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Review

How Do We Connect Brain Areas with Cognitive Functions? The Past, Present and the Future

Khushboo Verma 1* and Satwant Kumar 2*

[1] Department of Neurology, Dell Medical School at UT Austin; Khushboo.verma@utexas.edu
[2] Center for Perceptual Systems, UT Austin; satwant.kumar@utexas.edu
* Correspondence: khushboo.verma@utexas.edu (K.V.); Tel.: +1 202-509-4856 ; satwant.kumar@utexas.edu (S.K.); Tel.: +1 512-712-8409

Abstract: It is one of the central goals of cognitive neuroscience to understand how structure and function relate in the brain. We review how cognitive function characterization has been approached in the past. In addition, we examine the ongoing efforts, as well as the implications for the future. Clinical studies on patients with lesions have provided key insights into the relationship between brain areas and behavior over the past century. We describe cognitive function according to localization considering these early efforts for characterization. We chose a perceptual-cognitive function, namely body perception, to describe our current efforts. Using body perception as an example, we summarize contemporary techniques. Finally, we outline the trajectory of current progress into the future and discuss the implications for clinical and basic neuroscience.

Keywords: cognition; cognitive functions; localization; lesion studies; body perception; functional magnetic resonance imaging (fMRI); electrical microsimulation; transcranial magnetic stimulation; extrastriate body area; fusiform body area

1. Introduction

1.1. Characterizing cognition

Characterization of cognitive functions is the ultimate challenge for cognitive neuroscientists and neurologists. Characterization begins with the definition of the function, and its precise localization in the brain. Cognitive or executive control refers to the ability to accomplish a goal-directed task, that is, to direct attention to the task, to inhibit conflicting distractions, to self-monitor, and to use working memory efficiently to complete the task [1]. This definition of executive control encompasses multiple cognitive domains such as attention, inhibition, and working memory. It is imperative to define and localize the individual domains to characterize cognition. These domains have a variety of descriptions, and there is no consensus. Moreover, whether the individual cognitive domains are diffusely located or located discreetly, and work synchronously to result in an appropriate goal-directed action is debatable. The difficulties with localization exist as individual tasks do not guarantee the isolation a single cognitive function, this referred to as 'task impurity issue' [1]. Although the individual functions can be differentiated from one another, yet they share a commonality that prevents them from being discretely characterized. This concept of the coexistence of unity and diversity was first proposed by Teuber [2], and verified by Miyake et al. experimentally [3]. Considering these challenges, we propose utilizing a theoretical model to conceptualize the comprehensive characterization of cognitive functions.

1.2. Theoretical model

Marr provided a three-level description of the visual process [4] that can be used to characterize cognitive functions. An initial level is the computational one, which describes "what" a process involves. Details about input, output, and any constraints that need to

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be met to reach the output are included at this level. Second, there is the algorithmic level, which describes "how" a process occurs. This level emphasizes the representation of inputs and outputs and their algorithmic transformation. The third level deals with the implementation of the process [5]. The third level is the ultimate proof of understanding the cognitive process in question. This is because it entails the implementation of the function either on a natural system or an artificial system such as a computer. Figure 1 illustrates how these theoretical levels can be applied to a cognitive function of interest.

