Cognitive neuroanatomy of language

Dominique Cardebat
Institut National de la Santé et de la Recherche Medical
Toulouse, France

What you're looking at, represents one of the main starting points of the study of aphasia. They are very old data on aphasia explored with a modern imaging technique.

These high-resolution MR images were obtained, in 1994, by Cabanis and co-workers in Paris, from the still preserved brain of the first patient described hundred thirty years before by Paul Broca, in 1865. The patient, called Leborgne, was also known by his nick-name "Tan-Tan" which was the only stereotypic oral production he could produce after his stroke. You can see how this very large lesion destroys a fair amount of frontal cortex and the underlying white matter, and spreads towards the head of the caudate, far beyond the limits of what we call Broca's area.

Brain/language relationships : the "aphasia model"

Over the past century, many attempts have been made to find clear relationships between aphasia and brain lesions, that is to use aphasia as a pathophysiological model to study brain/language relationships. As we all know, some aspects of this model are quite well-established; the exact site of the lesion, its size and its etiology strongly influence the observed aphasia and its prognosis. There are few critical regions such as the posterior part of the left superior temporal region - also called Wernicke's area - whose lesions usually cause massive deficits on several language dimensions. However, most of aphasic symptoms, such as anomia, are related to various lesion sites and this is what I'm referring to on this slide as a distributed anatomy of lesions, suggesting that a given symptom may arise from lesions localized at different points of a network distributed over the left hemisphere if not the entire brain. Besides, the relationships between lesion anatomy and language disorders appear more stable when symptoms, rather than syndromes, such as Broca or Wernicke's aphasia, are considered In fact, the classical dogma on brain & language is frequently challenged by clinical observations and there are what Anna Basso and co-workers (1985) called Exceptions, such as fluent

aphasias with pre-rolandic lesions and vice-versa or even more paradoxical cases showing no aphasia at all despite destruction of the whole left peri-sylvian area, or crossed-aphasia resulting from right-sided lesions in right-handed subjects. Many "additional" factors have been invoked to explain such exceptional cases, not really exceptional as they were about 12 % in the Basso's series.

Apart from handiness, other subject-specific factors such as age and gender may influence aphasia type and severity; cultural factors starting from literacy to bi- or multi-lingualism and familiarity with language material or language exercises are obviously major factors, although only poorly understood.

Most importantly, the dynamics of post-lesional phenomena should be considered in this model, both in their neural and linguistic dimensions.

And finally, the effects of patient motivation and the influence of aphasia therapy should certainly not be overlooked.

Brain/language relationships : functional imaging data

Functional imaging techniques, and in particular PET, are potentially of great heuristic value to try and disentangle all these complex influences on the brain/language model. In particular, these techniques should sooner or later help us to understand more about recovery of language functions; indeed, aphasia should be considered not only, from a negative viewpoint, as a set of deficits caused by brain lesions but also, from a positive viewpoint, as the behavioral consequences of both reorganization of neural systems and cognitive strategies of compensation. In fact, there are different ways to use functional brain imaging to expand our knowledge beyond the limits of the classical lesion-based model.

Activation in normal subjects

The first one is to address whether the regions related to impairments of specific language functions when damaged, might be activated in normal subjects relying on the same functions during a language task. For instance, several authors such as Geschwind or Cappa et al. (1981) claimed that phonological disorders are associated with lesions close to the left sylvian fissure whereas lexical semantic disorders are linked to lesions of regions that are more distant to the fissure, such as the inferior parts of the parietal or the temporal lobes. Using PET and a language activation experiment, we addressed whether such a topographical segregation between phonological and lexical semantic processes might be observed in normal subjects when performing two language tasks, respectively related to each of these processes. We used monitoring tasks with 30% targets among distractors in series of stimuli presented binaurally

at a constant rate (1 per 3s); subjects responded by clicking on a button with right fingers. In the Phonemes task, stimuli were 3- or 4-syllable non-words and the target was the phoneme /b/ if, and only if, the phoneme /d/ was detected in a preceding syllable. In the Words task, targets were nouns of small animals (smaller than a chicken or a cat) preceded by a "positive" adjective in adjective-noun pairs. This slide represent statistical maps displaying voxels in the brain in which significant changes were observed as blood flow increases in the semantic task compared to the phonological one (this is the superior part of the slide) or blood flow increases in the phonological task compared to the semantic task in the lower part of the slide. These results are in very good accord with our hypotheses based on findings in aphasic patients, as the topography of blood flow increases matched well the distribution of lesions generating either phonemic disorders, namely regions close to the sylvian fissure or lexical semantic disorders, namely inferior temporal and inferior parietal localizations.

Resting state in patients

The second way to use functional imaging and explore brain correlates of aphasia is to investigate the metabolic abnormalities that are induced by the lesions and are seen in functional images during a resting state. A fair amount of studies have been done especially in the States during the eighties with a series of glucose steady-state PET studies in relatively small groups of patients. To my view, one of the major contributions of these studies was to demonstrate the existence of massive remote effects of lesions with metabolic depression spreading far away from the anatomical site of the actual lesion. The most striking example of these remote effects relates to so-called subcortical aphasia in which hypometabolism in the ipsilateral cortex is very frequently observed. This image is from one of our previous studies and represents an example of such remote effects with a sub-cortical ischemic lesion restricted to the white matter of the left frontal lobe, and, in this SPECT slice, a profound hypoperfusion in the corresponding frontal cortex. Some of these studies also reinforced previous finding that direct or indirect damage to specific lesion such as the left posterior temporal region has a critical role in both aphasia type and prognosis. Finally, some follow up studies have been done and some others are currently reported or going on. However, these longitudinal data are still unclear, if not contradictory. In general, the functional significance of the abnormalities or longitudinal changes in brain metabolism observed at rest, remains to be clarified. For instance, remote hypometabolic effects may represent, at least, two different phenomena. On the one hand, the affected regions may be only de-afferented but still can participate in functional activation via other connections or networks.

