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Neuropsychology and Location of Higher Brain Functions in Functional Magnetic Resonance Imaging Studies with Tasks.

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Abstract

Objective: To enhance the capacity of functional magnetic resonance imaging (fMRI) with tasks, to measure different higher brain functions by running paradigms that produce brain activation in regions involved. Highlighting the importance of the neuropsychologist in creating paradigms and interpretation of results.

Methods: A non-systematic review of the scientific literature in databases was conducted: Rev Neurol, Neurology, Radiología, Neuroimage, J Neuroimaging, Science, Brain, Neuroscience and biobehavioral reviews, journal of neuroscience, Eur J Radiol, Magnetic resonance in medicine, Neurosurgery, Neuroimagingclin, Neuropsidologia latinoamericana, International journal of neuroscience , Biol Psychiatry, Psychol Med, Arch Gen Psychiatry, Psychiatry Res Neuroimaging, Neuro Report, Neuron, J ClinExpNeuropsychol , Proc Natl Acad Sci U S A, Ann Neurol Neurobiol Aging, Neurosci Lett, Journal of Neuroscience.The descriptors used were: “functional MRI”, “Paradigms” and “Neuropsychology”. Spanish and English scientific articles of any kind were selected since the start of indexing the primary source until November 2014.

Results: 42 articles were retrieved. All concepts of: functional magnetic resonance imaging, neuropsychology, higher brain functions, activated brain areas paradigms, were analyzed.

Conclusion: The neural activation maps confirm the simultaneous involvement of different brain areas, even distant, during the execution of paradigms. Neuropsychologist participation within the multidisciplinary team is very important for its deep understanding of the factors involved in the performance of different cognitive tasks potentially assessable by fMRI.

Key words: *Neuropsychologist; Pparadigm; Brain áreas; Higher brain functions; Functional magnetic resonance imaging (fMRI)*

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The interest to understand the brain, its functioning and structural bases, is not new, in the attempt to give an explanation to this interest have arisen during history various theories, one of those theories was pure localization or “phrenological maps”, proposed At the beginning of the 19th century, among others, by Gall and Kleist, this theory suggested that higher brain functions could be located in specific brain areas. Paul Brocca, determined that when a major alteration occurs in the articulation of the language, a lesion is caused in the posterior third of the lower frontal gyrus of the brain, and postulated “the center of the motor images of the words”, and the German psychiatrist Carl Wernicke, associate the posterior third of the left upper temporal gyrus with the understanding of oral language, proposing “the center of sensory images of words” [1].

However, despite the clinical basis of the facts, Monakow and Goldstein, they questioned the veracity of the phrenological maps without denying that hearing, vision, movement and skin sensation are represented in specific areas of the cortex. The theory of equipotentiality or integrality or noetic voices of mental processes, where they believed that all neural tissue participated together in a cognitive task. This, like phrenology, loses value [1]. Subsequently Luria, based on the theories of Jackson, Vygotsky, Pavlov, Berstein and others, states that to understand the functioning of the brain, all the existing concepts of the time, in terms of brain-brain function relationship, should be reconsidered.

When talking about superior brain function, this should be understood as a complex functional system, not as an isolated function such as the thyroid and thyroxine secretion, but for example, as the respiratory system, which includes many organs of the body functioning at the same time and each one performs a specific functionand all are necessary for the final process, breathing [2]. By changing the concept of brain function to a complex functional system, they can not be located in restricted areas of the cerebral cortex or in groups of isolated cells, "but must be organized in systems of zones that work harmoniously, each of which exerts its role within the complex functional system, and which can be located in completely different areas, and often very distant in the brain. [3] For example, to perform a cognitive activity such as reading, several brain components are required, such as: 1. inhibitory control of behavior and attention, executed by the frontal lobes, 2. it is necessary to make a visual analysis that allows the recognition and discrimination of the graphemes and words, activity that executes the occipital lobe, 3. discrimination of similar graphemes and the space within the sheet, executed by temporo-parieto- occipital areas, and 4. Understanding of the meaning and punctuation marks on, executed by the frontal lobes, etc. [2]

To define the components of each cognitive activity Luria proposed the concept of "factor", which allows to relate the psychological level of human activity with its psychophysiological mechanisms. No action or cognitive activity can be performed with a single factor, or with the activation of a single brain area. The performance of each action or cognitive activity requires the participation of various neuropsychological factors, that is, the activation of different brain areas, which constitute a complex functional system [2,3].

