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Combined lesion-deficit and fMRI approaches in single-case studies: Unique contributions to cognitive neuroscience

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Abstract

Although lesion-deficit case studies are foundational in cognitive neuroscience, published papers presenting single lesion cases are declining. In this review, we argue that there is a valuable place for single-case lesion-deficit research, especially when combined with functional neuroimaging methods, such as functional magnetic resonance imaging (fMRI). To support this, we present a summary of notable findings from single-case combined lesion-deficit and fMRI studies published in recent years (2017–2020). These studies show the unique value that this combined approach brings to the understanding of complex functions, brain-level connectivity, and plasticity and recovery. We encourage researchers to consider combining lesion-deficit and functional imaging methods in the analysis of single cases, as this approach affords unique opportunities to address challenging unanswered questions about brain-behavior relationships.

Keywords

case studies; lesion method; fmri

Introduction

Single-case lesion-deficit studies form the foundations of cognitive neuroscience research. Famous cases such as Mr. Leborgne and S.M. are fundamental to our understanding of language and emotional processing, respectively, and are widely taught in introductory neuroscience textbooks [1,2]. Similarly, the stories of Phineas Gage and patient E.V.R. demonstrated the link between personality and brain tissue [3,4]. Patient H.M. provided researchers the ability to discern the role of the hippocampus in episodic memory, resulting in a landmark paper that is among the most cited in neuroscience [5,6]. In each of these

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examples, substantial impact on the understanding of brain-behavior relationships was made by groundbreaking single-case lesion-deficit studies.

Lesion-deficit case studies are essentially serendipitous in nature, as scientists lack experimental control over whether any participant will have an interesting focal brain lesion and associated deficits [7,8]. As such, single-case lesion-deficit studies have often featured participants with unique or paradoxical behavioral presentations. While lesion-deficit studies with multiple participants are well-suited for testing predictions of theoretical models, at times the patterns of behavior observed in a single case report are unexpected and cannot be explained using current models. Such singular cases may prompt entirely new formulations of brain-behavior relationships [8]. The power of compelling case studies to reshape models and theories is one of the valuable features of single-case lesion studies. For example, the report of a patient who had lost the ability to name verbs but not nouns helped establish the non-intuitive dissociation between these two lexical processes [9].

Despite their potential to make impactful contributions, single-case studies seem to have fallen out of favor in neuroscience. Journals are increasingly unwilling to publish single-case studies [8,10] or limit publication to occurrences that are "strikingly unusual" [11]. Journals that do accept single-case studies report that the number of manuscript submissions on single-case studies is decreasing [7]. The advent of neuroimaging techniques has largely been blamed for this decline [12]. However, researchers could take this as an opportunity to "join forces" – viz., to use the classic lesion-deficit approach in single-case studies and combine this with neuroimaging methods, particularly functional magnetic resonance imaging (fMRI). Figure 1 illustrates an example of this approach.

Combining lesion-deficit and fMRI methods can give insight into a variety of neural processes, such as the roles of circumscribed brain regions within larger network activation, recovery processes following brain injury, and the impact of rehabilitation therapies on brain function. In this review, we present a summary of recent (2017–2020) contributions this combined approach has made to the field of neuroscience. We argue that studies combining single-case lesion-deficit with fMRI methods can make significant and meaningful contributions to our understanding of brain-behavior relationships, particularly in the areas of connectivity and plasticity.

Connectivity

Functional imaging methods afford researchers a window into patterns of connectivity within the brain. The entire brain can be surveyed and areas whose activation patterns oscillate in tandem can be interpreted as functionally connected. The lesion-deficit method may be used in conjunction with fMRI methods to enhance our understanding of network function and organization [13]. By comparing the network activation patterns of patients with unique lesions to those of an appropriately-matched comparison group, valuable insights can be gleaned regarding the role that a particular brain region may play (or not) within the network.