On the other hand, these hypometabolic regions, particularly when they lie not too far away from the actual lesion or within the same vascular territory, may be actually affected by a neuronal loss, meaning an irreversible lack of function.

Activation in patients

The shortcomings of resting state PET studies obviously incline to explore the functionality of the undamaged brain by using activation tasks to test which spared territories in damaged brains could be involved when patients performed these tasks. This will constitute the third, and last, part of my talk. In fact very little has been done so far using up-to-date methodological standards of PET activation that is high-resolution rCBF recordings using the O15 technique.

Here are the results of one of such rare studies which was published last year in Annals of Neurology, by Cornelius Weiller and Walter Huber and their co-workers from Essen and Aachen. They've studied 6 Wernicke type aphasic patients with retro-rolandic lesions and a good recovery. By comparison to the activations observed in a non-word repetition task and in a verb generation task in normal subjects, aphasic demonstrated of course no activation in the damaged region and increased supra-normal activations in the right hemisphere, both in the superior temporal and the inferior frontal regions and in both tasks. Although appealing at first glance, this type of studies soon appear particularly complex because they combine two main sources of variance:

— one is related to brain lesions and aphasia and we've already seen some of these factors in the first part of this presentation

— the other source of variance comes from the many factors that may distort the results of cognitive activation even in normal subjects. In general such a complexity suggests that activation can only be explored on the basis of single-subject studies. Among factors related to the paradigm, I'd like to show only two brief examples.

The first one is related to the influence of stimulating conditions such as rate of presentation and exposure duration of stimuli. These factors have been recently investigated in great details by Cathy Price from London. As you can see here, there is a linear relationships between the amount of activation in the primary auditory cortex and the increasing number of words that subjects were listening to during conditions b to f, whereas a is a silent condition. Such linear relationship is not observed however in Wernicke's area which tends to respond equally to words presentation whatever the rate of presentation.

Another very important factor is related to the degree of familiarity with the task; these results were published in 1994 by Marcus Raichle and his co-workers in St Louis. On the left, are the activation observed in subjects who performed a verb generation task for the first time. As you can see in the middle part of the image, the activations seen in the naive stage, in particular that in the left frontal cortex, almost completely vanished after subjects had over-practiced the task and the same word list stimuli.

These factors should certainly be controlled in any activation studies and particularly in aphasic patients. However, the major factor related to aphasia is obviously the lesion. This is a massive lesion inducing, among other language disorders, a deep dyslexia. During a reading task in which patient performance were impaired, an activation of the right hemisphere was

observed. But in fact, what else could be predicted? , as only very few regions were spared in the left hemisphere.

The question of the specificity of such activations in the right hemisphere can be illustrated by data recently obtained in another patient by Liz Walburton, Cathy Price and Richard Wise from London. These are PET activation results co-registered with the actual MRI of this particular patient who presented a left posterior lesion. The experimental task was verb generation in which this patient performed well. Although right hemispheric activations were seen in the verb generation minus rest comparison, these were no longer apparent in the verb generation minus listening comparison, suggesting that right sided signals do not correspond to some sort of vicarious processes that can be involved in the verb generation task but are rather related to listening to words.

Thus, as the key issue of such studies is the mechanism of recovery and compensation of aphasia disorders, we are facing an even more complex problem. This is to specify activations in terms of signal localization, task-specificity and time curse after lesion onset and to establish causal relationships between such functional data and recovered performance. Many aspects of this problem remain to be addressed in the future. I'd like to close my talk by giving you an example of activation of a particular case of aphasia in which activation data provided some hints on the mechanisms of functional compensation in aphasia.

This young man suffered from an ischemic stoke which destroyed the left posterior sylvian region. He presented a severe Wernicke's aphasia in the first stage of evolution; after few months, he evolved towards a rare syndrome called deep dysphasia in which the main symptom is a deficit of repetition: repetition of concrete nouns is possible but with semantic paraphasias such as fork instead of plate, whereas repetition of abstract nouns, grammatical words, and non-words is just impossible. Auditory comprehension is quite good but again far better for concrete nouns than for abstract ones. In general performances on semantic tasks are fairly good but on phonological tasks, he is really poor. The patient condition can be summarized as understanding the meaning of words (at least concrete words) without accurate processing of their phonological forms.

We activated this patient, unfortunately only using SPECT but still, with, I think, interesting results. By comparison to a reference condition (listening to connected speech spoken in a foreign language), we observed activations in two tasks in which performances were very different. During a phonological task, which was phoneme monitoring in connected French speech, patient performances were at chance level, despite increases of CBF that were seen in almost all the undamaged cerebral territories. During a semantic task, which was monitoring for animal names in connected speech, his performances were fairly good and this was specifically associated with an activation in the right posterior temporal region just as if the activation of this right-sided region could compensate for the lesion effects in a semantic task but not in a phonological task. Whatever the technical limitations of this work, I think it shows how the combination of brain imaging methods with single-case studies of clear-cut psycholinguistic

dissociations may have a major impact on our understanding of the brain correlates of language functions and dysfunctions.

In any case, this would give us the opportunity to reconcile two sometimes antagonist approaches to cognitive neuroscience.