Function and the brain areas involved. [4]. It is considered that these factors are insufficient to explain all cognitive processes, especially the more elaborate ones such as: abstraction, analysis, synthesis, decision making, etc.

Factor	Function	Cerebral Area
Programming and control	Guarantees the process of executing a task according to the objective (instruction or established rules)	Pre-frontal sectors of the left hemisphere
Sequential organization of movements and actions	Guarantees the fluent passage from one movement to another, inhibits the previous motor link for flexible passage to the subsequent motor link	Pre-motor areas of the left hemisphere
Phonematic ear	Guarantees the differentiation of verbal sounds of the language	Temporal zones of the left or right hemisphere for some languages
Analysis and Cenesthetic Synthesis	Fine tactile sensitivity, as well as the precision of postures and poses, articulation of language according to the point and mode of articulation	Parietal areas of the left hemisphere
Audio-verbal retention	Stability of the mnesic trace in verbal audio mode	Mesial temporal zones of the left hemisphere
Visual retention	Stability of the mnesic trace in the visual mode	Occipital areas
Perceptive Analytical	Perception and adequate production of essential features and their location and the spatial relationships between the elements of the situation.	Temporo-Parieto-Occipital left hemisphere

Global perceptive	Perception and adequate production of the general form, of the metric aspects and the proportions of objects.	Temporo-Parieto-Occipital Right hemisphere
General non-specific activation background	Background and stability of the execution of the action.	Subcortical structures reticular formation
Non-specific emotional general background	Emotional stability and background.	Medial Basal structure

Table 1: *Neuropsychological factors, definition and brain area involved.*

The analysis of each factor that is involved in certain cognitive activity and the brain structures that constitute its base, is the work of the neuropsychologist, and is carried out through the evaluation with test or neuropsychological batteries [2]. This analysis, previously based exclusively on the neuropsychological clinic, can now be done with the support of neuroimaging techniques. Radiology and Neuropsychology come together to do a joint work thanks to the development of neuroimaging techniques [5], especially functional magnetic resonance imaging, which allows the study of the physiological changes of the brain related to mental processes, during the execution of a task [6]. If we start from the perspective of traditional neuropsychology, in which each functional system (constituted by different cognitive factors, understood as processing stages) corresponds a brain system (work from different regions), then we can establish that the information we will obtain from Functional magnetic resonance imaging is aimed at knowing the anatomical substrates of the factors. [7]

The use of functional magnetic resonance was initially given by Belleveau and his collaborators in 1991, to demonstrate that the perception of visual stimuli increases blood flow in the primary visual cortex [8,9]. The popularity of this technique can be seen in multiple research works in the scientific literature, although not all works reach the same conclusions. Some of these jobs are: -Studies with patients with obsessive-compulsive disorder (OCD) [10-16], where comparison of the areas activated with certain tasks with healthy subjects is made, and it has been shown that Possible areas involved in OCD include the orbitofrontal cortex, the striatum and the anterior cingulate. Other authors have found hyperactivity in the cingulate cortex, both anterior and posterior. It has been proposed that in patients diagnosed with schizophrenia [17-20] and auditory hallucinations in schizophrenia, the basis of hallucinations would be a dysfunction of the neural networks responsible for the generation of oral language through an activation in parallel of the areas of perception of the external language (auditory-linguistic cortex) and of the motor areas involved in the subvocal language.

-In other studies with multiple sclerosis [21,22], using different paradigms to evaluate processes such as: working memory and processing speed, greater activation of the frontal cortex and sometimes in the parietal cortex was found in patients compared with healthy participants, also it was established that patients diagnosed with multiple sclerosis when they have mild cognitive impairment and manage to successfully complete the proposed tasks require activating more brain areas than a healthy person, which has been defined as compensatory activation. In addition, the patterns of resting inactivation (default-mode network) are different in these patients, they are not inversely proportional to the pattern of activation, especially in patients with the primary progressive phenotype. [23-25].

Research proposing functional magnetic resonance imaging studies as a biomarker for the diagnosis of early Alzheimer's disease. In these, it has been established with episodic memory tasks, that the areas that are activated in healthy subjects are those of the medial temporal lobe, including activation of the hippocampus and related structures [26-29]. This activation is diminished in people with a family history of dementia such as Alzheimer's disease and people with a diagnosis of mild cognitive deficit, a condition that is considered a predictor of the disease. [30,31].

