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Ideomotor Apraxia: A Multi-Study Lesion Mapping Perspective

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ABSTRACT

Ideomotor Apraxia is seen as a deficit of skilled movement in the absence of motor impairment (Rothi & Heilman, 1997). It is commonly associated with left hemisphere damage due to stroke, tumors, or neurodegenerative diseases like corticobasal degeneration. The discourse around Apraxia and its subtypes can be traced back 100 years to Liepmann's discovery, however, there is a lot of ambiguity around terminology. This can be traced back to a task-based versus a process-based understanding of the praxis network. The present study is the outcome of a systematic analysis of the literature about Ideomotor Apraxia in patients with unilateral, left brain damage as a result of stroke or tumors. Structural neuroimaging studies were retrieved through a literature search. We found 318 studies, from which, based on specified inclusion and exclusion criteria, a database with 25 papers was created.

Heterogeneous neuroimaging data from these papers was used to extract lesion coordinates using a specialised software for reconstructing 3D lesions in a standardised space. The area of maximum overlap of lesions within each paper was used to extract coordinates. These coordinate sets were then analysed using Activation Likelihood Estimation meta-analysis to derive two clusters. These clusters were analysed using a brain behaviour connectivity toolkit to create disconnectome maps of white matter tracts with the highest probability of disconnection associated with these clusters. Broadly, our data suggests disconnection of parieto-tempero-frontal white matter tracts. Using this methodology, we are able to use data from heterogeneous templates to obtain a comprehensive, albeit not precise, view of the anatomy related to Ideomotor Apraxia.

INTRODUCTION

1.1 Apraxia: An overview

Apraxia is recognized as an inability to perform a series of movements in the absence of muscular motor and sensory deficits. As such, it has been recognized as a syndrome that is at the boundary of cognitive and motor control (Goldenberg, 2013). Apraxia is defined as a neurological disorder of learned purposive movement skill that is not explained by deficits of elemental motor or sensory systems (Rothi & Heilman, 1997). Apraxia has been reported as dissociated from the motor, sensory, and language deficits (Goodglass & Kaplan, Rothi and Heilman 1984, 1997).

It has been observed in several prevalent neurological disorders such as Alzheimer's Disease, Parkinson's Disease, corticobasal degeneration, and as an outcome of cardiovascular diseases and traumatic brain injury (Leiguarda et al., 1997; Foundas, 2013). Apraxia is more common in individuals with left-hemisphere damage and is characterized by a disruption in the performance of familiar gestures (Rothi & Heilman, 1997).

Although he didn't refer to it as so, the first clinical description of apraxia is attributed to Hughling Jackson in 1866 as an inability (in certain patients with aphasia) to perform voluntary actions such as protruding of the tongue which could not be attributed to a weakness of the muscles (Brown, 1972).

The term "apraxia" first appeared in an 1871 book published by a linguist, Chaim Steinthal while explaining it as an amplification of another disorder, aphasia. The term has Greek roots and literally means without action. Thirty years later, Hugo Karl Liepmann, through his work at a psychiatric hospital in Germany, wrote a series of reports about a man referred to as *The Regierungsrat* ("the imperial counsellor") which provided the basis for his development of a comprehensive theory of Apraxia.

Liepmann noted a peculiarity in his motor behavior of the right upper extremity. He was unable to follow instructions such as picking up a card using his right hand but when forced to use his left hand he was able to do so efficiently. The same was true when he was asked to imitate Leipmann's foot gesture, he could imitate it with his left foot, not his right. He also had difficulties performing simple movements of the head or tongue. He noted that "the right hand acted as if it could not understand anything at all". As Goldenberg (2013) notes, the important

observations that lead to the conceptualization of Apraxia were tasks of smoking a cigar and buttoning. He had difficulty initiating the gesture of buttoning without his hand being moved for him. When asked to copy gestures or use imaginary objects he did so in a clumsy fashion.

Liepmann discussed the concepts of Mind-Palsy, Asymbolia, and Apraxia as they existed in literature at the time to develop a conceptual framework of Apraxia. Liepmann distinguished his contribution to understanding apraxia by using the term "motor apraxia" or "ideo-kinetic apraxia" (Goldenberg, 2013). His postulation of apraxia was faithful to associationist thinking. While reporting the case of the imperial counselor, he noted a lesion in the fiber bundle tracts rather than a lesion of the cortical areas by themselves. He notes in his paper:

"...I never proposed that the apraxia of the imperial counselor was caused only by the focus in the supramarginal gyrus. I postulated a separation of the sensorimotor region of the right limbs from cortical areas of both hemispheres and believed that this was achieved by interruptions in the white matter of the supramarginal gyrus and of callosal connections to the other hemisphere" (Liepmann, 1908, p.77).

About four months before this, De Buck published a paper on "parakinesia" based on an identical formulation (Goldenberg, 2003, p.17).

As he continued his studies, Liepmann examined 42 patients with left and 41 patients with right hemiparesis, and 5 patients with aphasia. He had them perform expressive gestures (such as saying goodbye), transitive gestures (like knocking on a door), manipulation of objects (like sealing a letter), or had them imitate gestures using the hand ipsilateral to the lesion. He noted that while the patients with left-side paresis and the control group did not commit any errors in their performance, approximately half the patients (20/41) with right-side paresis and three of the seven patients with aphasia performed severe errors in expressive and transitive movements. Moreover, 6 of the patients with apraxia did not have aphasia and 4 of the aphasic patients had Apraxia. He thus concluded that they are independent phenomena. (Liepmann 1908; Goldenberg, 2013). Shortly after, in collaboration with neurologist Maas, he concluded through observations of people with callosal atrophy that left-hand apraxia also affects the imitation of gestures (Maas, 1907; Liepmann, 1908; Adapted from Goldenberg, 2013).