Recent work has used this approach to further clarify vision pathways. Canonical understandings of visual processing describe a flow of information from retina to thalamus to primary visual cortex, at which point information is distributed to various cortical areas responsible for processing motion, color, objects, faces, and location in space. However, recent papers report on individuals who retained some level of visual processing despite destruction of this pathway. Two studies report on participants with damage to the occipital lobe; the participants have no static (form) vision yet can perceive motion. Motion tasks conducted in the scanner elicited activation in middle temporal cortex [14*,15]. An additional case-report describes a 7-year-old who maintained conscious perception of visual stimuli and residual fMRI activation during visual tasks despite destruction of the white matter tracts that carry information to visual cortex [16]. Taken together, these studies indicate the existence of additional visual pathways, possibly subcortical in nature, that bypass primary visual cortex. A recent report of a patient with prosopagnosia has also challenged the assumption that face processing is linear and hierarchical. When presented with images of unfamiliar faces, the patient activated anterior portions of a face-processing network, despite having damage to key posterior regions crucial for face processing [17*]. This study suggests that face recognition may emerge from multiple parallel pathways that relay information from the visual cortex to various face-processing regions throughout cortex.

Language networks have also been further elucidated using a combined lesion-deficit and fMRI approach. Compared to vision, the precise pathways by which language is processed are less firmly established. Experiments in a surgical patient have supported the role of a recently-identified frontal fiber pathway in connecting brain regions important for planning to those important for lexical processing [18]. A peculiar case of a bilingual man whose stroke-induced aphasia was worse in his non-dominant language also helped to elucidate brain regions active in language processing, particularly in bilingual individuals. Functional neuroimaging showed that brain areas associated with two language processing networks exhibited decreased connectivity when compared to a matched comparison, yet connectivity between brain areas involved in the language control network were not found to be similarly affected [19]. It was concluded that the disconnection between the language control network and language processing networks led to the participant being unable to inhibit his dominant language, leading to more severe aphasia symptoms in his non-dominant language. In a third report, resting state fMRI in a 43-year-old woman who exhibited non-sequential spelling following a cerebellar lesion demonstrated an impairment of cerebellar connectivity to areas known to be involved in handwritten spelling [20].

Other notable recent works have shown that damage to anterior cingulate cortex is associated with diminution of the body’s “chill” response to pleasant and unpleasant sounds. Activation in areas involved in auditory recognition and working memory, as well as the subjective experience of “chills,” was preserved [21]. Another study indicated that lesions to periaqueductal gray and superior colliculus may be implicated in a psychotic behavior phenotype due to connectivity between these brainstem structures and the amygdala [22].

Plasticity

Single-case studies utilizing fMRI approaches are particularly well-suited for the investigation of plasticity and reorganization following brain injury. Plasticity outcomes following brain lesions can be variable and are influenced by individual factors [23,24], and repeated measurements of groups may be potentially insensitive to highly different patterns of changes across participants. Thus, following one participant over time may yield valuable results.

FMRI methods can be used to elucidate changes in brain network structure after injury [25]. One such example is a patient who developed severe amnesia following a thalamic lesion. Upon further study of this patient, a prior lesion to the hippocampus was discovered. The study authors suggest that this prior damage may have caused the participant to rely on right-hemisphere-based memory circuits, which were then disrupted following the new thalamic lesion [26*]. This reorganization of function can happen quickly; Gould and colleagues report the case of a patient whose motor cortex became compressed under subdural fluid following brain surgery. The motor regions were shown to reorganize and shift to adjacent brain regions in the same hemisphere in a matter of months, then shift again over the course of 4 months once the pressure subsided [27]. Functional connectivity has also been proposed to serve as a valuable tool for understanding plasticity following childhood lesions [28]. For example, reorganization of language has recently been reported in a case of penetrating brain injury experienced in infancy [29]. The unusual nature of these reports highlights the importance of publishing single-case lesion-deficit studies that include fMRI measures.