In Colombia there are no studies and the use of functional magnetic resonance is not frequent, it is done occasionally and only to establish the lateralization of the superior cerebral functions to define surgical maps.

Functions of the Neuropsychologist in studies with functional magnetic resonance.

In order to perform a functional magnetic resonance with success, the participation of a multidisciplinary team, consisting of neuroradiology, resonance technician, bioengineer and neuropsychologist, is essential. The function of the neuropsychologist for studies with functional magnetic resonance is determinant and irreplaceable, includes aspects such as:

1. Perform a neuropsychological assessment prior to functional magnetic resonance imaging, which allows: set a neuropsychological profile of the patient, and with this information select the appropriate paradigms for evaluation according to the findings, and on the other hand, train the patient to the study of functional magnetic resonance. It is important to set the neuropsychological profile of the patient because the functional magnetic resonance does not allow assessing the state of all cognitive processes nor determine the degree of severity of a cognitive impairment. Nor can you know the performance of the subject in different tasks such as writing, written calculation and praxias, by the limitation in mobility within the magnet.
2. Design of tasks or paradigms. A paradigm is a set of stimuli that, organized with certain temporal patterns and designs, make up the tasks that the subject must perform during the acquisition of the images by functional magnetic resonance. Through the paradigms, cognitive processes can be set in motion to locate the functional architecture underlying them. The design of the paradigms must have a high specificity, comparable to the specificity of the neuropsychological batteries where the factors of each higher brain function are independent to evaluate what is really intended, they should be replicable for control studies and be designed according to the educational level of the subject,should be based on a solid knowledge of the cognitive processes to be studied, as well as their possible interactions with other processes that may be recruited during the experiment [32]. There are basically two types of designs:
3. Block designs: two situations are presented, one of activation with a specific stimulus and another of control or rest, with a neutral stimulus that prevents activation. The characteristics that ensure its success are: Duration to obtain a maximum contrast power between activation and control (usually between 20 and 30 seconds), periodicity of the blocks (every 5 seconds and that the resting condition Matches the respiration of the subject to avoid strange variables), number of blocks (A greater number of blocks, greater contrast power) and finally, number of conditions (4 for each series of blocks). The block design has the advantage of being easily implemented and analyzed and of having high statistical power.
4. Designs linked to events: They are characterized by presenting conditions in a random way, such is the case of oddball tasks, it is a task of recognition of an infrequent stimulus that is randomly interspersed with the probability of low occurrence among a series repetitive of another more frequent stimulus, before which he should not give any response [33]. The designs linked to events are less susceptible to phenomena of habituation, expectation and to the decrease of attention. However, compared to the block design they have a lower statistical power [34].
5. Supervision of the patient while executing the paradigms, for experimental control of external variables such as tiredness, sleep or disinterest [35]. And, Support for the interpretation of the results, establishing a relationship between the activated brain areas and the factors of brain function evaluated by means of the paradigms [5].

Applications and uses of functional magnetic resonance in the clinical context.

There are several areas and disciplines where functional magnetic resonance plays an important role:

1. It allows to locate a cognitive process, both to define the functional organization of the brain and to plan a surgery [36,37]. Functional and pre-surgical maps. It allows to define the distance between a certain function and the lesion to be treated and to identify the effects of the lesion in the cortical representation of the function [38-40].
2. Study the irregular functioning of the brain in patients, establishing if there are changes in the activated areas compared with healthy subjects. Characterize neurological and psychiatric diseases.
3. Characterize the responses and function of certain regions of the brain.
4. To evaluate how cerebral plasticity processes occur due to cognitive rehabilitation and compensatory activities. For example, in patients with multiple sclerosis [41], hearing comprehension in patients with aphasia [42] and new pattern of connectivity between cerebral hemispheres months after the start of treatment in patients with aphasia [43].

5. Establish functional and effective connectivity, which differ from the structural connectivity observed through diffusion tensor images. This functional connectivity allows the study of activation patterns in different regions of the brain as well as their interaction, fundamentally in neurological or psychiatric pathologies that are not due to focal damage, but to alterations in the transfer of information between neuronal regions. [44,45].
6. Follow up on pharmacological treatments. Target biomarker to evaluate the therapeutic response and the prognosis of patients. [46].
7. Define hemispheric dominance for specific brain functions.

