CORTICAL ACTIVITY IN LEFT AND RIGHT HEMISPHERE DURING LANGUAGE RELATED BRAIN FUNCTIONS

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The blood flow through the brain cortex varies with the functional state of the tissue. Just as in skeletal muscle or in various glands, an enhanced level of nerve cell activity invokes an increase in tissue metabolism and in blood flow. Thus, it was found by Olesen from our group that rhythmical movement of the hand augments regional blood flow in the contralateral central (hand) cortex by 20 to 30 per cent. It was subsequently verified that indeed not only flow but also oxygen uptake is increased in that same area during hand exercise. We have used regional blood flow measurements to map the cortical areas active in various types of language related brain functions. A summary of our findings will be given.

The method used for measurement of regional cerebral blood flow in man

The radioactive isotope Xenon-133 is used. It is produced in a nuclear reactor as a split product of uranium. Like the non-radioactive Xenon isotopes, Xe-133 is an inert gas and (like nitrogen, N_2) it does not react chemically with any molecules in the body. It is simply distributed according to the tissues' solubility. We use it in the form of a physical solution in saline in a dose of approximately 5 MilliCuries per injection (1.5 ml). The radiation exposure is negligible; it is much less than that of a single conventional X-ray study. This means that a series of repeated injections with an interval of 15 minutes can be made in the same setting without any radiation hazard. We take advantage of this by usually performing a series of 4 or 5 injections in one study: first at rest and then during a series of different forms of brain work - in this case involving various language related types of brain functions.

The Xenon-133 containing sterile saline is injected into a big artery on one side of the neck, the internal carotid artery. It supplies the anterior 3/4 of the brain (usually the posterior

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1) The paper was given by N.A. Lassen.

part of the brain, the occipital lobe's inner side, is not receiving the isotope by this injection as its arterial supply comes from a different artery, namely from the vertebral artery). With each internal carotid supplying (normally) only the ipsilateral cerebral hemisphere, and by injecting only one side, we obtain maps of blood flow distribution in one hemisphere only. This is a distinct limitation with regard to studying hemispheric differences: we have to rely on comparing a series of left hemisphere observations with those on the right side in other subjects, and cannot in the same subject observe both sides simultaneously.

Using a special isotope camera with 254 small detectors, we observe the arrival and subsequent wash-out of the Xenon-133 in regions of the size of approximately 1 cm^2. The tissue element "seen" has the form of a cone traversing the injected hemisphere. Due to absorption of radiation it is, however, the superficial cortex we see best. The regional blood flow is calculated from the slope of the Xenon-133 wash-out curve during the first minute following the injection of the radioactive bolus (that takes only one second). When a test is performed, such as counting or reading, the subject is asked to start performing approximately 10 seconds before the Xenon-133 injection, and then continue for 60 seconds (the injection is not felt by the subject). The interval of approximately 15 minutes between injections is necessary in order to clear the brain of radioactivity before injecting the next dose (we can actually use a shorter interval, and then compensate for remaining radioactivity).

The technique is not entirely atraumatic: it involves the cannulation and injection into the blood flowing to the brain and a risk of compromizing this flow exists. We have not encountered any complications in the series of 350 subjects studied in our laboratory (over a period of 4 years) with the technique described here. Yet, this risk restricts us to study patients with neurological symptoms in whom cerebral angiography is indicated, i.e. in whom a cannula is placed in the carotid artery for X-ray study. This means that normal subjects cannot be studied. Nevertheless, our series of neurological patients comprises cases without focal tissue abnormalities (patients studied because of arterial aneurisms or because of an epileptic seizure, cases of suspected brain tumor, etc.). The results obtained in such cases (approximately 20% of our patients) constitute our equivalent of normal man. The main part of the studies reported below pertain to such "normal" cases. The consistency of the results leaves no doubt that the data may indeed be taken to pertain to normal man.

Results

A. The awake resting state. With closed eyes in a darkened silent room and completely at rest the normal pattern of blood flow distribution shows the highest values in the frontal lobe (approximately 10% above the hemispheric mean).

B. Listening to words. Simple noise produced with Barany noise apparatus increases flow in the hearing cortex only minimally. Listening to sounds (Seashore test) or onomatopoetica as "crack", "bang", "whiz", on the other hand, clearly activates this area on both sides (15-30% increase in flow). The area comprises Wernicke's center of language on the left side (all our subjects were right handed). Listening to music caused the same effect. Our data do not suggest a hemispheric difference with these two forms of simple listening tests.