Current research on the underlying mechanisms suggests that reorganization includes recruitment of additional brain regions and return of neural activation back to baseline [30**], but the physiological underpinnings of global connectivity changes are not yet understood [31]. The ability to study one participant over time and acquire multiple fMRI scans at various stages of recovery affords a unique opportunity to capture plastic changes that may be taking place. For example, a recent report described a woman who presented with severe deficits in lexical processing following a stroke and was assessed over the course of one year. She recovered her abilities to read and spell, and improvement of these functions was associated with increased activation in areas involved in orthographic lexical processing. Notably, these areas were distinct from the area affected by the stroke [32]. This finding indicates that strokes can disrupt connectivity in distant areas, and that successful recovery may include reestablishing these connections. Similarly, in a patient who developed hemispatial neglect due to stroke, and then recovered, resting state fMRI scans acquired 4 days and 6 months after the stroke showed that improvement in symptoms was associated with additional multisensory integration [33].

In addition to improving our understanding of plasticity, combining lesion-deficit and fMRI methods may yield valuable insights into the mechanisms and effectiveness of rehabilitation. For example, after a 14-week period of rehabilitation, a stroke patient with spatial neglect demonstrated improvement in their attention, along with increased activity in bilateral frontal areas [34]. This suggests that rehabilitation can induce sustained increases in brain activity, and that frontal involvement may be a key part of recovery from neglect. Similarly, rehabilitation after stroke can lead to changes in network organization. One study showed that a virtual reality rehabilitation protocol led not only to improvements in function, but also increased network metrics in the ipsilesional hemisphere [35]. This supports the possibility that an increase in functional connectivity is an important component of recovery.

Changes in patterns of activation after rehabilitation can also be used to assess the efficacy of novel treatments [36]. This has been particularly true in reports of novel treatments for aphasia. How the brain may reorganize in response to treatment for aphasia remains unclear, and the reorganization that takes place may depend on various factors, including the specific deficit, language process assessed, lesion site, treatment type, and intensity of treatment [37**]. Due to heterogeneity across patients, a single-case study approach with robust functional imaging measures prior to and following intervention may be valuable for assessing treatment efficacy. FMRI measures have been shown to be correlated with success in language therapy [38]. In a patient with conduction aphasia, investigators described no improvement in language abilities after two months of speech language therapy. However, after repetitive transcranial magnetic stimulation (rTMS) to left Broca's area, language ability significantly improved. Application of rTMS was also associated with a shift from loose and extensive activation patterns to more focused activation of areas associated with the left language network [39]. Additional research has shown that a novel rehabilitation technique for treating aphasia is associated with changes in areas involved with sensorimotor interactions, attention, motor planning, and internal models for speech [40]. In addition to their scientific contributions, these studies highlight the importance of individualized treatment options for patients.

Taken together, the above works underscore the importance of single-case studies in elucidating the neural reorganization that takes place following focal injury. Single-case studies provide detail and nuance that is not available in studies where multiple individuals are averaged together, and as such, single-case studies are ideal for investigating heterogeneous recovery trajectories. Moreover, single-case studies afford researchers the opportunity to identify underlying patterns of plasticity that may be common between individuals. Additionally, single-case studies may provide empirical evidence to support proposed mechanisms of reorganization.

Discussion

Single-case studies combining lesion-deficit and fMRI methods have a place in modern neuroscience. In recent years, research utilizing this combined approach has provided valuable insights regarding network organization in the brain, particularly regarding vision, language, and attention processing networks. It has also broadened our understanding of plasticity after focal injury, including giving further insight into mechanisms that may be at play and the impact of rehabilitation techniques on brain reorganization.

Contemporary cognitive neuroscience has become enamored of "big data" approaches in fMRI studies, which include large cohorts of many hundreds of participants. While these studies have yielded valuable knowledge, they are not without drawbacks. FMRI studies are low-powered [41] and require large sample sizes [42]. While fMRI studies can infer relationships, they lack the causal impact of lesion-deficit methods, and thus depend heavily on existing cognitive theories to draw meaningful conclusions about brain-behavior relationships [8]. Additionally, due to large sample sizes and standardized data collection methods, it is difficult to gather the types of nuanced data that a thorough study of a single participant can provide. Finally, big data approaches are not ideal for understanding the nuanced reorganization that occurs following an injury or rehabilitation intervention.