Liepmann's theory of Apraxia begins with an understanding of movement as a consequence of an idea which is carried out according to a sketch (that includes space, time, and the form) of said movement. The sketch contains information about the purpose and ways of performing

an action, this type of a visuo-kinesthetic representation was thought to be stored in the left occipito-parietal cortex (Liepmann, 1913; Pearce, 2009). He believed that the execution of such a movement involved the retrieval of the idea through cortical connections in the sensory motor area which convey information to the left primary motor area. For the left limb to perform a movement, this information has to be transmitted to the right sensory motor area via the corpus callosum (Leipmann, 1920; Leiguarda & Mardsen, 2000; Pearce, 2009).

This theory has since faced several criticisms, for example, for not addressing the difference between short and long amplitude movements because disruptions in movement are more commonly found in long amplitude than short amplitude movements. (Rothi & Hielman, 1997; Heilman & Rothi, Valenstein, 1982) Liepmann did not take into consideration the specific processes (like temporal ordering) or memory stores that would elaborate on the idea of a movement (Harrington & Haaland, 1992).

Goldenberg (2013) notes, the uniqueness of Liepmann's contribution was his acknowledgement of the mind-body dichotomy. Proponents of mind-palsy were hyper-focused on physiology, ignoring the psychological aspect of the disorder, and those that advocated for asymbolia, or the older understanding of Apraxia, did not acknowledge the anatomical underpinnings.

Liepmann's observation about the dissociation between apraxia and aphasia has been corroborated as well as challenged in recent times. Neuroimaging studies have shown at times a partial overlap and at other times a complete overlap between motor areas for gesture production and language areas (Papagno et al., 1993; Osiurak & Bartolo, 2020).

Another influential theory about apraxia was presented by American neurologist, Norman Geschwind, whose expertise was in understanding neurological behavior through a disconnection model. He proposed that apraxia is a result of a disruption in the superior longitudinal fasciculus that connects the left premotor and Wernicke's Area. Bilateral Ideomotor Apraxia was then explained as a possible consequence of the disconnection of the white matter connections between the premotor areas of the left hemisphere (Geshwind, 1965; Mesulam, 2015). He attributed the difficulty of gesture imitation to the shared white matter tracts that connect the visual association areas, premotor cortex, the language and motor areas (Geshwind, 1975).

Literature reveals two approaches at the micro-level of action used in the diagnosis of apraxia:

i. Kinematic measurement of gestures and actions

ii. Investigation of more simple actions like pouting and grasping (Poizner, 1990; Iestwaart et al., 2006; Goldenberg, 2013).

1.1 Classifications of Apraxia

Liepmann developed a model of voluntary action control that served as the basis for the subtypes of apraxia. This model rested upon the conversion of images of the potential action into a motor command.

Liepmann distinguished between:

Ideo-kinetic (Ideo-motor) Apraxia: Resulting from a disruption of fibres that lead to the somatotopic connections in the motor cortex and impairs the use of tools and objects, which makes it difficult to estimate the "how" of a single movement. He believed that it results from the severance of kinematic and ideational memories.

Ideational Apraxia: Using Pick's (1905) clinical observations, Liepmann proposed a variant of apraxia that manifests in the domain of action but is not caused by motor control-specific deficits. This subtype is characterized by the loss of an understanding of sequence, i.e., the temporal and spatial components.

Limb Kinetic Apraxia: Resulting from a disturbance of images of limb movements (kinesthetic images) which leads to an awkward, clumsy movement and a loss of fine, delicate movement (Goldenberg, 2003; Pearce, 2009).

There are references in literature to other sub-types of apraxia such as:

i. Conceptual Apraxia: Characterised by a loss of knowledge related to the tool-object association. They misuse objects and cannot report between ill-used and well-used objects. (Heilmann & Rothi, 2003)

ii. Orofacial Apraxia: An impairment of movement of the face, mouth, tongue, larynx & pharynx. (Ozsancak et al., 2004)

iii. Constructional Apraxia: A difficulty in drawing or copying a visually presented image (Damasio, 2000).

iv. Other apraxia such as dressing apraxia (attributed to inattention to the left side), eyelid opening apraxia (An inability to open the eyelid on command), and gait apraxia, visual-motor and tactile apraxia are also identified (Wheaton & Hallett, 2007; Pearce, 2009).

1.2 Debate about terminology

More than thirty subtypes of apraxia have been identified depending on the impaired activity or nature of gestures, the input modality, the type of errors (e.g., spatiotemporal errors in ideomotor apraxia, content errors in ideational apraxia), and the affected limb (Petreska et al., 2007).

In a review published in a special edition focusing on apraxia in the 100 years after Liepmann, Baumard and Le Gall (2021) address the challenge of an operational definition in studying apraxia. They comment that the term is used to diagnose different clinical conditions leading to confusion (they use the term obscure) among neuropsychologists, students, and academics alike. For instance, Conceptual Apraxia has been used interchangeably with Ideational Apraxia (Buxbaum, 2003) or as a more severe form of ideomotor Ataxia (Huang, 2021), or an independent subtype (Wheaton, 2007). A review by Hanna-Plady and Rothi (2001) trace the confusion back to Liepmann, himself.

Referring to Ideomotor Apraxia, Alexander et al. (1992), remarked that all definitions currently used focus on one claim or the other, none of which are widely accepted.

Baumard and Le Gall (2021) observe a shift in reliance on a task-based approach to describe impairments rather than using a subtype terminology. In their quantitative review of the literature, they note that this might be caused by a shift from a diagnostic understanding towards a process-based approach to recognize the underlying cognitive processes. Some papers have explicitly refrained from using diagnostic terminology acknowledging this debate, and focused on using commonly known motor deficits and error types (Eg. Dovern et al., 2011).

Although Baumard and Le Gall (2021) focus on limb apraxia, they invite a focus in apraxia research on two characteristics:

- Specificity, that is, asking if apraxia is explained by the change in cognitive processes dedicated to gesture production and
- Consistency, i.e., asking if the impairment is consistent in all tasks.

1.3 Ideomotor Apraxia

Ideomotor Apraxia is seen as a deficit of skilled movement in the absence of motor impairment. (Goldman Gross & Gross, 2008). Baumard and Le Gall (2021) noted that in their literature review of a 100 papers, disorder of skilled deficit was more commonly featured in relation to Ideomotor than other types of apraxia. Another, the more descriptive definition used, points to a deficit in voluntary tool-related control, gesture imitation, and fine motor control (Goldenberg, 2009; O'Neal et al., 2021).