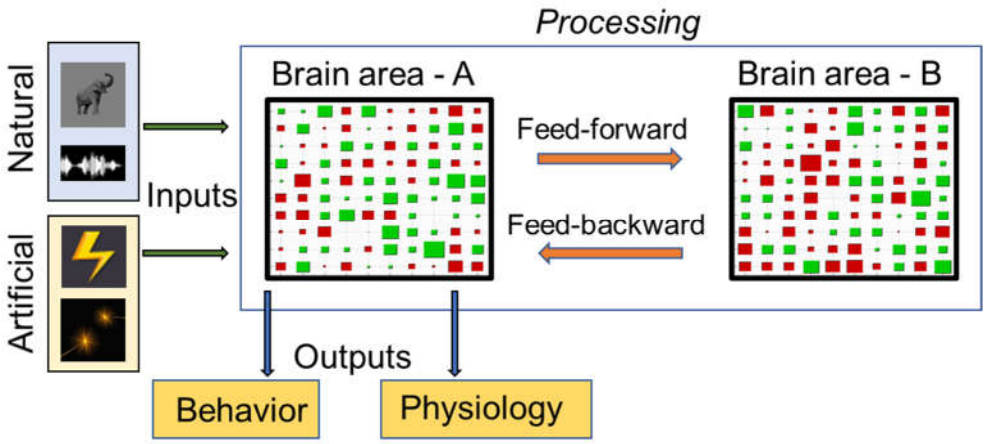

Figure 1. Envisioning Marr's theoretical framework for characterization of a cognitive function. At computational level, inputs are shown on the extreme left as natural (visual and auditory) and artificial (electrical microsimulation and optogenetic stimulation) stimuli. Outputs are shown as behavioral and physiological manifestations. This level also takes into account the relative compositions of areas A and B with two subtypes of neurons, that is excitatory (indicated as green rectangles), and inhibitory (indicated as red rectangles). At algorithmic level, the processing is shown in light blue box which considers both feed-forward and feed-backward communications and relative firing rates of neurons (indicated with sizes of red and green rectangles).

In the question pertaining to this review "How are brain areas connected to cognitive functions?", "connection" refers to the essential evidence required to establish a link between a brain area and a particular cognitive function. This essential evidence entails the necessity and functional specificity of a brain area. Necessity implies the causal role of the brain area in the cognitive function, that is if there is a lesion in an area it will lead to the loss of that cognitive function. This is an example of a single dissociation study. When this concept is applied for two separate subjects with different lesion locations and loss of separate functions, it is termed as double dissociation. When these two cases are considered in conjugation one has a higher degree of confidence that these two functions are modular and located in non-overlapping manner. This is considered as "conclusive proof" and "indicates specificity even in absence of accurate localization" [6]. Figure 1 demonstrates this concept.

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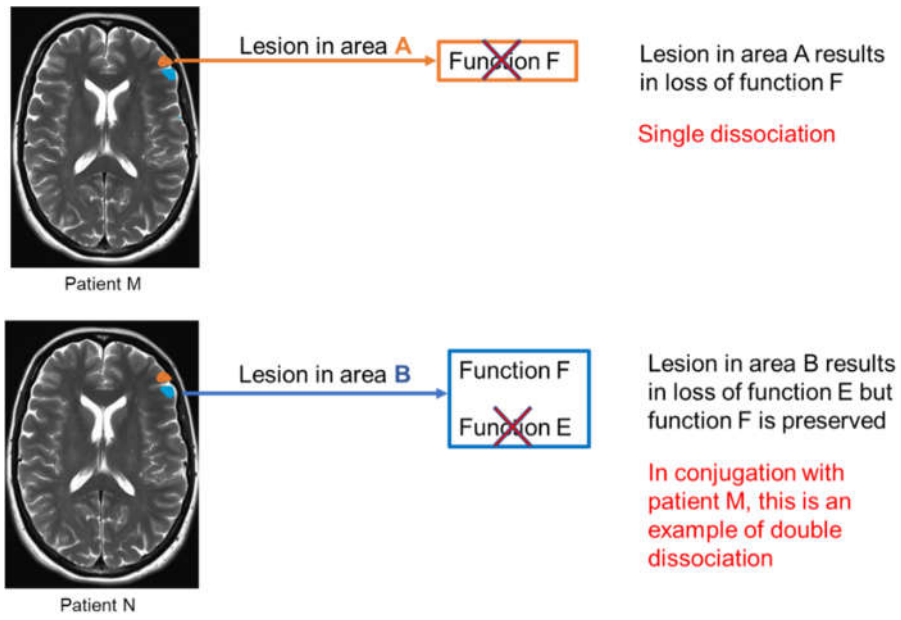

Figure 2. Schematic representation of single and double dissociation. In this example a lesion in area A (marked with orange in MR image) leads to a loss of function F and a lesion in area B (marked with blue in MR image) leads to loss of function E.

In this review, we discuss how characterization of cognitive functions has been approached in the past. We also explore the ongoing efforts, and their future implications. We have therefore divided the review into the past, the present, and the future. Since the early efforts for characterization focused on localization, we give an account of cognitive function in terms of localization. To describe the present efforts, we have chosen a perceptual-cognitive function, that is body perception [7]. Taking body perception as an example, we summarize contemporary techniques. We ask questions throughout the narrative and seek answers together with the readers to evoke curiosity in the audience.