Activation of brain areas in functional magnetic resonance in different cognitive tasks.

For the interpretation of brain activation areas, in addition to having knowledge of the neurocognitive processes involved in the paradigms used in the study, several considerations must be taken into account and errors in interpretation must be avoided: First, the individual differences: know that different situations that affect neurovascular coupling and generate differences between the individuals in the oxygenation state, such as: chronic cerebral ischemia, the proliferation of astrocytes due to brain injury causing gliosis, hypertension, diabetes or hypercholesterolemia, and the effects of some medications [47]. Second: During rest in the paradigms of block design, regions such as the ventral medial prefrontal cortex or Brodmann area 10 and the precursor or area 7 of Brodmann can be activated, which corresponds to activation of the "default-mode network" widely characterized in functional resonance in rest state. The higher the level of education and therefore the cognitive reserve greater activity will be observed in the resting state [48]. Third: The fact that an area is activated during the execution of a task does not imply that this area is indispensable for the task in question [49]. Fourth: Failure to activate some areas expected during the execution of a task, does not allow assuming that they do not participate in the process. It is possible that it participates but that it is not catch. [50].

Below in table 2, show the areas that are activated by different paradigms, obtained in studies with healthy subjects, without neurological, metabolic, psychiatric or pharmacological treatments

Superior brain function	Paradigm	Activated brain areas
Oral language/denomination, with auditory and visual stimulation	Blocks Activation: the patient is asked to read some sentences, for example: What do you write? and then select the appropriate answer within a group of words. It can be done orally but, the subject's response must be generating the word silently Control: a series of non-linguistic symbols are displayed	-Inferior frontal cortex -Superior temporal cortex -Bilateral Heschl area (primary auditory cortex), when the stimulus is auditory. -Medial frontal gyry -Parietal structures. When the stimulus is visual.
Oral language/Semantic decision. Visual stimulus	Blocks Activation: The subject is presented with a pair of words that have a semantic relationship and one of the two words represents a subordinate category and two words without semantic category. It must say yes or no, the exposed words have a semantic relationship. Control: You are presented with pairs of non-linguistic symbols matched by the form and you must select which are the same. Paradigm created by Mary Machulda, PhD, L.P. Mayo clinic, Rochester and Others [51]	-Broca left area -Lower left dorsolateral prefrontal cortex. -Union of the posterior superior temporal gyrus and supramarginal gyrus of the parietal lobe. -Temporal medial and inferior left Gyrus -Supplementary areas of ocular movements -Frontal areas of the gaze. And to a lesser degree Bilateral primary visual cortex

Language/Reading of text Vs Non- linguistic symbols	Blocks Activation: You are presented with a very short narrative for 10 seconds and then a different one, which you must read and understand silently. Control: You are presented with non- linguistic symbols at the same time as the narration. [52]	-Posterior superior temporal gyrus of the dominant hemisphere for language. -Parietal angular gyry (Wernicke area) -Medial frontal gyry. When there is an answer -Primary and secondary visual areas with non-linguistic symbols
Oral Language/Rhymes	Blocks Activation: patients are presented pairs of words, some rhyme and others not. It must answer if they rhyme or not. Control: You are presented with pairs of identical or not symbols and you must answer yes or no, if they are equal. Paradigma created by: JT Laurito, MD, PhD. [53-56]	-Dorsolateral prefrontal cortex. - Inferior Frontal Gyry -Superior temporal gyry -Cortical coating of the superior temporal sulcus. -Fusiform gyrus of the ventral temporo- occipital cortex: visual area of the words
Oral language/Production of silent words	Blocks Activation: The patient is presented with a letter and must think of all the words that start with that letter except for derived words. Control: the subject is presented with a non-linguistic symbol [57].	-Dorsolateral prefrontal cortex -Inferior frontal gyry -Cingulum - language area. -Supplementary motor areas -Motor and premotor regions -To a lesser extent, the posterior cortex of the language (Wernicke) and the ventral temporo-occipital cortex.
Oral language/Designation of simple objects	Blocks Activation: You are presented with simple or everyday objects that the patient must silently name. Control: You are presented with a non-linguistic symbol. Paradigma created by: JT Laurito, MD, PhD. [53.58]	-Inferior frontal gyry/frontal operculum -Dorsolateral prefrontal cortex or Premotor cortex. -Supplementary motor areas -Ventral temporo-occipital cortex -Posterior parietal temporal language cortex -Inferior temporal Gyry -Occasionally, the cortex of the temporo - parietal operculum and parietal temporo cortex. -Areas for object recognition: Posterior inferior temporal gyrus and bilateral temporo-occipital cortex. -Parietal visual areas including the intraparietal sulcus for visual attention and visuospatial processes
Oral language/Passive listening	Blocks Activation: the evaluator reads the patient a short narration that he must listen to. Control: The narration is done upside down. [59]	-Superior temporal gyrus -Mantle of the cortex of the superior temporal in the Wernicke are -Superior temporal sulcus and medial temporal gyry. -In some subjects the inferior frontal gyry is activated.