Ideomotor Apraxia can be seen after injuries to frontal, parietal, and sometimes callosal regions and has been noted in patients with subcortical vascular injuries (Petreska et al., 2007). Ideomotor Apraxia has also been seen in patients with neurodegenerative disorders such as Corticobasal Degeneration (Goldmann Gross & Grossman, 2008), Parkinson's Disease, Supranuclear Palsy, (Leiguarda et al., 1997), Huntington's Disease (Shelton & Knop,1991), and Creutzfeldt-Jakob Disease (Wang et al., 2021). Case reports of Ideomotor Apraxia following brain tumors have also been narrated (Eg. Jang, 2016). The presence of Ideomotor Apraxia has been speculated in association with Marchiafava Bignami Disease, although, these are just isolated case reports (Brown, 1972).

Deficits in Ideomotor Apraxia are seen in pantomime imitation, tool use, tool-use pantomime, and sometimes in communicative gestures. When asked to make a writing gesture, people with ideomotor apraxia have been noted to stretch out their index and thumb fingers and then make a pinch (Haaland et al., 2000). People with Ideomotor Apraxia can also make clumsy, hurried movements when trying to follow instructions. For example, it has been noted that when asked to pantomime cutting a turkey, they make jerky vertical instead of horizontal errors (Poizner et al., 1998). Goldenberg and Hagmann (1997) found that patients with Ideomotor Apraxia were unable to pantomime static postures that required the positioning of the hand in relation to the head. They were also unable to position a mannequin to imitate the posture of an examiner, suggesting that the deficit is not limited to execution.

Patients with Ideomotor Apraxia are also seen to perform errors characterized as Body-as-part object (Wheaton et al., 2007). However, it has been noted that this type of error may describe a convention in symbolizing gestures rather than pathology (Mcdonald et al., 1994). It has been observed that the focus on gesture imitation and pantomime of tool use has shifted focus away from research on functional ability in Ideomotor Apraxia. Of note, the deficit-impaired postural representation that leads to an inability to solve problems of object manipulation unrelated to memory is an important life skill which is not studied clinical research that aims to understand the praxis systems (Sunderland & Shinner, 2007). Few attempts have been made at providing a qualitative summary of the nature of errors seen in Ideomotor Apraxia.

Ideomotor limb apraxia underscores the complex functional connections between internal cognitive operations and physical motor events (Rothi & Heilman, 1997). Several frameworks have attempted to explain theoretical models of Ideomotor Apraxia.

Roy and Square (1985) propose a model with a conceptual and production system. The conceptual system holds information about the functions and actions associated with objects and knowledge of action that is independent of the objects. Different tools and objects can "fit" into this and the knowledge can convert to actions. The production system on the other hand holds sensorimotor, perceptual, and motor knowledge of action and organizes and executes the action. According to this model Ideomotor Apraxia results from damage to the production system.

Rothi et al., (1991) explain that there is a direct and indirect route in gesture production and imitation. The indirect, lexical, route processes actions by accessing the semantics and the movement representations. The direct route bypasses gesture representations and semantics and allows the imitation of meaningless gestures.

Both models report two systems necessary to produce actions, one that contains the information, and the other that processes spatio-motor information (Bauxbaum, 2010). These representations have been noted to be located in the left parietal cortex. It has been suggested that damage to these areas would affect the performance and recognition of pantomimes. (Rizzolatti et al., 1997).

Evidence has been found for the possibility that Ideomotor Apraxia could be due to a deficit in parsing serial motor events to construct higher-order, complex events. It has also been

suggested that the ability to select optimal response parameters for simple movements is impaired but only for certain types of movements (Harrington & Haaland, 1992).

More recently, Bauxbaum (2000) proposed a model based on a system for praxis, where memory representations and the dynamic procedures involved are stored in a network of nodes that go "online" based on the demands provided by the task at hand. Her model invites research-oriented, process-based applications and an ecological understanding of the deficits related to Ideomotor Apraxia.

This model comprises of a ventral stream where representations of object identity are stored in a declarative format and a dorsal stream where spatial body representations are stored, corresponding to the left frontal lobe and inferior parietal lobules. She equates the dorsal system to a "how" system. The dorsal system also holds procedural information for mapping others' body position relative to one's own representations. This is important for processing gestures, more so, with meaningless gestures. Her model suggests that Liepmann's engrams would be created by the merging of dorsal and ventral systems. The ventral system holds the memory and representation features and the dorsal stream holds the dynamic motor movements, spatially.

She suggests that the activation of a gesture engram is 'read' by the declarative semantic system to derive knowledge about how to manipulate an object. Alternatively, she suggests that the spatio-motor nodes encode gestures using a distributed multi-modal semantic system.

Using this model, Ideomotor Apraxia is categorized into the following subtypes:

a. Disconnection type: This is ascribed as a problem in calculating information about one body part relative to the others. This has also been studied as 'somatesthethic spatial coding' (Hielman et al., 1986). She suggests that these patients have deficits in translating a set of spatial codes that are external to their body into internal representation spatial codes. She traces the neuroanatomical correlates between the anterior and the inferior parietal lobule.

b. Representational type: Patients with this type of deficit would make errors in recognizing gestures and perform object manipulation tasks with spatio-temporal errors. She believes that this is caused because of an inability to either store or access the representational memory of postures and movements that need internal spatial

coding. These patients have lesions in the angular and supramarginal gyri. While their knowledge of function is unimpaired their ability to manipulate the knowledge is compromised and they have trouble learning new gestures.

c. 'Ventral' Apraxia: She asserts this as a possible subtype of apraxia that could be attributed to patients with a deficit in the functional (semantic) knowledge of object use. The errors in action would reflect a conceptual problem with knowledge of the object.

