of different imaging modalities might be able to partially compensate the specific disadvantages of each single imaging method. Combining different imaging tech-

niques might furthermore reveal common sites of pathology, thereby providing pathophysiologic insight, especially into the relationship between functional and structural alterations in disease. Changes in 1 single imaging technique, often also limited to a distinct brain region or structure, often lack effect size for accurate diagnosis. Therefore it is often not sufficient to rely on only 1 parameter. Pooling multimodal imaging information, therefore, appears to be a promising future direction to reach sufficient statistical power for individual clinical application.

This aim of combining different imaging approaches is closely related to a second important recent development: the application of sophisticated multivariate analysis and variable selection methods like support vector machines (eg, to predict a binary outcome like disease−no disease on the basis of an imaging score) or elastic net regression (to train a composite imaging score to best predict the continuous outcome of psychological or genetic test scores). Also, rather than relying on an a priori hypothesis of a brain region that is most likely affected by the disease, it might be more promising to use data-driven approaches (eg, principal component analysis or factor analysis if parameters are not independent) to detect patterns of alterations highly dominated by disease. Such an approach was recently used by Plant et al.[65] By applying feature-selection algorithms to VBM data to identify brain regions showing the highest accuracy for the discrimination between patients with AD and healthy controls, a classification accuracy of ≥92% could be reached.

A known statistical challenge, particularly in whole-brain studies, is the correction for multiple comparisons that can be overcome by multivariate methods that compare overall patterns rather than single locations of significant changes. Applying previously defined masks for pattern matching or goodness-of-fit analysis allows the combination of data-driven exploration (to derive a mask of disease-specific patterns) without facing the problems of reduced statistical power of whole-brain comparisons.

In summary, further work is required to overcome the discussed technical limitations to finally make advanced MR imaging techniques applicable in individual patients with psychiatric disorders. Nonetheless, these imaging modalities are, even to date, extremely valuable and have contributed tremendously to our understanding of the pathophysiology underlying neuropsychiatric diseases. Imaging biomarkers furthermore provide a tool for the evaluation of therapy effects. For a comprehensive review of imaging biomarkers in Alzheimer disease, for instance, see Hampel et al.[66]

Genetic imaging is an additional emerging field of research in which advanced MR imaging techniques prove acutely valuable. An increasing number of clinical-association studies that compare genetic data from patients and controls identify a growing body of novel genetic risk variants for several mental disorders, including Alzheimer disease,[67] schizophrenia,[68] and autism.[69] Using disease-specific imaging patterns as intermediate phenotypes provides a tool to investigate the impact of these polymorphisms on brain function and structure, thereby furthering insight into how they might influence behavior. These intermediate phenotypes based on direct observation of brain functional and structural architecture are supposed to be closer to the genetic substrate than are clinically diagnosed disorders,[70] also because they avoid the abovementioned heterogeneity and arbitrary boundaries inherent in DSM-IV diagnostic categories. Characterizing the effects of risk genes and variations on brain function and structure as a resulting intermediate phenotype is, therefore, crucial for transforming genomic advances into a pathophysiologic understanding of psychiatric disorders that can inform the development of more effective tools for the treatment and prevention of psychiatric disorders.

Disclosures: Stefan Teipel—*UNRELATED: Grants/Grants Pending*: Janssen-Cilag, Comments: grant provided from 2005 to 2009.

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