Oral language/Understanding language with visual stimulation	Blocks Activation: The subject is presented with a couple of sentences, the second sentence is a question related to the first and must answer yes or no are related.	-Medial frontal gyrus (Work Memory) -Left Broca area in the inferior left frontal cortex
	Control: Non-linguistic symbol. Paradigm created by: Keith Thulborn, MD, PhD, L.P. University of Illinois, Chicago.	-Superior posterior temporal gyrus. Wernicke area. -Hippocampal areas. -Prefrontal cortex -Occipital lobes: extra visual area. -Frontal visual area. -Eye movements: Precentral sulcus. Medial frontal lobe and intraparietal sulcus.
Oral language/Word listening	Blocks Activation: the patient must listen to words and the subject is stimulated to repeat it silently. Control: fixing point. [60]	-Temporal areas of language reception including: -Bilateral temporal auditory primary cortex. - Wernicke area.
Memory/Visual memory	Blocks: Activation: Two conditions: The patient is presented with several pictures of objects and the patient is asked to memorize them, then another list is	-Right hippocampus -Cortical mesiotemporal and dorsolateral prefrontal regions.
	Presented where there is one or two of the objects that were previously asked to memorize. You must answer yes or no, they are present. The photos are placed at an angle where the eye movements are decreased. Control: fixing point Paradigm created by: Keith Thulborn, MD, PhD, L.P. University of Illinois, Chicago	-Occipital lobes
Attention/Selective attention	Blocks: Activation of two conditions: Write names of different colors for example blue, red and green, but written in ink of different colors. For example blue written in green. The subject is asked to silently say the color of the ink in which the word is written and to inhibit the reading. Another condition is written the same three colors with inks of the same color.	-Anterior cingulum, area 32 of Brodmann of the right hemisphere. -Central cingulum, areas 31 and 23 of Brodmann of the left hemisphere. -Caudate nucleus: right corpus and left cauda. -Bilateral thalamus. [61]

Table 2: *Cognitive tasks of language, memory and attention and the brain areas that are activated.*

Conclusion

The functional magnetic resonance represents an advance of the neurosciences and is helping to elucidate in vivo the cerebral functioning, it allows due to the activation, the location of the different factors of the cerebral functions in certain areas of the brain, factors defined until now but, conscious that they are insufficient to explain all the cognitive processes, it allows to understand the cerebral functioning in healthy subjects unlike other techniques that are only carried out when the lesions occur, it broadens the knowledge of the neurological and psychiatric diseases, especially those that can not be observed in neuroimaging techniques, it being perhaps possible to bring these historically dissociated specialties closer together.

Thanks to the different brain activation maps, we are closer to the classic neuropsychology of Luria and we move away from pure localizationism or phrenology or the noetic voices of brain functions. It is confirmed that a cognitive task requires several brain areas, even distant, working harmoniously since it is a functional system. However, to understand the structural neural networks that establish a relationship between the activated areas, it is necessary to complete the studies with diffusion tensor images.

The role of the neuropsychologist is crucial in the performance of studies of functional resonance with tasks, can create paradigms thanks to knowledge about the superior brain functions and what underlies these, can make the "factors" independent to avoid contamination or artifacts that substract study validity, can adapt the paradigms to the limitations of the patient, as the educational level, should help to control the subject during the study to avoid the introduction of strange variables and to support in the interpretation of the results.

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