She recognizes that it would be difficult to find 'pure' occurrences of any of the subtypes as such, her model is based on the dissociations and associations in the praxis skills. As an example, it is explained that meaningful gesture imitation can occur through the dorsal system alone or with information from the gesture representation system. Results of studies conducted comparing meaningless gestures on self-versus meaningless gestures on a manikin echo the implications of this model.

For example, Goldenberg (1995) examined meaningless gestures in patients with left brain damage with apraxia, without apraxia, and patients with right brain damage. The study revealed a faulty spatial relationship between body parts on self as well as the mannequin. This was linked to an inability to access conceptual knowledge for planning motor tasks. More recently in a meta-analysis studying pantomime Niessen et al. (2014) argued that execution and recognition of gesture both rely on the activation of the same motor schema, which can be related to the confluence of the dorsal-ventral stream as Buxbaum suggests.

Wheaton & Hallett (2007) note that two tests are commonly used to assess ideomotor apraxia, the Test of Oral and Limb Apraxia (TOLA) and the Florida Apraxia Battery. The TOLA consists of 6 categories of tasks performed to verbal command and then imitation. These categories are proximal intransitive, proximal transitive, distal intransitive, distal transitive, oral non-respiratory and oral respiratory. The Florida Apraxia battery has gesture command, gesture-to-visual tool, gesture-to-tactile tool, gesture imitation, tool-to-object matching, gesture to named object movement verification and gesture-to-conceptual tool subtests. (Rothi et al., 1992) Assessing activities of daily living and analyzing motion as patients make movements have also been recommended.

Some research paradigms have used mannequins to discriminate between gestures that are pantomimed by the self, versus gestures that are replicated onto another. Some others use object

manipulation tasks using different wrist positions on which kinetic analyses are performed to understand motor adaptation (Eg. Mutha, 2017).

In their review of Ideomotor Apraxia, Wheaton & Halett (2007) suggest that an ideal assessment would include a component for tool use and one for gestures. For the tool use, they recommend, pantomime to verbal command, imitation, performance upon seeing a tool and performance with the tool. For testing gesture related errors, they suggest including pantomime, imitation and performance in real situations. They also suggest discrimination between meaningful and meaningless gestures as well as discrimination between right and wrong gestures.

A 24-Item test with single as well as sequential movements of the arm, hand, or fingers with meaningful or meaningless movements designed by De Renzi and colleagues is also used. (De Renzi et al., 1982). A Short Test for Ideomotor Apraxia (STIMA) has been proposed based on Buxbaum's proposed model (reffered to earlier) of praxis and deficits in Ideomotor Apraxia. The test allows the identification of imitative process that are impaired and narrows the body segment involved. It comprises 18 familiar and unfamiliar gestures, categorized as proximal or distal (Tessari et al., 2015).

Ideomotor Apraxia has most commonly been associated with left parietal or fronto-parietal damage (Buxbaum, 2001). This form of apraxia was associated with the destruction of fibers connecting posterior brain regions to the callosal, parietal and frontal areas. Liepmann suggested that deep lesions of the inferior parietal lobe and the supramarginal gyrus may cause IMA (Liepmann 1920; Goldenberg, 2009).

Primarily, lesions in the left hemisphere are attributed to Ideomotor Apraxia, however, some studies have found that patients with damage to the right hemisphere perform worse than controls when assessing for Apraxia (De Renzi et al., 1980). Heilman and Rothi (1993) attributed Ideomotor Apraxia to damage to the left inferior parietal lobe which they explained to store spatiotemporal representation of gestures. In a later publication in 2003, they also attributed the symptoms to damage to cortical structures such as the angular or supramarginal gyrus. Damage to Supplementary Motor Area has also been known to contribute to Ideomotor Apraxia (Watson et al., 1986).

Lesions of the left basal ganglia, involved in maintaining spatio-temporal control over movements, in response initiation as well as response inhibition have been noted in patients

with Ideomotor Apraxia. (Buxbaum, 2001). In the studies with Maas, Liepmann also attributed the involvement of the corpus callosum in apraxia. Lesions of the corpus callosum have been studied in the context of many disconnection symptoms, while cases of callosal damage have been associated with single case studies (Eg. Goldenberg et al., 2001) of Apraxia, some larger studies have found damage in of the corpus callosum as well in Ideomotor Apraxia (Giroud & Dimas, 1995).

Correlates of Ideomotor Apraxia have been studied using patients with brain damage as well as with healthy subjects, it has been suggested that the two routes are associated with the production and imitation of gestures. The semantic route related to the left hemisphere inferior temporal, parahippocampal, and angular gyri, and a direct route involves networks of cortical areas such as superior parietal cortex, right parieto-occipital/ occipito-temporal junctions, and left superior temporal cortex (Rumiati et al., 2005; Tessari et al., 2015).

Evidence gathered from EEG studies contributed to the understanding of the praxis network being dynamic across multiple areas in distinct cortical regions. A self-paced task was used to identify a coherent left-hemisphere parietal premotor motor network. Studies have also shown that parietal-premotor circuits are important for vision to action translations and for matching observations to actions (Wheaton & Hallett, 2007).

In summary, Ideomotor Apraxia is a deficit of voluntary skilled movement, most prominently seen in tasks of fine motor control related to tool use and pantomime. It has been commonly reported in patients with left brain damage after stroke, TBI and neurodegenerative diseases. Several models have been proposed to explain the development of Ideomotor Apraxia using lesion studies, most models agree that the deficit lies in the interaction of a ventral and dorsal stream of information. While there is a general agreement about the involvement of parietal, temporal and frontal lobes, the specific tracts involved and the involvement of subcortical structures has been debated. The heterogeneity of the findings is because of the differences between researchers and clinicians in selecting patients, assessments and neuroanatomical damage in different studies depending on their criteria. It is thus essential to find a method to integrate this information to find an anatomical model that explains Ideomotor Apraxia.

1.4 Lesion Mapping and its advancements

A significant understanding of brain behaviour relationship in neuropsychology and neurology are rooted in understanding seminal single cases of brain damage and reveal changes in behaviour as a function of a disturbed or inability to perform a task. (Eg. Phineas Gage or the imperial counselor referred to above)

Lesions provide insight into the function of brain structures and allow an understanding of dissociations in cognition. Characterization of such lesions provides information about impairments as well as compensation patterns and resolution over time. The rapid growth and preference for fMRI studies could be complemented by large-scale lesion studies to separate or combine processes to understand the architectures of cognition (Adolphs, 2016).