2. The Past

The journey begins with Franz Gall in the late eighteenth century. He encounters patients with certain neurological deficits, but neuroimaging was not available to visualize the brain *in vivo*. He postulated that personality traits and aspects of cognition such as language are localized in different regions of the cerebrum. Moreover, he hypothesized that this information can be inferred from the bumps on the skull. Although there is a lack of scientific rigor in this approach, this is one of the first attempts at proposing the concept of localization for cognitive functions. The theory implies that distinct subparts of the brain perform specific functions independently [8].

2.1. Were there any techniques available to test Gall's hypothesis experimentally?

One possibility was to create artificial lesions in animals and study the effects. This technique was utilized by Pierre Flourens, a French physician and anatomist. Since the neurosurgical instruments at this time are not sophisticated enough to create precise lesions, therefore he did not find specific cognitive deficits with discrete lesions. Consequently, he removed different parts of the brain and examined the results. When the cerebellum was removed there was a loss of coordination and balance. Similarly, when the cerebrum was removed there was a loss of motor function and judgment. Based on his experiments he concluded that cognitive functions are diffusely located all over the cerebrum [9].

Since this was done in animals, one gets curious and asks – *Was there a way to look at the brains of patients with specific cognitive deficits?* Paul Broca was faced with this question when he met a patient famously nicknamed 'Tan'. This patient could understand what

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was spoken to him, was able to gesture to communicate, and had intact emotional responses, however, he had no spontaneous speech except the word 'tan'. After his death, Broca performed an autopsy and discovered a lesion in the left frontal lobe. He concluded that the patient's speech deficit was due to this lesion [10]. Figure 3 shows the gross anatomical findings of the two of Broca's patients who had expressive aphasia.

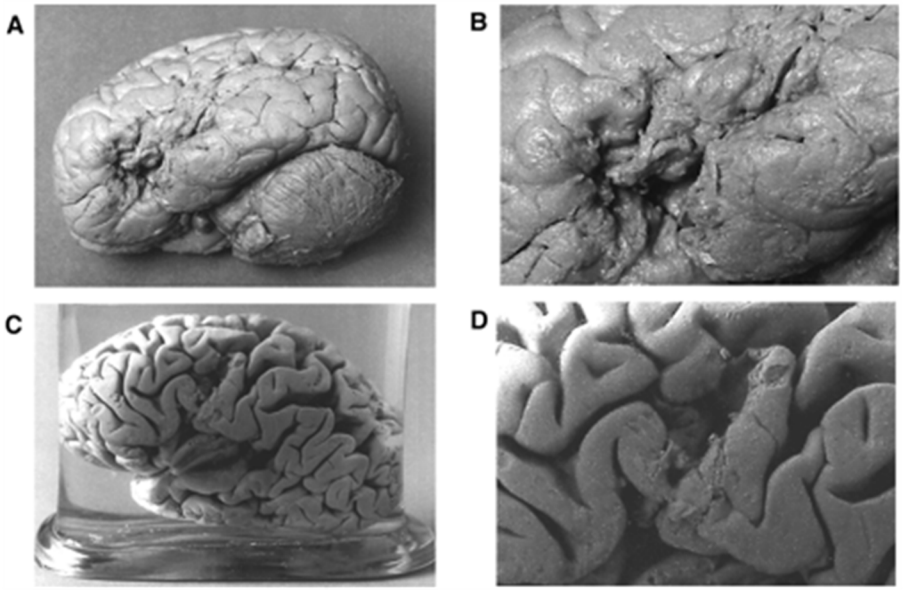

Figure 3. Gross anatomical features of brains of Broca's patients, L1(nicknamed 'tan') and L2 with aphasia. A) and C) Lateral views of patient L1 and L2's brain; B), and D) close-up of view of the brain lesions for patients L1 and L2, respectively. Panels A-D adapted with permission from Dronkers et al. (2007).

Of note, with the conclusion that the lesion was responsible for the patients' deficit Broca concurred with Gall's hypothesis of localization. He additionally proposed that the major anatomical sulci and gyri are not arbitrary rather they divide the brain into lobes which subserve specific roles [10]. A major drawback of his method was that an autopsy was required to study the brain. Consequently, the sample size was inadvertently constrained by the inability to follow patients for life [11].