Listening to more complex spoken language produces increased flow on the left side. But since this area overlies the basal ganglia and since a flow increase here is often seen with the unspecific more global flow increase accompanying increased attention, we cannot assert the specificity of this activation.

C. Talking. Automatic talk in the form of counting repeatedly to twenty at a rate of one digit per second activates the hearing cortex, the primary (rolandic) mouth area and the supplementary motor area.

All these changes are bilateral. The pattern tends to be less sharply demarcated on the right side than on the left.

Word naming in the form of finding words of 5 flowers, 5 types of furniture, etc., activated the same three areas and caused a constant activation of the whole prefrontal region as well (cf. the comments made under reading aloud and internal speech).

D. Reading aloud. This activates six areas in both hemispheres. In addition to the three areas seen during automatic talk, the following areas also become active: the visual association cortex in the posterior part of the brain, the frontal eye field that often merges with the mouth area, and the low-posterior part of the frontal lobe (with Broca's area on the left side) which we commented on above.

We cannot - in most of our cases - see the primary visual cortex as it is usually supplied by the vertebral artery. But from animal studies it is evident that this area becomes more active during visual stimulation. Hence, including this area, a total of fourteen discrete cortical areas, seven on each side, are active during reading aloud. Often, the prefrontal cortex anterior to the supplementary motor area, is also activated.

Reading a text aloud is a prime example of the fundamental mode of operation of the cerebral cortex in performing complex tasks (and there are probably no simple ones!): collaboration between discrete cortical areas, each performing a specific job. It is the pattern of activation that is related to the task, not any single area. There are, in other words, no isolated center solely responsible for solving a complex task as also emphasized by the late Alexander R. Luria.

So far we have not been able to discern individual patterns of cortical activity of such a nature as to suggest fundamental differences between individuals.

The role of the right hemisphere in this complex language function is not clear. But data from the literature suggest that production and analysis of language melody and perhaps even of gestures related to speaking may predominantly reside on the right side.

E. Reading silently. If the same subject after reading aloud reads silently, the change in the map of blood flow, compared to that at rest, is particularly easy to interpret: then the primary sensori-motor mouth area and the auditory cortex do not become active. All the other areas are, however, seen to be active.

F. Internal speech. Memorizing the text internally causes a small increase in the mean blood flow, predominantly in the frontal lobe (often especially in the prefrontal cortex).

This type of "global" activation is seen with any task that the subject makes an intellectual effort in accomplishing.

In our opinion, internal speech is a mental function which is just as real as love, hate, or memories. It is a solid fact of introspection. This is supported by the fact that one can readily think in different languages. But, while asserting the psychological reality of internal language, we would consider it imprudent to follow Luria's speculation that this language function has a special grammatical construction.

It is tempting to revert the argument and to state that internal speech is the only true or "essential" language function.

How about a patient paralyzed by a disease or Curare and who tries to speak? Can one state that he has no language function? In a way, all the external manifestations of language functions are nonessential - solely the internal functions of language understanding and production - both comprized in the concept of internal speech - are truly essential.

G. Aphasia. We have studied the blood flow map on the left side in a series of classical aphasia patients, mostly cerebro-vascular accidents ("apoplexy"). Confirming well-known facts, the "fluent" aphasia cases had defects (on the flow map) in the posterior speech area of Wernicke, "non-fluent" or "motor" aphasia had defects in the primary mouth area (sometimes but not always extending to Broca's area), "global" aphasia had large defects covering both Wernicke's area and the mouth area. No studies were made on the right hemisphere.

H. Auditory agnosia (comprising word deafness). A rare case of sensory aphasia due to bilateral temporal lobe infarcts was studied in some detail. The patient, a 63 year old man, first suffered an attack of mild fluent aphasia, lasting one month. Some months later, he suddenly lost all ability to understand any spoken words and had some difficulty in recognizing non-verbal sounds. Yet, his threshold for perceiving pure tones was normal for his age. In other words, he was not deaf. But he could no identify any words. Not even his own name, or simple words, such as yes and no. All other language functions were intact: talking, reading, writing. This state is in neurological terminology called "auditory agnosia".

Specialized investigations suggested that an acute right-sided lesion of the hearing cortex had cut off ("disconnected") the remaining posterior part of the left superior temporal gyrus (Wernicke's center) from its remaining input (that from the left side having been destroyed by the first stroke). Computerized tomography (CT-scanning) showed the bi-temporal infarcts as hypodense lesions involving Heschl's gyrus bilaterally. Regional blood flow studies during listening to sounds showed no activation of the upper part of the left temporal lobe area (Wernicke's area): The sound analyzer was not turned on!