In a lesion mapping approach, the behavioral performance of one group of patients with a common area of damage is compared to another group of patients or to a healthy control group. This gives an assessment of the functional roles of a region of interest (ROI). Lesion reconstruction from patients with the deficit is overlapped to find common areas of damage/injury and compared to lesion overlays from patients without such an injury. This can also be done to create a subtraction between two sets of patients that share a certain deficit, with varying comorbidities. This allows the delineation of regions that contribute to a certain cognitive skill. When applying this to behavioral data which tends to be on a continuum, a cut-off has to be applied to address the risk of various degrees of performance being overlooked (Bates et al., 2003; Adolphs et al., 2000).

Thinking about which kind of neuropsychological or cognitive conditions to study is an important preliminary consideration. As explored above, the term “Apraxia” is used in different contexts, and each study that understands something about the praxis network might be right, in its own accord, but still be studying heterogeneous phenomena altogether. It has been suggested that patient characteristics, the time at which the examination is made, co-morbidities, and the etiology of brain damage are important considerations to make while selecting patients for a lesion mapping study (Sperber & Karnath, 2018).

In a guide for lesion mapping, it was noted that a large majority of studies on lesion methods between 1995 and 2015 focused on stroke patients. Acute stroke patients were seen to be highly suitable for such studies. When selecting patients, other than etiology, lesion location is another important consideration. The guide encourages focusing on the intention the of study (framing

a precise question) to form inclusion criteria. If the interest is in understanding what function a specific part of the prefrontal cortex has, it wouldn't make sense to include patients with posterior deficits.

However, they add, this would mean that inferences about potential influences of brain networks cannot be made. They caution against the use of the absence of a behavioral deficit as an exclusion criterion as it could reduce variance in the data and reduce the statistical value of the analysis. As different criteria are involved in recommending CT vs MRI scans for patients, they recommend the inclusion of both (de Haan & Karnath, 2018).

Methods of lesion delineation involve observer-dependent, automated, or semi-automated processes. While observer-dependent methodology can be time-consuming and require knowledge of neuroanatomy, the automated methods could be influenced by imaging artifacts which would influence the lesion mapping results. For this reason, the current gold standard remains manual lesion delineation (Moore, 2021). This step is followed by a normalization process to ensure that anatomically correlate across the data is comparable. It is recommended that a template that matches the population of the lesion study is selected for comparability, neuroimaging software like the Clinical Toolbox allows for a spectrum of modifications to allow for these processes (Rorden et al., 2012). This data can then be used to relate lesion location to behavior using methods such as subtraction analysis or voxelwise statistical lesion-behaviour mapping analyses.

The lesion mapping approach alongside studies that correlate the continuous metabolic data for several ROIs with continuous behavioral measures (Metter, 1990) and voxel-based morphometry studies that correlate gray and white matter density to behavior (Macguire et al., 2000) laid the ground work to voxel based lesion symptom mapping. It was suggested as a bridge between classical lesion mapping techniques and modern neuroimaging methods. (Bates et al., 2003). The statistical analyses would render significant or meaningful voxels with the help of an atlas. Several choices of brain atlases are available for this purpose, one can choose between the anatomy toolkit, Brodmann atlas, AAL Atlas, or atlases based on histology, functional connectivity or white matter tracts. (Moore, 2022; de Haan & Karnath, 2018, Thiebaut de Schotten et al., 2011)

The extent of overlap between a lesion and cortical region (understood in percentages) allows inference about the degree of damage to a region to make interpretations about the involvement

of the region/regions in modulating an aspect of the behavior in question. However, it is important to keep in mind that using different atlases could lead to different anatomical interpretations of the same kind of lesion mapping outcomes. (de Haan & Karnath, 2018)

There is an emerging trend in the field of voxel-based lesion mapping and its analyses, towards considering multiple voxels or lesion clusters to understand the relationship between structural damage and corresponding functional damage. This shift was partly a consequence of the finding that lesions might follow a pattern related to the underlying blood vessels (Mah et al., 2014), this would mean that voxels are not unrelated to one another and lesions to a specific focal point would imply direct damage and a degree of diaschisis. Parallelly, the development of multivariate lesion mapping based approaches have created opportunities to study what is referred to as "hidden lesions" of white matter networks. (Forkel, 2020 & Thiebaut de Schotten and Foulon, 2018)

Lesions of white matter pathways and the consequential disconnections are studied using a technique called white matter tractography derived from diffusion-weighted imaging MRI (DWI). This technique measures the diffusion and direction of water molecules, which are altered to varying extents depending on the degree of damage. Tractography has been found to be sensitive to recognizing functional deficits in patients with white matter tract damage. Tractography is most commonly done in association with lesion-symptom mapping methods of functional analysis of white matter tracts. (Forkel at al., 2014; Forkel & Catani, 2018; Forkel & Thiebaut de Schotten, 2020; Forkel, 2020)

In the context of Apraxia, this series of methodologies have been used to understand the network involved in tool use following damage to the brain due to stroke. Voxel based and functional connection based lesion symptom mapping was used to understand lesion sites related to tool use gestures, they found that the disconnection of the inferior parietal lobule, left temporal lobe and ventral temporal cortex caused the behavior deficits associated with tool use gestures (a recognized symptom of ideomotor apraxia). Their findings support evidence about the disconnection of conceptual (related to the temporal areas) and action based representations (related to the inferior parietal area). (Garcea at al., 2020).

