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A novel approach to clinical–radiological correlations: Anatomo-Clinical Overlapping Maps (AnaCOM): Method and validation

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We present a new clinical–radiological correlation method (AnaCOM) that aims at establishing structure–function relationships. We validated AnaCOM by assessing the location of lesions that are associated with altered performances in a well-studied task: the verbal fluency task. We retrospectively reviewed 64 brain-damaged patients who had focal lesions in a variety of cortical sites due to stroke, hemorrhage or tumor surgery. All patients were tested for verbal fluency at the time of the MRI examination. MRI volumes were normalized using a mask covering brain lesions and artifacts. The brain lesions were then segmented using the normalized MRI. In each patient, a verbal fluency score was assigned to each voxel in the segmented area. Subsequently, segmentations were superimposed and voxels were gathered in clusters defined by the overlap of the patients' lesion. For each cluster, the scores were statistically compared to those obtained by controls for the same task. This process allowed the construction of cluster-by-cluster statistical maps of anatomo-clinical correlations. As expected, the statistical map indicated that two regions were significantly associated with a deficit in the fluency task: one located in Broca's area and the other in the preSMA. AnaCOM does not require a priori selection of the location of lesions or task scores. The method complements the functional imaging techniques, as it tells which regions are necessary for a given function and it explores cortical regions as well as the white matter.

Keywords: AnaCOM; Anatomo-Clinical Overlapping Map; Anatomical MRI; Neuropsychological test; Verbal fluency; Brain lesion

Introduction

Paul Broca made a great contribution to the study of the brain by introducing the concept of localization of functions to different regions of the brain. He postulated that the brain damage of the patient "Tan", who suffered from aphasia, was precisely located in the area which controls speech. By studying the brain damage of aphasic patients after their death, Broca demonstrated that there was a relatively circumscribed center located in the posterior and inferior convolutions of the left frontal lobe, now known as "Broca's area," that was responsible for speech (langage articulé) (Broca, 1861a,b,c,d, 1863, 1865). These pioneering studies estab-

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lished the clinico-pathological correlation technique, which consists of relating a functional deficit to a specific brain lesion observed after the death of the patient or through the use of structural brain imaging. The clinico-pathological correlation technique has been widely used since then to correlate functional deficiencies with brain lesions both in patients and in healthy animals (Cromwell and Berridge, 1993).

With the arrival of new tools in neuroimagery that allow one to be able to "see" inside the living body, it is now easier to produce correlations between human functional deficits and brain lesions. Magnetic resonance imaging (MRI) allows for more precise observation of tissue damage in vivo. Approaches to anatomo-clinical correlations fall into one of three groups. The first group is similar to clinico-pathological correlation, but describes patient lesions, as shown by structural MRI, through case reports (Pierrot-Deseilligny et al., 1991; Rivaud et al., 1994; Gaymard et al., 1998), compilations of case reports (Kertesz, 1993), or recruitment of subjects with similar lesions (Braun et al., 1992; Regan et al., 1992; Lekwuwa and Barnes, 1996; Greenlee and Smith, 1997; Stuss et al., 1998; Beblo et al., 1999; Ayotte et al., 2000; Furst et al., 2000). This approach works well if we assume that the occurrence of a deficit depends on the lesion of a single structure (Godefroy et al., 1998).

The second type of approach can be generalized under the term "maximum overlap". Since all patients experience a similar functional deficit, the region of maximum overlap (i.e., the area most commonly damaged) is the region of voxels associated with the deficient function (Clarke et al., 1997; Lippitz et al., 1997; Tranel et al., 1997; Haaland et al., 2000; Stufflebeam et al., 2000; Makale et al., 2002; Milea et al., 2003; Parvizi and Damasio, 2003; Van der Werf et al., 2003). Maximum overlapping techniques, however, focus on a single region that is linked to a function and do not provide any information on the potential implication of other areas that may or may not be involved in a particular function.