This case is interesting for three reasons:

1) A right hemisphere lesion (lesion no. 2) produced a massive language handling defect in a right-handed subject. There are other cases of this type recorded in the literature.

2) Preservation of normal speech in a subject deprived of all meaningful auditory feed-back. The fact that completely deaf patients can speak fairly normally also confirms that some of the speculations concerning the necessity of the normal auditory feed-back for speech production have been exaggerated. The importance of this feed-back for language acquisition is not questioned in this argumentation.

3) The patient had completely normal early components in his auditory evoked response. Hence this response cannot originate in the primary auditory cortex -Heschl's gyri- as these were massively destroyed bilaterally.

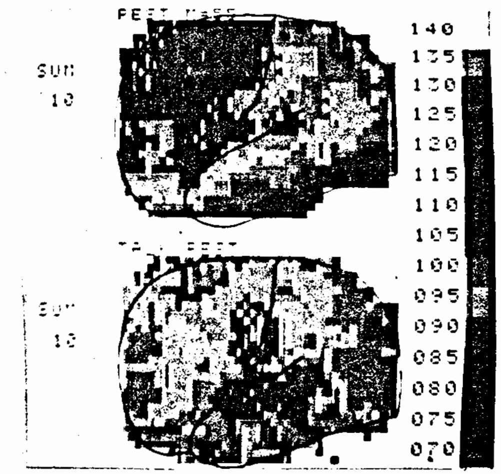
<u>Concluding comments</u>

Many linguistic and phonetic problems related to cortical function could be posed in relation to the findings we have summarized in this paper. However, it is appropriate here to stress the poor temporal resolution (1 minute) and spatial resolution (1 cm^2 with superposition of deeper layers) involved in the registration of the regional blood flow. Certainly, we cannot by this approach say anything about the detailed way in which the cortical areas collaborate in language functions.

It surprised us to find that a simple sound-rhythm discrimination test (Seashore) activated the auditory association cortex to much the same extent as do music or language. Apparently, the whole sound analyzer works as a unit.

The major finding was in our opinion the bilateral and practically symmetrical cortical involvement in all language functions. The possibility of a special role of the right side for prosody is mentioned. We have no data pertaining specifically to this point.

A comment on memory may be appropriate. It appears that this function is <u>disseminated</u> in the brain: visual memory in the visual association cortex, tactile memory in the sensory cortex, etc. Thus it is not surprising that word memory resides in the auditory association cortex in the temporal lobe. That it is predominantly on the left side is, however, completely mysterious! Could it be that the speed of language perception (and production) precludes major inter-hemispheric information exchange in this most human or "highest" of all types of brain work?



<u>Fig. 1</u> Intact normal man, regional cerebral blood flow, rCBF, map, <u>left</u> hemisphere.
The original illustration is in colours and therefore the black and white reproduction has distorted the scale. The legend to this figure gives a verbal description of the increase in flow clearly seen on the original and also visible on this reproduction.
The upper frame shows the <u>rCBF map at rest</u>, average picture of 10 cases. The map is expressed in <u>percent</u> flow deviation from the mean hemispheric value (averaging 55 ml/100g/min in these cases).
The lower frame shows the average <u>rCBF map during automatic speech</u> expressed as percentage deviation from the map at rest. Three areas of consistent flow increase ("activation") are seen (in this black and white reproduction the areas are slightly darker than the rest, with still darker edges): the supplementary motor area (at the top), the sensory-motor mouth area (upper mid), and the posterior part of the superior temporal gyrus (lower mid, Heschl's gyri and Wernicke's area).
Changes in the right rCBF map during automatic speech are practically the same. Broca's area is usually seen with fluent speech.

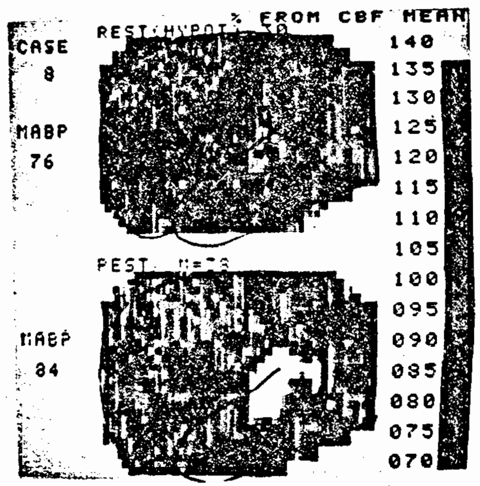


Fig. 2 Stroke case with aphasia (case 8 of our series), regional cerebral blood flow map, left hemisphere.
The upper frame shows rCBF map at rest during normotension (mean arterial blood pressure 84, mean rCBF 38 ml/100g/min).
Note the dramatic increase of flow in Wernicke's area (white) as flow rises: Luxury perfusion 8 days after onset of stroke, probably overlying an infarct, with abnormal pressure passive flow regulation.