As explored above, there are several cognitive and neuropsychological theories and studies dedicated to understanding the broad disorder of Apraxia, its subtypes, and or specific symptoms. A feasible step towards integrating the information to allow the kind of

understanding provided in the study above, was to initiate a meta-analysis exploring the structural and functional correlates of Apraxia, by Niessen et al. (2014) their study evaluated suitable structural and functional studies related to pantomime deficits in Apraxia. The structural and functional studies provided some contrasting neuroanatomical evidence, the structural studies reflected the involvement of frontal, parietal and temporal areas but the functional studies indicated the involvement of parietal areas with or without the involvement of frontal or temporal areas. Their analysis suggested that structural and functional studies contribute to the understanding of the fronto-tempero-parietal network involvement in the pantomime of object use. Future studies will need to clarify inconsistent findings through the use of different approaches for a coherent understanding of the praxis network.

THE PRESENT STUDY

The objectives of our study are to use a multisource approach that allows the use of lesion mapping data from a large stream of studies in the literature to further the understanding of the neural correlates implicated in Ideomotor Apraxia. We did this by conducting a systematic review of the literature on Ideomotor Apraxia whereby we selected all papers published until 2021 with the keyword "Ideomotor Apraxia" in the title or the abstract. Then we used a lesion reconstruction tool to extract the coordinates of lesions in each of the papers in our inclusion criteria. Finally, these were added to a common template, therefore, allowing an analysis that "virtually" included all the papers published so far on this topic. Finally, we analysed the resulting areas to identify significant clusters associated with the symptoms. We used these clusters to derive probabilistic maps of the structural disconnections related to Ideomotor Apraxia. This novel approach allows the cumulative use of structural neuroimaging data that have been collected through the years across several labs in many countries/continents. In such a way and despite the heterogeneous methods and neuroimaging templates used it is possible to have a very comprehensive, albeit not fully precise, view of the pathophysiology related to Ideomotor Apraxia. The methodology used in the study is described in this section.

METHODOLOGY

2.1. Systematic Review

A comprehensive literature search strategy was used to screen through and retrieve articles relevant to our objective. We conducted a systematic review of literature following guidelines prescribed by the Preffered Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The flow of information through the recommended stages that records the number of exclusions, reasons for exclusion, inclusions are reported using the recommended flowchart on the PRISMA guidelines website (https://www.prismastatement.org/PRISMAStatement/FlowDiagram) in Figure 1 at the end of this section.

Protocols are a key feature of systematic reviews as they ensure careful planning and documentation of the process and reduce arbitrariness in decision making when extracting data from primary research like this study intends to (Moher et al., 2015). This section explores key features of the protocols used for all the steps to synthesize a database of studies essential to our objectives.

First, we searched databases like Pubmed, EBSCOHOST, Europe PMC with the keyword: "Ideomotor Apraxia". This search was limited to title or the abstract. The initial database yielded a result of 318 papers. While we did not set a limit on the date of publication, our search . We inserted the information from these papers into an excel sheet with the following 10 headings that served as identifying information. We also established an agreement about the content under each of those headings, some were binary, some were more descriptive. This was to allow us to apply our criteria easily using filters. These are presented in the Table 1.

Table 1: List of columns used to identify studies to be included in the systematic review

Heading(s)	Possible Alternatives	Where to look for the information
Number, Name of Article, Date and Journal of Publication	As Applicable	Abstract, Title.
Type of article	Review; Study; Meta-analysis; Commentary; Other	Title and or Abstract
Age of patients	Average Age of patients in study	Patient Description Table
Handedness	Left; Right	Patient Description Table
Type of Study	patient single case; patients group study; only healthy subjects (no patients)	Title and or Abstract
Number of Patients	Number of patients	Methodology
Control Group	present; absent	Methodology
Type of Control Group	patients; healthy subjects	Methodology
Number in Control Group	Number of participants in the control group	Methodology
Brain Lesion Images	Present; Absent	Images in the paper
Brain Lesion Localization	Present; Absent	Tables reporting results or discussion
Lesion Hemisphere	Left; Right; Both	Abstract and Methodology
Tasks to Assess Ideomotor Apraxia	Reported tests or tasks used	Methodology
Average Months from Lesions	Number of months or days converted to months	Methodology/ Discussion/Table with patient description
Other cognitive tests	As Applicable	Methodology/ Discussion
Measures of Independence such as FIM or NHS	As Applicable	Methodology

Some papers were inaccessible because of licenses that were difficult to procure or subscriptions that were inaccessible. 16 articles were excluded because they were not in English.

As the systematic review was the subject of an internship program within the department the people involved in collecting the initial data set were different from the people who cross checked the database and used it for further analysis. The four students who conducted the check did so independently, and met three times to discuss the discrepancies found in their reading of the papers and the information entered in the database, thus resolving many of the entries initially registered as not applicable or information not available. Disagreements between the students was resolved by going over the papers together.

After a consensus was reached about the content of the database, we began to apply exclusionary criteria relevant to the subject of our study to narrow down our search. Our criteria were that the studies should be limited to:

i. Patients with unilateral brain damage
ii. Ideomotor Apraxia only as a consequence of Stroke or tumors
iii. Availability of neuroimaging data

As a rule, single case studies, reviews, commentaries and studies without neuroimaging data were excluded because the goal of the study was to ultimately perform a statistical analysis using the available lesion mapping data.

All studies in our final database had structural neuroimaging data with cortical and subcortical lesion representations. This included CT Scans and or MRI that were mapped onto standardised templates using procedures recommended by Damasio and Damasio (1989) (Eg. Ietswaart et al., 2001), lesion reconstructions derived from the atlas by DeArmond et al., (1989) (Eg. Haaland et al., 1999) and then computerized; schematic representations of lesions (Eg. Agostoni, 1983), lesion overlays (Eg. Mutha, 2017) and lesion subtraction overlays (Eg. Buxbaum et al, 2005). One of the papers (Giroud & Dumas, 1995) highlighted the MRI features of callosal lesions by representing the same in a tabular form with shading the corresponding lesion location (Anterior, posterior or medial). Another study (Alexander at al., 1992) used a neuroanatomical checklist and a CT atlas (Matsui & Hirano, 1978) to assign values to regions with lesions to mark anterior and posterior lesions with a type of indexing.