Given the limitations with human lesions studies, one asks – *Could smaller lesions be created in animals to test the hypothesis of localization?* Two German scientists Gustav Fritsch and Eduard Hitzig performed electrical stimulation of the awake dogs and noticed that the stimulation of specific cortical sites led to extension or flexion movements of the front or rear paws. This was considered as potential evidence for localization and sparked a debate in the scientific community, which subsequently led to further experiments to confirm the findings [12].

This leads to the questions – *Was electrical stimulation of human brains possible and would similar effects be observed?* Wilder Penfield, a neurosurgeon in the 1930s who operated on patients with epilepsy and tumors, considered this question. He and Edwin Boldery meticulously studied the motor and sensory cortex by electrically stimulating specific areas of the cortex [13]. Figure 4 is an operative photograph of the of one such patient.

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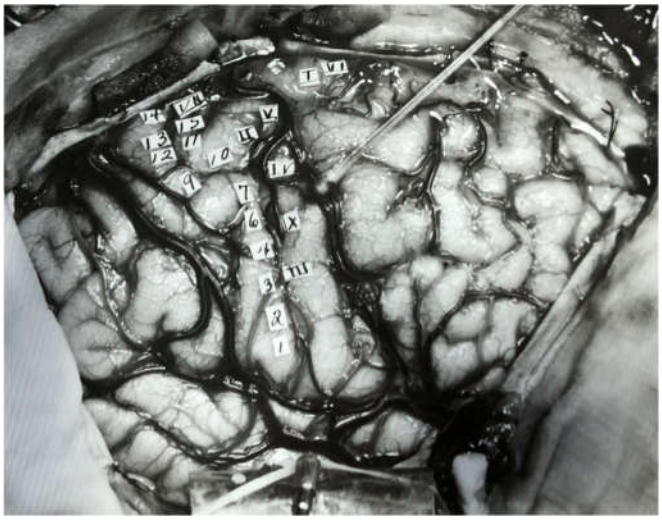

Figure 4. Regions in the right hemisphere indicated with Roman and Arabic numeral labels. The Roman numerals represent sites where electrical stimulation led to sensory perception, and the Arabic numerals indicate sites where stimulation lead to motor responses. Figure adapted with permission from Leblanc (2021).

Their work led to the creation of motor and sensory homunculi, which are still widely used by neurologists to ascertain localization of motor and sensory deficits [13]. Figure 5 illustrates the evolution of homunculus from 1937 to 1950.

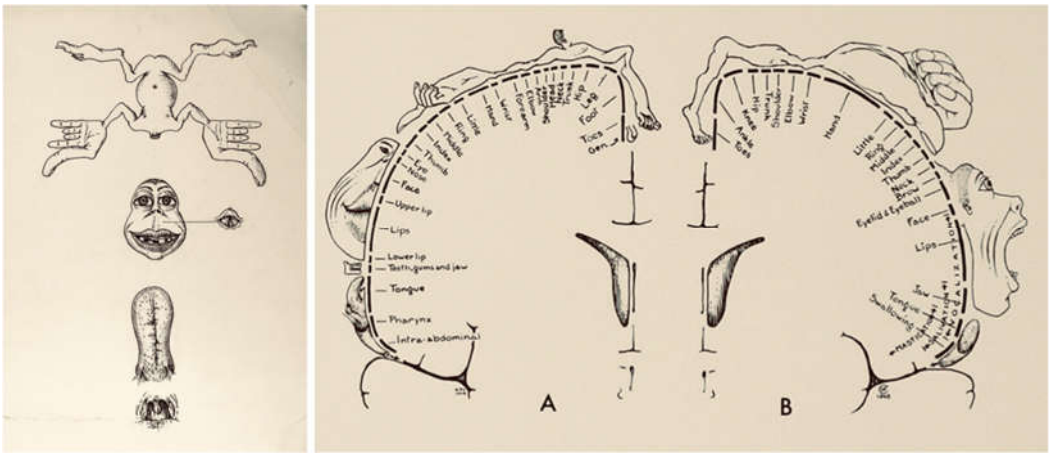

Figure 5. Evolution of homunculus. The illustration of the left is the 1937 homunculus, and the illustration on the right is the 1950 homunculus. The 1937 homunculus had a single figurine accounting for sensorimotor function. Illustrations adapted with permission from Leblanc (2021). The figurine is divided into 4 parts, that is body, face, tongue, and nasopharynx. 1950 homunculus has distinct figurines showing the A) sensory and B) motor homunculus.

Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Interventional studies involving animals or humans, and other studies that require ethical approval, must list the authority that provided approval and the corresponding ethical approval code.

3. The present

Now we will embark on an exciting journey into contemporary neuroscience. We will study the evolution of our understanding of a specialized cognitive function: body

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perception. It is a unique cognitive function that encompasses a wealth of social information. In addition to age, sex, and identity of an individual, it includes abstract elements such as intention and emotion [7].

The first question we ask is *"Do we have discrete areas for body perception?"* In 2001, Downing et al. explored this question using functional magnetic resonance imaging (fMRI). In this study, subjects viewed images of bodies while undergoing fMRI. A specific area in the right lateral occipitotemporal cortex was noted to be selectively responsive to human bodies and body parts excluding the face [14]. This area is shown in coronal slices with green arrow in figure 6.

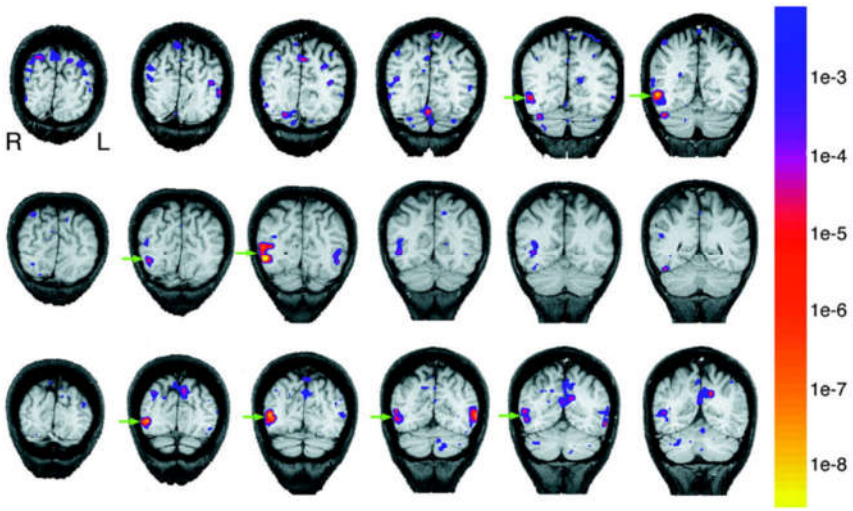

Figure 6. Coronal sections of three subjects arranged in separate rows. The anatomical slices are overlaid with statistical maps of voxels with selective response for human bodies and body parts. Adapted with permission from Downing et al. (2001). The green arrow indicates the region with maximal response. The color scale on the right stands for the P values of activations.

However, if we carefully consider all possibilities, there are multiple alternative explanations. A few examples are: What if this area was responsive to low level features of visual stimuli such as shades and textures? What if this area responds to any objects or any kinds of bodies say animal bodies as well? What if this area responds to anything human such as human faces? All these questions refer to the selectivity of response to the stimulus of interest (in this case it is bodies) and a single question that incorporates all the above questions is - *Does this region selectively respond to bodies?* To answer this the authors showed the subjects multiple stimuli belonging to various categories as shown in Figure 7.

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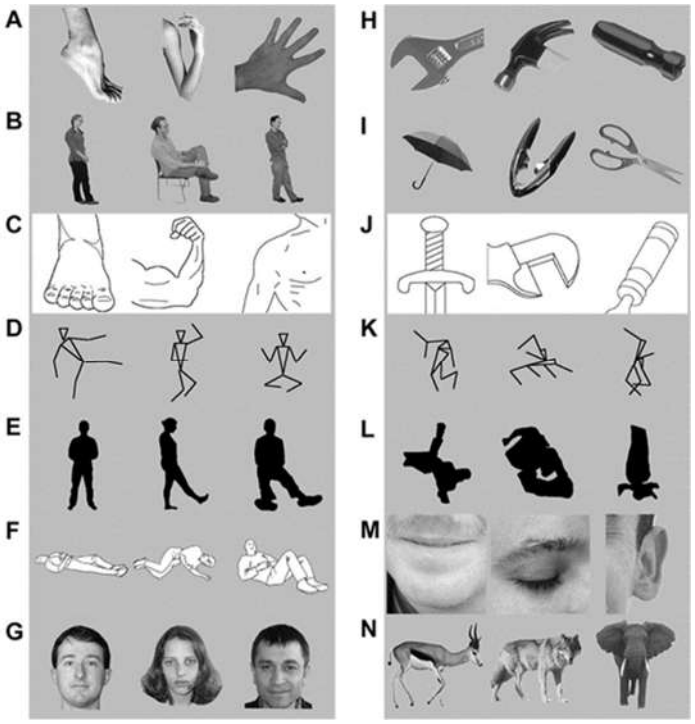