References

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DISCUSSION

Victoria Fromkin, Michael Studdert-Kennedy and Peter MacNeilage opened the discussion.

Victoria Fromkin quoted Fournier's statement (in the late 19th century): "Speech is the only window through which the physiologist can view the cerebral life" and added that it should also be recognized that the brain is a window through which we will be able to observe the linguistic life.

Victoria Fromkin then expressed her hope that these new techniques would reveal to what degree language is a special function of the brain rather than a particular case of more general faculties. We ought to find out whether patients show differences in brain activity when they are subjected to stimuli of varying degrees of phonetic or linguistic complexity. And she mentioned that there might be different reactions to known versus unknown language stimuli, which again might be different from clearly non-linguistic input. Finally, different reactions might also be expected from patients automatically repeating memorized formulae rather than producing or reacting to free, creative speech.

In connection with the supposedly unexpected activity of the right hemisphere during automatic speech Victoria Fromkin mentioned that it is well known that even people who display a marked hemispheric specialization will always show some activity even in their right hemisphere during speech.

Victoria Fromkin further pointed to the dangers of drawing too far-reaching conclusions from observations based solely on patients with abnormalities of the brain. And she stressed the importance of looking for a convergence of results from different techniques.

Finally, she mentioned the importance of sensory aphasia cases, such as had been described in the lecture, for the debate on whether grammar exists apart from perception and production.

Michael Studdert-Kennedy: I think it is quite clear that techniques of this kind, such as the blood flow techniques, the more advanced analyses through EEG work, and perhaps the development of cooling techniques for isolating parts of the brain in the normal brain, are going to be much more important in the future than the type of behavioural studies that we have had to rely on in the past.

Michael Studdert-Kennedy then mentioned the problem raised by Victoria Fromkin in that these techniques are always used with patients. And he pointed out that in cases of apoplexy the right hemisphere could slowly be taking over functions normally performed by the left hemisphere. Therefore these new techniques should be developed and be made usable with normals.

He then continued: Obviously, the finding that there is a large amount of right hemisphere activity as well as left hemisphere activity is not a surprise. Because presumably there is a coordination of function between the two sides of the brain.

Nonetheless, there are certain properties of one side of the brain rather than the other that do arouse interest. And that seems to me to be important in understanding the nature of linguistic communication. I am referring here particularly to the famous relationship between speech and handedness.

It seems to me that an understanding of that relationship would take us rather a long way to understanding what the prior signalling conditions are for communication.

In this regard I think that the current developments in the work on sign language is tremendously important. Because it does seem that a prerequisite for linguistic communication is a motor system that is capable of very fine, rapid articulation.

One has only got to ask oneself what sort of a sign language could be developed if one was forced to use one's feet to realize that one absolutely has to have pieces of machinery that can be moved very, very fast. And so the motor control of that machinery which appears to be in some way common between the speech mechanism and the hand mechanisms, are of great interest. And I think that one very exciting possibility that these techniques look forward to is an elaboration and an understanding of these links.

In that respect I wonder, too, what the prospects are for looking at these processes developmentally.

Michael Studdert-Kennedy then drew attention to the sensory-motor integration functions described by Niels Lassen, particularly those concerned with speech and hand movements. These integration functions would appear to be a necessary prerequisite for the development of language. And he mentioned how children exposed to sign language will start imitating this at the same time as spoken language is normally developed.

Finally, he, too, suggested that the new techniques be used with different types of linguistic stimuli.

Peter MacNeilage was particularly interested in the spreading of activity from the temporal to the parietal lobes, having observed in the slides an upward spreading of activity in the parietal lobe during reading as compared to counting, and a still further spreading during listening. And he continued: The reason I am interested in the parietal lobe is its involvement in what is usually called conduction aphasia, and because I believe at the moment that the posterior and inferior parietal lobe is of some importance in the formulation of complex, voluntary movements.

