

Coincidence between Functional and Morphological MR Abnormalities as a New Biomarker in Schizophrenic Patients with Chronic Auditory Hallucinations

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SCHIZOPHRENIA is a chronic brain disorder that affects approximately one percent of the world's population. Those afflicted may experience hallucinations, delusional thoughts, cognitive deficits and disorganized thinking. The disease has a peak of onset in young adulthood and is thought to result from genetic and environmental factors. Understanding the neural network hypothetically responsible for the pathogenesis of schizophrenia, or neural substrates, requires a precise determination of the extent and distribution of abnormalities in brain anatomy and function. Although there is no known cure, it is treatable with drugs, which are the mainstay of treatment, and also with psychotherapy.

Schizophrenia is a heterogeneous illness whose biological bases are mediated by complex interactions. There is now high evidence about the existence of structural and functional brain abnormalities in these patients. Morphologic and functional changes are widespread but subtle and with a variable level of evidence and expression. Even in first episode patients, the lateral and the third ventricles are to some extent larger and the total brain volume is slightly smaller. Quite relevant, some of these changes predate full clinical manifestations, are progressive and fairly correlate with clinical symptoms and response to treatment in a yet poorly understandable way.

Models linking brain function, structure and clinical manifestations are necessary to understand these mechanisms. Magnetic Resonance (MR) imaging can be used to show structural and functional abnormalities in specific brain areas of schizophrenic patients. Unfortunately, and although many brain abnormalities have been implicated in schizophrenia by means of MR imaging, no single region has been consistently reported to »

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be abnormal. The differences in patient clinical manifestations (phenotype) and the procedure in acquiring and processing the images (methodology) among studies may explain the inconsistencies of the results.

Our research group has used the 'core symptom' approach (auditory hallucinations) and has looked for new technical approaches in neuroimaging in order to help to disentangle these controversies. These morphological and functional MR studies support the multiplicity of areas involved in the pathogenesis of auditory hallucinations with particular emphasis in those areas involved in normal processing of auditory stimuli. Emotional response is also known to play a significant role in schizophrenia. Its alterations have been mainly studied through visual paradigms, which have led to a better understanding of

its relationships with negative and cognitive symptoms, but not with the positive symptoms such as auditory hallucinations.

Given these limitations, we first designed an auditory emotional paradigm to be used in our functional studies. This new paradigm was aimed to study the emotional response of patients with schizophrenia in front of words that were selected to reproduce patients' experiences when hearing voices.

We have evaluated not only morphometric and functional MR abnormalities in these patients. Our approach was based in the hypothesis that functional auditory emotional MR abnormalities may coexist with focal brain reductions in specific brain regions of schizophrenic patients with chronic auditory hallucinations. If so, these areas should be analyzed to demonstrate that they are different from a healthy paired control group.

As technical procedures are concerned, a better understanding of the biological bases of a clinical phenotype is to be expected by coupling functional and morphological approaches. Thus, a neurophysiological interaction among specific psychopathology (auditory hallucinations phenotype), brain function (increased hemodynamic response to emotional auditory stimuli) and structure (gray matter deficits) can be traced with newly developed MR biomarkers. To do this, we coupled functional EPI T2* weighted (with two

different emotional and neutral auditory stimulation) and morphometric 3D T1 weighted gradient echo MR images.

The images were analyzed using statistical parametric mapping software. In the functional experiment, brain activation to auditory emotional stimuli was obtained after contrast-subtracted images between emotional and non-emotional words. The morphological differences were evaluated with an optimized voxel-based method. Different statistical analyses were used to pick-up volume elements (voxels) with differences between patients and controls. The functional and morphometric MR images showing these differences overlaid to depict only those voxels that were statistically reported by both techniques. Then, a Coincidence Map (regions with both an abnormal functional response and a neuronal reduction) was generated by multiplying the emotional functional MR images and the volume decrement morphometric maps (Figure 1).

The use of analytical maps showing coinciding regions of functional and structural brain abnormalities were generated with many coinciding areas following the same pattern of reduction of volume and overreaction to emotion. This new imaging biomarker of abnormal interactions between function and morphology showed large brain clusters in the left and right middle temporal and »



Figure 1 Patient with schizophrenia and persistent auditory hallucinations. The MR images show the areas of grey matter reduction (a), auditory abnormal emotional functional response (b) and those where these two anomalous findings coexist (c)



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superior temporal gyri, and smaller coinciding clusters in the left posterior and right anterior cingular gyri, left inferior frontal gyrus and middle occipital gyrus. These anomalies appear jointly in brain regions that regulate emotion and process human voices, being related to the abnormal neural network involved in the auditory emotional dysfunction seen in these patients.

Superior and middle temporal gyri are known to be involved in processing auditory stimuli including their emotional content and are probably the most important structural and functional areas implicated in the pathogenesis of auditory hallucinations. The posterior cingular gyrus is involved with the association of recognized words and probably reflects the retrieval of emotional verbal memories during an experience similar to the patients' hallucinations. It is probably indicat-

ing self-relatedness for these patients. The anterior cingular gyrus is involved with attention and has also been related to the processing of emotional stimuli and the pathogenesis of auditory hallucinations. The left inferior frontal gyrus was the first area to be described in functional studies of auditory hallucinations. Although aligned with some controversial reports, it can be now considered a replicated finding.