Combined single-case lesion-deficit and fMRI approaches capitalize on the strengths of both methods and offer unique opportunities that large-scale fMRI studies or lesion-deficit studies alone cannot. Unlike fMRI, lesion-deficit studies can identify key brain regions necessary for function, and such studies are typically highly powered due to extremely large effect sizes. However, while lesion-deficit methods can determine the extent to which a participant may have lost and later regained a function, they cannot be used to discern where or how the neuronal basis for that function has reorganized. By combining lesion-deficit and fMRI approaches, researchers can leverage an approach that provides strong evidence of localization of function while also describing whole-brain changes in patterns of activation. Due to the compelling nature of this combined approach, a study with a sample size of one can lead to meaningful scientific discovery.

Of course, there are important limitations of single-case studies, particularly regarding lesion-deficit and fMRI methods. Due to the “serendipitous” nature of single-case lesion-deficit studies, researchers lack rigorous experimental control over potential confounds, such as comorbidities or socioeconomic factors, that may influence both neuroimaging results and the neuropsychological profile. For this reason, appropriately matched individuals should be included as comparison participants. Statistical methods specifically formulated for comparing single-cases to a matched group should also be employed[43,44]. These statistical methods can also be used when assessing functional imaging results[45,46]. Additionally, fMRI analyses require statistical modeling to account for potential confounds when data are not being averaged across individuals [47]. Collecting longer bouts of imaging data for the participant may help mitigate this concern [41,48].

In this review, we have underscored the value of combined single-case lesion-deficit and fMRI studies. We appreciate that the debate regarding the value of single-case studies is longstanding [49,50], and the inclusion of recent neuroimaging techniques presents exciting new opportunities to revisit this debate. Researchers wishing to report on unique and interesting single-cases with focal lesions could consider including fMRI measures of connectivity or plasticity in their data collection to broaden what questions might be asked or what conclusions might be drawn. Similarly, journals currently eschewing case-studies could reconsider the potential value of multimodal single-case study approaches.

Conclusion

In conclusion, a combined single-case lesion-deficit and fMRI approach provides researchers with a compelling, unique opportunity to study neural organization, plasticity, and recovery.

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Highlights

- The number of published neuroscience papers on single-case studies is declining
- Combining lesion-deficit case studies and functional imaging yields valuable insights
- These insights go beyond those obtained by lesion-deficit or functional imaging alone

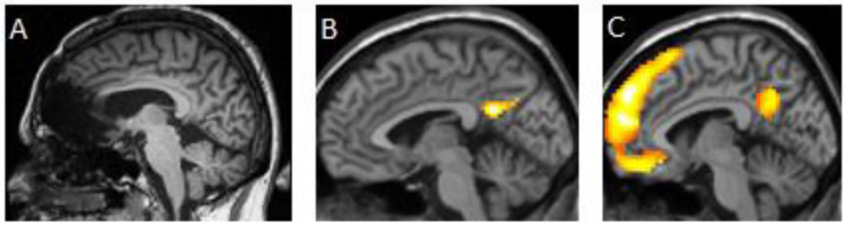

Fig 1.
Sample images indicating how a combined single-case lesion deficit and fMRI approach may be used to understand emotional processing. (A) MR image (mid-sagittal view of right hemisphere) depicting a lesion to the ventromedial prefrontal cortex in one participant. (B) Brain regions activated ($p<.01$) in this participant during an emotional processing task, plotted on a template brain (same mid-sagittal perspective as in A). (C) Brain regions activated in a matched, neurotypical comparison cohort engaging in the same task (same mid-sagittal perspective as in A and B). The activation depicted in (B) suggests that the patient is using a preserved remnant of an emotion processing circuit to achieve some degree of correct performance on the task.