Peter MacNeilage, too, mentioned the possibility of reorganization of brain functions after hemispheric lesions. And he suggested in the specific case mentioned by Lassen that possible simultaneous damage to Heschl's gyrus should be considered.

He then said: You may not exactly have intended to say this. But when you were talking about the finger movement task, you pointed to the fact that there was a rather circumscribed and small area of high activity in area four, that did not extend very anteriorly. On the other hand, there was a much larger and more widespread area of activity in the somatic-sensory cortex. And I believe you said that you thought the somatic-sensory activity was of more importance than the motor activity. I would like you to clarify this remark. [Niels Lassen: "That is correct."] Because it seems to me to relate to a rather general question about the extent to which we can simply assume a linear relation between the amount of activity, or wideness of distribution of activity, and the importance of the function.

It seems from my point of view that there may be parts of the cortex that can get their job done with less blood flow than other parts.

In your Scientific American paper you talked a little more of the role of the supplementary motor cortex than you have here. You still believe that the supplementary motor cortex has an important organising role in the production of speech? Because an alternative hypothesis is possible, namely that it simply has to do with initiation, or facilitation, of action in a rather general sense.

One could possibly argue that it has the equivalent of an attentional role on the motor side. It facilitates things happening without actually having much to do with the details of the control function themselves.

Coming back to the question of skilled, voluntary movement, I would like to ask to what extent you have studied unskilled voluntary control versus skilled voluntary control. That is in particular in relation to learning a skilled voluntary task.

And finally, I have heard that Brenda Milner, using sodium amytal studies, has shown a rather interesting relationship between the controlling hemisphere in left handers for speech, and for skilled voluntary movement of other kinds.

Niels Lassen, answering the first three discussants, said how surprised he and his colleagues had been when they saw to what degree the entire auditory association cortex was activated when a patient was stimulated with even very simple sounds. Stimulation with longer sequences and more complex stimuli was found to raise the level of activity a little more, but in the same area. Since the difference in reaction to simple and complex stimuli was found to be so small, the general rise in activity may be thought of as a sort of local attention phenomenon, where the whole auditory system is activated by any incoming signal.

Concerning the proposals to use more differentiated stimuli, Niels Lassen mentioned that he had received a stimulus tape from the Phonetics Institute, Copenhagen, containing white noise, isolated vowels, simple CV-syllables as well as connected speech, and was planning to use this in further experiments.

About the questions concerning the supplementary motor area, Niels Lassen said that he had found this area particularly active during complex movements. The relatively high level of activity in this area during speech could therefore be explained by the fact that speech is produced by very fast and complex movements.

As to the question about Heschl's gyrus, Niels Lassen said that there were damages to that area on both sides, but that he was not sure whether it had been completely destroyed. What was clear was that there no longer arrived any information to the auditory association cortex on the left side. That was evident from the lack of flow increase in that area when listening to words.

Niels Lassen confirmed that the parietal lobe is indeed very active, also during speech. But this appears to be part of the general arousal of the brain, since this area becomes active with any kind of activity on the part of the patient.

Barbara Prohovnik mentioned that people in Lund were using Xenon inhalation methods, which are non-invasive, to obtain similar traces.

Niels Lassen answered that the inhalation methods gave less well defined results because of limitations in the time constants of these methods.

Prompted by several people, Niels Lassen stated that the method he described measures the average activity of the brain over at least ten or fifteen seconds. Generally, a recording averages over the first thirty or forty seconds where the important information is concentrated. It is known from animal studies that there is a time lag of two or three seconds from the time of the injection to the time when changes in the blood flow can be clearly detected, and it disappears over ten to fifteen seconds. A new injection may be made after about three minutes. But successive recordings have even been made with only one minute intervals.

Vincent van Heuven suggested that we look not only for the areas of increased blood flow, but that we also examine what areas are inactive during a particular task. Both Vincent van Heuven and Niels Lassen commented on the fact that the brain always shows activity somewhere, even when the patient is at rest. But Niels Lassen said that he had observed not only increases but even reductions in the level of activity in certain areas when the level rose in other areas because the patient concentrated on a particular task.

John Laver was sceptical about the reported case of a bilateral lesion which had made auditory feed-back impossible. Experience shows that this should cause a progressive deterioration of the articulatory accuracy of the patient's speech, which apparently it had failed to do in this case.

H. Mol mentioned that he knew of a totally blind and deaf man, who has excellent speech performance. His deafness developed suddenly at the age of 31 as the result of meningitis.

Niels Lassen said that this case, just as his own, strongly supports the notion of the unimportance of auditory feed-back for speaking a well established language.