Figure 7. The range of stimuli included in the study, with various depictions of bodies such as body parts (A), complete human bodies (B), line drawings of body parts (C), stick figure (D), silhouettes I and images with inferred motion (F). Panels A-N adapted with permission from Downing et al. (2001). The EBA response was high in all these stimuli as compared to low response for stimuli H through N. These stimuli are object parts (H), complete objects (I), line drawings of objects (J), scrambled stick figures (K), scrambled silhouettes (L). The responses were intermediate for human faces (G), face parts (M) and mammals.

In this experiment, the response to these control stimuli was studied only in the area that had initially responded to the bodies. It was found that this brain region was selectively responsive to human bodies and body parts, and the region was termed as the extrastriate body area (EBA). In conclusion, using fMRI, a discrete area selective for body perception was identified [14].

Let us ask a more challenging question - *Can we establish the causal role of these areas in body perception with the help of fMRI?* This is not possible as fMRI is not a direct measurement of neural activity rather a measurement of blood oxygen level dependent signal (BOLD) which is a proxy for neural activity. This renders the evidence correlational and not causal. Another limitation is the temporal and spatial resolution in relation to our question. The temporal resolution of fMRI is in the order of seconds [15]. The greatest advantage of fMRI is that it offers the finest spatial resolution in an awake human noninvasively. Therefore, fMRI scans have a role in exploratory studies which identify the regions of interest [16].

This brings us to the question - *What techniques can help establish the causal role of body patches?* From the time of Broca to the present, human lesion studies continue to stand the test of time as they provide strong causal evidence. As compared Broca's era, we have neuroimaging which enables visualization of the brain *in vivo*. Given this lead, we can conduct group studies rather than single patient studies which confers statistical validity [17]. Furthermore, computer vision algorithms facilitate faster analysis of group studies involving neuroimaging data. [11]. While there are numerous patients with brain lesions, it is difficult to find subjects with discrete lesions in the EBA. A case report describes a patient with bilateral lesions in the occipitotemporal cortex who developed deficits in movement perception. Unfortunately, no tests were conducted to assess body perception [18]. Apart from this natural lesions such as strokes offer no experimental control over the

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size and location of the lesion, and involve some cortical regions more frequently than the other [11].

In the progression from natural to artificial lesions, we would like to draw parallels with the past. Similar to the electrical microstimulation performed by Gustav Fritsch, Eduard Hitzig and Wilder Penfield modern intracranial electrical microstimulation (iEM) can create precise artificial lesions [19]. By creating artificial lesions using iEM we can test causality [20]. In clinical setting, intracranial EEG (iEEG) is done which includes electrocorticography done with subdural electrodes and stereo EEG done via depth electrodes. Typically, iEEG is done to passively record neural activity to confirm seizure foci, however, this setup can be used to conduct iEM studies wherein current can be delivered and artificial lesions can be created [19]. It has an excellent spatial and temporal resolution and as the subjects are typically conscious, there is a direct reporting of perceptual experience rather than having to draw inferences about the experience. This offers unique opportunity to study human cognitive functions [21].

Despite these advantages, there is little mechanistic understanding of how iEM works, that is, whether it causes neuronal excitation, inhibition, or both. Additionally, it is unclear if the current extends further than targeted, and, if it influences neighboring regions or passing fibers. Therefore, despite presenting strong causal evidence, one must exercise caution while drawing inferences from iEM studies [22,23]. Another limitation is that the electrode placement is dictated by the clinical presentation which results in sparse sampling. The areas with high seizure frequency including the medial temporal lobe, hippocampus, and amygdala, are more readily accessible, whereas other regions are not typically targeted in iEEG, therefore are not accessible for iEM studies [19]. Lastly, given the highly invasive nature of the technique, human iEM studies for purely research purposes is not viable. As of yet, no study has examined the causal role of body patches using iEM in humans.

In conclusion, lesion studies both natural and artificial, offer strong causal evidence in structure-function relationship. However, both natural and artificial lesion studies (iEM here) entail studying a diseased brain thereby endangering the generalizability of inferences [17,19].