In his review of Ideomotor Apraxia, Wheaton (2007) explains, many investigators only study IMA in cases of relatively focal stroke and avoid the confounds of degenerative cases, in which the lesions are likely more widespread and present with complex pathologies, unless adequately evaluated before testing. We did not check for the evaluation before testing and excluded degenerative diseases as a general rule.

The implementation of the above described criteria resulted in the inclusion of 23 studies. We excluded two of these studies. One of the studies was about glioma resections and did not have images pertaining to the lesion for Ideomotor Apraxia (Rossi et al., 2013). The other study did not clearly distinguish between patients with apraxia and other neurological deficits with respect to the lesion mapping image presented in the study (Frenkel-Toledo et al., 2016).

Considering the heterogeneity of the classification of apraxia we conducted another, independent, literature search with different terminology criteria. This search consisted of running keywords “Pantomime” and “Pantomime +Lesions” through the previously used database as well as cross referencing citations which had the word Ideomotor Apraxia in the title. After this search we added 4 more papers to our search, we now had 25 studies in our final database that met all our criteria (Table 2). Two studies from this list were eliminated before the meta-analysis, we will discuss this in the next section.

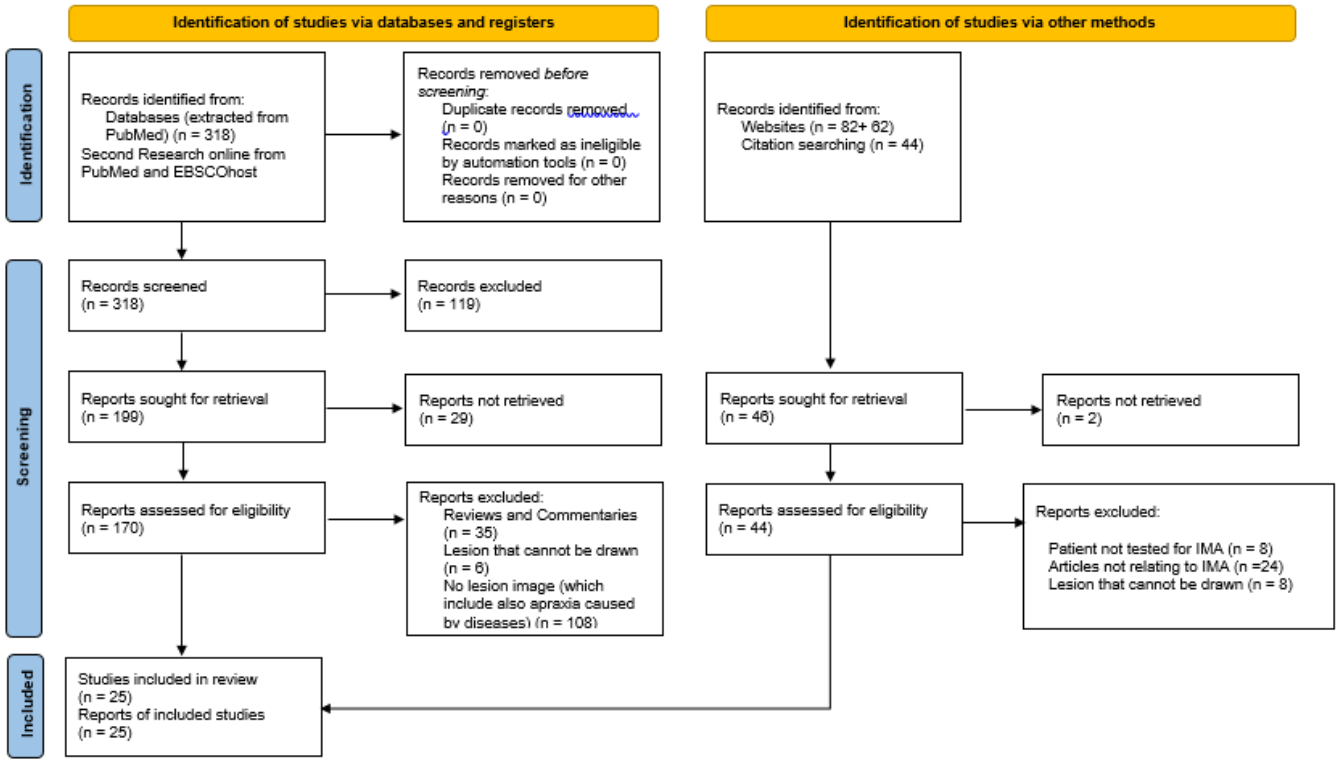
Table 2: Summary of the structural neuroimaging in the final database

N	First Author	Journal/Book	Publication Year	Title	Pathology	Type of lesion images	No. of Patients with Ideomotor Apraxia	Mean Age
1	Mutha PK	J Int Neuropsychol Soc	2017	Motor Adaptation Deficits in Ideomotor Apraxia	Stroke	Overlay Plot (reconstructed from CT and MRI scans)	12	65
2	Bolognini N	Brain	2015	Improving ideomotor limb apraxia by electrical stimulation of the left posterior parietal cortex	Stroke	Individual images (from CT scans)	6	72.16
3	Sunderland A	Brain Cogn	2013	Tool-use and the left hemisphere: what is lost in ideomotor apraxia?	Stroke	Overlay Plot (reconstructed from MRI scans)	18	66
4	Manuel AL	Cereb Cortex	2013	Inter- and intrahemispheric dissociations in ideomotor apraxia: a large-scale lesion-symptom mapping study in subacute brain-damaged patients	Stroke + Tumor	Overlay Plots of VLSM(reconstructed from CT and MRI scans)	150	60.5
5	Mutha PK	Neuropsychologia	2010	Coordination deficits in ideomotor apraxia during visually targeted reaching reflect impaired visuomotor transformations	Stroke	Overlay Plot (reconstructed from CT and MRI scans)	9	62.5
6	Buxbaum LJ	Cortex	2007	Left inferior parietal representations for skilled hand-object interactions: evidence from stroke and corticobasal degeneration	Stroke + CBD	Overlay Plot	20	62.5
7	Ambrosoni E	Arch Clin Neuropsychol	2006	Gesture imitation with lower limbs following left hemisphere strok	Stroke	Superimposed lesions (from CT scans)	35	67.1
8	Buxbaum LJ	Brain Res Cogn Brain Res	2005	On beyond mirror neurons: internal representations subserving imitation and recognition of skilled object-related actions in humans	Stroke	Subtraction plot (from MRI scans)	44	59.5
9	Buxbaum LJ	Neuropsychologia	2005	Deficient internal models for planning hand-object interactions in apraxia	Stroke	Subtraction plot (from MRI scans)	13	53.6
10	Ietswaart M	Neuropsychologia	2001	Memory-driven movements in limb apraxia: is there evidence for impaired	Stroke	Individual images (reconstructed from CT scans)	10	67