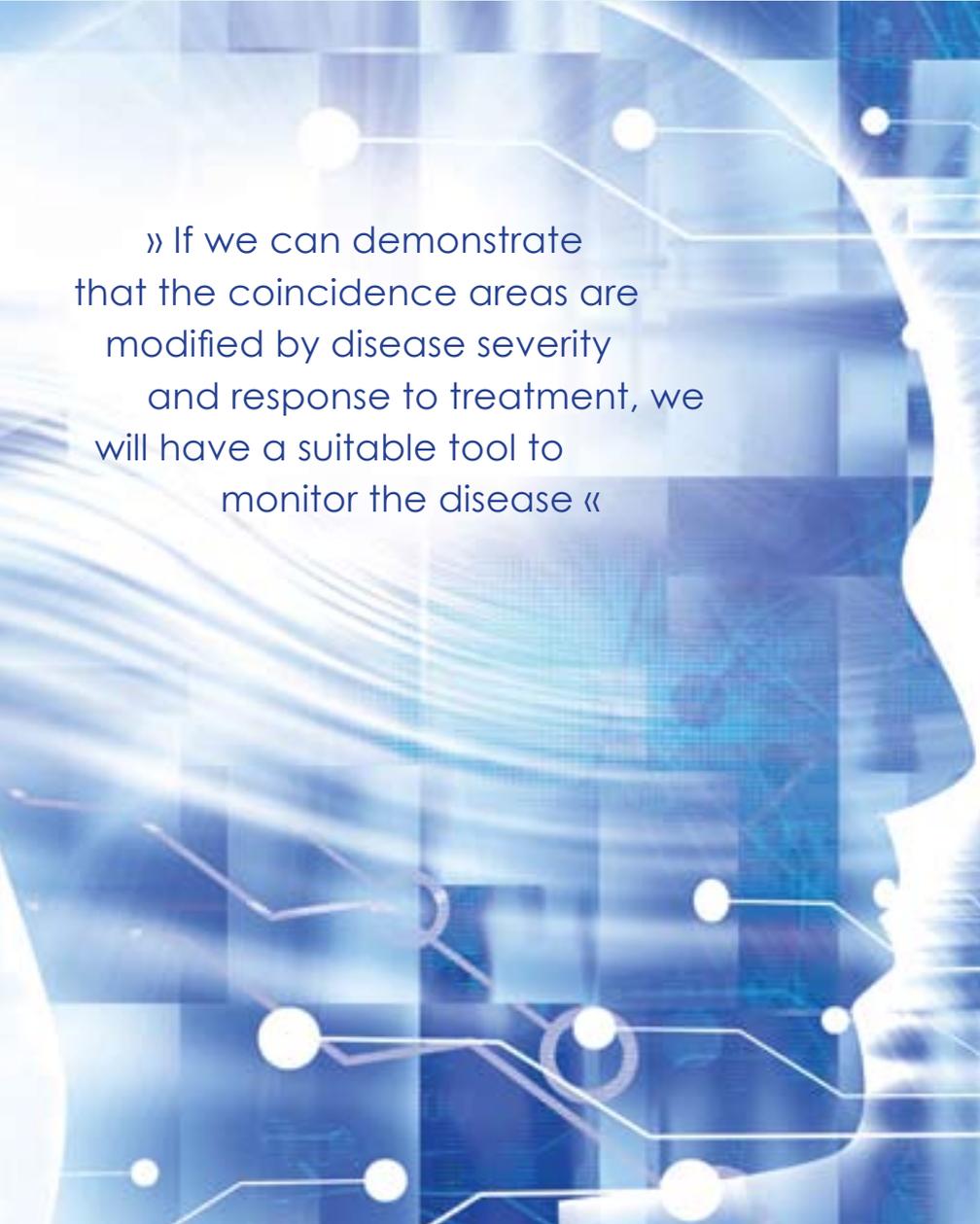
It is generally accepted that areas of decreased perfusion parallel decreases in gray matter concentration. However, our findings show that in patients with schizophrenia, enhanced activation is found in areas of maximal neural density decrement. These areas of coincidence where the same voxels have hemodynamic functional changes associated with the emotional auditory-triggered response and focal decreased volume could

possibly express a compensation phenomenon in which regions with decreased volume need a larger hemodynamic dysfunctional response to a defined paradigm.

These results could improve the diagnosis, evaluation and treatment of schizophrenia. Neuroimaging variables may represent good alternative phenotypes in these fields. They may be reliably obtained in vivo, have stronger statistical power than other phenotypes such as clinical manifestations, and may even be more sensitive. A significant number of neuroimaging studies have used longitudinal designs to investigate the effects of medication treatments (not yet the psychotherapeutic approaches) on brain functioning among patients with schizophrenia but strong methodological limitations appear in the existing literature. In spite of this, there is now growing evidence that at least second-generation antipsychotic drugs might normalize structural and functional changes in these patients. However, the predictive validity of these variables and the relationships with other phenotypes and relevant genetic polymorphisms are far from clear yet.

This new biomarker opens up the use of MR coincidence maps for specific diagnosis and follow-up of schizophrenic patients after treatment. There are several issues to take into account for future research in this field. First the core symptom approach (particularly in the extreme group: patients with persistent auditory hallucinations) could give us more specific findings on to the studies in schizophrenia spectrum disorders. Second it would be important to see if these findings correlate with molecular genetic susceptibility. Finally, if we can demonstrate that the coincidence areas are modified by disease severity and response to treatment, we will have a suitable tool to monitor the disease.

■ References available on request (jenna.wilson@iirme.com)



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