This leads us to the next question - *Can we test the causal role of body patches in healthy humans?* This is possible with transcranial magnetic stimulation (TMS), which is a noninvasive technique that is safe for humans [24]. It is based on Faraday's principle of electromagnetic induction, which states that an electric current flowing through a coil generates a time-varying magnetic field, which induces an electric current in a conductor nearby [25]. In the case of TMS, a coil is placed near the subject's scalp which produces a time-varying magnetic field. This induces a small current in the brain and causes a "virtual lesion" [26]. Such an effect can be induced either by a single pulse or by a series of high-frequency stimuli, that is repetitive transcranial magnetic stimulation (rTMS) [27].

Since superficial regions of the brain are easily accessible for disruption by rTMS [27], a virtual lesion can be created in EBA as it is in proximity to the skull. As represented in Figure 8, Urgesi et al. targeted the EBA with rTMS and found that the subjects had difficulties with body-part-related tasks [28].

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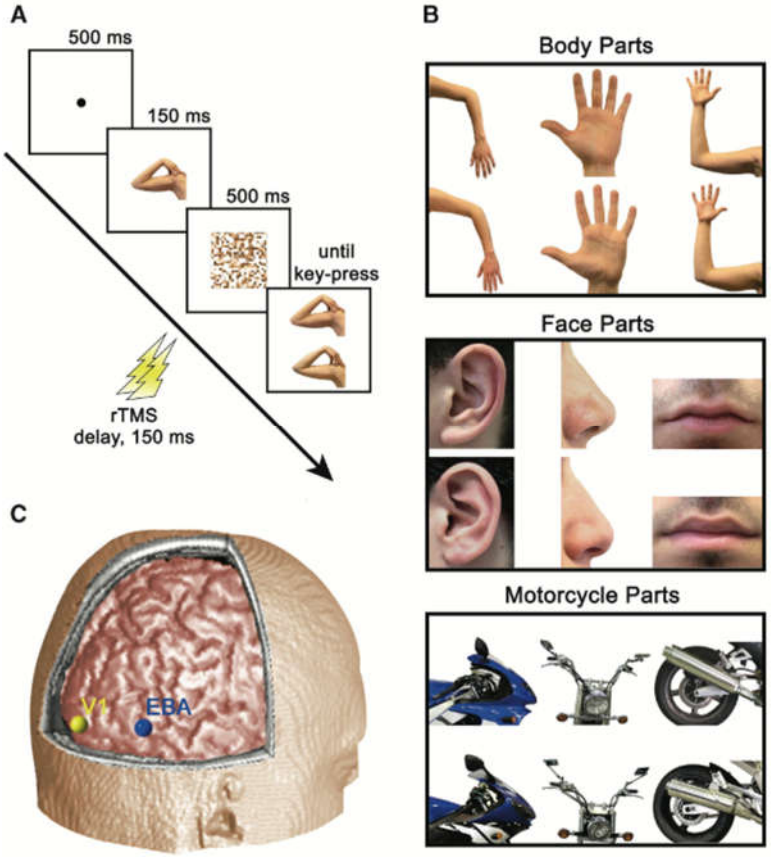

Figure 8. The experiment done by Urgesi et al. wherein in (A) depicts rTMS being delivered after 150ms of stimulus presentation, (B) shows stimulus categories, (C) displays the positions of stimulation sites which includes EBA (shown in blue) and primary visual cortex-V1 (shown in yellow). Panels A-C adapted with permission from Urgesi et al. (2004).

The fusiform body area (FBA) is another region that is implicated in body perception; however, it is not accessible to rTMS due to its deep location [27]. Moreover, when targeting rTMS as rTMS is agnostic to neuron subtype and circuitry it can affect passing fibers. Therefore, it can be challenging to determine whether the observed effects are due to disruption in the targeted region or passing fibers [29].

In summary, rTMS can create reversible virtual lesions in healthy humans. However, the causal inferences that can be drawn from TMS studies are limited due to inadequate spatial precision for deeper brain regions, and poor mechanistic understanding of TMS [27,29].