More recently, several authors have attempted to take into account the possibility of detecting multiple areas for a function. They set up a new method inspired by both the voxel-based approach and the maximum overlap approach. These methods aim to obtain a map showing regions which are linked to a neuropsychological deficit. Another approach was to segment lesions in a normalized standardized space and to weight the voxels inside lesions either positively or negatively (Cohen et al., 2003) or with the score obtained by a patient in a neuropsychological test (Frank et al., 1997; Kinkingnéhun et al., 2004). These techniques allow one to obtain maps presenting averaged scores for each voxel. These two techniques permit one to find several sets of contiguous voxels (clusters) of the brain participating in a single function, but they are not statistical methods. To improve the effectiveness, the neuropsychological score of those who have lesions in a particular voxel can be statistically compared with those who do not have lesions in the studied voxel (Bates et al., 2003; Dronkers et al., 2004; Karnath et al., 2004a; Committeri et al., 2007). These voxel-based methods greatly improve on the classical anatomo-clinical method, as they do not require a priori selection of patients based on their scores at neuropsychological tests or selection on the basis of the location of the lesions. Statistical comparison of patients with the deficit vs. control patients without the deficit, instead of patients vs. healthy controls can be discussed. Moreover, the stringent Bonferroni correction that is applied to voxel by voxel statistical method greatly reduces the statistical power (Rorden and Karnath, 2004).

Therefore, we developed a cluster-of-voxels-based method, called the Anatomo-Clinical Overlapping Maps (AnaCOM) method, that allows for the generation of statistical anatomo-functional maps from patients with brain lesions (Kinkingnéhun et al., 2004). We also optimized the lesion segmentation and lesion normalization stages of the procedure. By rating the performance of patients on neuropsychological tests and capturing their brain structure with a structural MRI scan, we were able to develop maps that correlated a set of contiguous voxels in the brain with the degree of neuropsychological deficit when compared to the score of normal control subjects.

Application of the AnaCOM method was performed with a verbal fluency task. We chose the phonemic verbal fluency task (Cardebat et al., 1990) because it is related to a well-known and reliable cerebral network. Word generation tasks have also been used to map Broca's area in electrophysical and fMRI studies in a reliable and accurate correspondence (Brannen et al., 2001). We expected AnaCOM to show areas of the fronto-temporo-parietal network usually involved in verbal fluency tasks. A voxel-based approach, the voxel-based lesion-symptom mapping (VSLM) (Bates et al., 2003), was also performed on the same data set and in the same conditions in order to compare the results of the two methods. AnaCOM was predicted to be more sensitive than the VSLM.

Anatomo-Clinical Overlapping Maps

Overview

The aim of this method is to create anatomo-clinical maps from patients with brain lesions. These maps are created using the anatomical MRI of patients who are administered neuropsychological tests (see Fig. 1). First, MRIs are normalized to a common standardized space. Second, brain lesions are segmented to obtain regions of interest (ROI). Third, the score obtained by the patient in the neuropsychological test is introduced in the voxels of the segmented ROI. Lesions are overlapped and voxels are gathered in clusters according to the patients' brain lesions which cover them. Finally, the patient's score for each cluster is statistically compared to normal values, which allows for the creation of statistical maps.

Image acquisition

The MRI images required for AnaCOM studies are anatomical scans on which lesion boundaries are clearly visible. 3D T1 anatomical MRI allows one to see both vascular and tumor excision lesions.

Structural MRI normalization

Patient anatomical MRI scans are normalized to allow comparison. Damaged areas of the images (lesions and artifacts) are masked to reduce their influence in the normalization process (Brett et al., 2001). MRI scans are normalized to fit each patient's brain, according to the T1 Montreal Neurological Institute (MNI) Atlas (see Fig. 2).

Mask

As the registration process uses signal intensity of the voxels, artifacts and the signal generated by lesions can influence the normalization process (Ashburner et al., 1997). Thus, the signal