Next, we ask - *What is the nature of body representations, and how do these representations transform as information progresses in the brain?* To answer this, a combination of neuroimaging and electrophysiological techniques is required to answer. Such a study was done in 2019 which involved macaques as subjects [30]. The first step was to identify the areas of the brain that responded selectively to macaque body stimuli using fMRI. This included two regions in the brain termed MSB (mid-STS body patch) and ASB (anterior STS body patch) shown in Figure 9.

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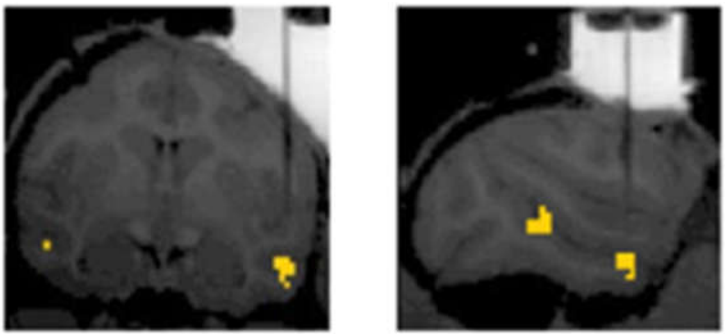

Figure 9. Electrophysiological recordings in non-human primates guided by FMRI. Adapted with permission from Kumar et al. (2019). BOLD activations in yellow indicate differences in BOLD responses evoked by the images of monkey bodies and objects. A vertical shadow indicates an electrode aimed at the ASB.

An MRI-compatible guide tube was then used to insert electrodes to record local field potentials (LFPs) and multi-unit activity (MUAs) from these regions. LFPs and MUAs represent the extracellular activity of an ensemble of neurons [31–33]. The recordings from both MSB and ASB showed category selectivity for body stimuli. Another interesting finding in this study was its insight into visual information's transformation as it traverses the ventral visual stream. Specifically, MSB neurons showed greater sensitivity to body versus non-body categorization while ASB neurons showed a viewpoint-invariant preference for posture and identity. This could imply that the posteriorly located MSB neurons determine whether the stimulus is an animal or not. The anteriorly located ASB neurons integrate that information, and further process features such as posture and identity [30]. A major advantage of electrophysiological studies is their exceptional spatial and temporal resolution [34]. Since this technique is invasive, it has only been tested on non-human primates. When studying cognition, this is critical to consider as unlike humans, nonhuman primates cannot verbally report their perceptions, so perception is inferred from their behavior. Another limitation of this technique is it is agnostic to neural type and neural circuitry [23].

A technique that allows selecting individual neurons and neural circuits is optogenetics. In this technique, the activity of individual neurons can be controlled by the genetic introduction of light-sensitive proteins [35]. Due to the fact that light activates the neurons, it has an unsurpassed spatial and temporal resolution [36].

4. The future: Clinical and basic neuroscience implications

In this review, we have discussed the thrilling journey of cognitive neuroscience from phrenology to optogenetics. Neural correlates of behavior can be studied at various levels– the single neurons, ensembles of neurons, circuits, and systems. Among these understanding of circuit dynamics has been identified by the BRAIN initiative as the potential to transform the field [37]. Circuit level disease models of the various behavioral and neuropsychiatric conditions exist [38] These monogenic animal models offer an insight into how the diseased brain has atypical structural and functional dynamics, additionally offers a window for studying the effect of interventions and plasticity [38].

Referring to Marr levels of organization again, complete description of the circuits involved in cognition and behavior requires three levels of understanding [39]. At the computation level, we will need to better characterization qualities of individual neurons and their synaptic and supplementary communications with the other neurons. At an algorithmic level we will require the elucidation how the information transforms through the circuit and results in behavior. Finally, at the implementation level we should be able to implement the proposed circuit naturally or artificially.

The BRAIN initiative declares that an interdisciplinary approach is required for characterization of fundamental brain functions [40]. This includes integration across fields such as data science, neuroimaging, engineering; and bringing together inferences both

human, and non-human models [37]. This integrative approach will require widespread dataset and data analysis sharing [37]. With the advent of the advent of large neuroimaging dataset in combination with voxel-based lesion-symptom mapping will enable precise lesion localization. Such evidence already exists with VLSM studies in stroke patients with deficits in cognition[41], language[42], memory[43] and executive functions[44]. The advancements in the characterization of cognitive functions will ultimately progress our understanding of the fundamental brain processes [37]. This in turn will lay foundation for better diagnosis, management and finally treatment and reversal of the diseased brain states.

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