				communication between the dorsal and the ventral streams?				
11	Haaland KY	Brain	1999	Spatial deficits in ideomotor limb apraxia. A kinematic analysis of aiming movements	Stroke	Individual images (reconstructed from CT and MRI scans)	10	67
12	Rushworth MF	Neuropsychologia	1997	The left parietal cortex and motor attention	Stroke	Individual images (from templates)	18	56.5
13	Giroud M	J Neurol Neurosurg Psychiatry	1995	Clinical and topographical range of callosal infarction: a clinical and radiological correlation study	Stroke	Individual images (from templates reconstructed from CT and MRI scans)	8	71.5
14	Agostoni E	J Neurol Neurosurg Psychiatry	1983	Apraxia in deep cerebral lesions	Stroke	Individual images (from CT scans)	7	59.5
15	Basso A	J Neurol Neurosurg Psychiatry	1980	Is ideomotor apraxia the outcome of damage to well-defined regions of the left hemisphere? Neuropsychological study of CAT correlation	Stroke	Individual images (from templates reconstructed from CT scans)	48	58.2
16	Jax SA	J Cogn Neurosci	2006	Deficits in movement planning and intrinsic coordinate control in ideomotor apraxia	Stroke	Subtraction plot (from MRI and CT scans)	15	62.9
17	Platz T	Eur J Neurosci	1995	Human motor planning, motor programming, and use of new task-relevant information with different apraxic syndromes	Stroke	Individual Images (from CT scans)	6	Not Specified
18	Alexander MP	Brain	1992	Neuropsychological and neuroanatomical dimensions of ideomotor apraxia	Stroke	Superimposed schematic representations (reconstructed based on CT scans)	55	Not Specified
19	Motomura N	Int J Neurosci	1989	Motor learning in ideomotor apraxia	Stroke	Individual images (Schematic representations from CT scans)	34	62
20	Basso A	Brain	1987	Recovery from ideomotor apraxia. A study on acute stroke patients	Stroke	Individual images (from CT scans and schematic representation)	26	56.7
21	Kertesz A	Brain	1984	Lesion size and location in ideomotor apraxia	Stroke	Superimposed lesion sites(from CT scans)	177	62.9
22	Buxbaum	Brain & Language	2002	Knowledge of object manipulation and object function: dissociations in apraxic and nonapraxic subjects	Stroke	Superimposed lesion sites (from CT scans)	7	60.3
23	Evans	Neuropsychologia	2016	Perceptual decisions regarding object manipulation are selectively impaired in apraxia or when tDCS is applied over the left IPL	Stroke	Overlay Plot (reconstructed from CT and MRI scans)	14	68
24	Haaland	Brain	2000	Neural representations of skilled movement.	Stroke	Overlay Plot (reconstructed from CT and MRI scans)	41	67
25	Hermsdorfer	Brain	1996	Kinematic analysis of movement imitation in apraxia	Stroke	Individual images (reconstructed from CT scans)	20	50.5

Note: The studies highlighted in red were excluded in the meta-analysis. The studies highlighted in yellow were added in the second phase of the literature search.

Figure 1: PRISMA 2020 flow diagram for searches of databases, registers and other sources



Flowchart template taken from PRISMA 2020 statement: an updated guideline for reporting systematic reviews (Page et al.,2021)

2.2 Lesion Mapping & Coordinate Extraction

From the studies in the data base, we either reconstructed the available scan data in the form of CT and/or structural MRI scans using manual delineation into lesion maps or reconstructed the lesion maps from the studies. We used MRIcron for the lesion reconstruction. MRIcron is a cross-platform NIfTI image viewer which can load multiple layers of image while allowing drawing of volumes of interest. Its appeal lies in being an easily accessible, free software which can run on most popular operating systems that allows users to present lesions in terms of images normalized to a standard stereotaxic space. (Rorden et al., 2007). All our reconstructed lesions were on the template ch2.nii.gz

Our reconstruction was classified into three subtypes based on the images in the original studies:

i. Reconstructing the region of the highest overlap in studies of Ideomotor Apraxia
ii. Creating an overlap in the case studies with individual lesion images of patients
iii. Reconstruction of region of subtraction plots from patients with and without apraxia

We will briefly discuss the process adapted for each of these subtypes using one example each. One of the papers in our database also reported bilateral lesions as a control in their study, however, as our focus has been on unilateral lesions and since the data about bilateral lesions in limited and inconclusive in Ideomotor Apraxia, we only reconstructed the lesions from this study, we did not derive coordinates from it. All the lesions reconstructed in this study can be reviewed in the appendix.

Subtype 1: Reconstruction of the region of highest overlap

Studies that presented the voxel based lesion symptom mapping depicted lesion plots in their study. In such cases the reconstruction was simpler, we considered only the region of highest overlap in such studies. In the study by Manuel et al. (2013), a large scale voxel based lesion-symptom mapping analyses was conducted using configural/spatial and body-part-as-object pantomime errors in 81 patients with stroke and 69 patients with tumors. In this study we focused on the configural/spatial pantomime errors, and reconstructed the region of most overlap highlighted in yellow. The study provided the coordinate for the z axis in the MNI coordinate which was used as a guide to ensure precision in the reconstruction. The images in the study have a R/L flip which was taken into account. As this study had two patient subgroups, we reconstructed two sets of lesion images. These are depicted in the figures below as Figure 2(a) and 2(b).

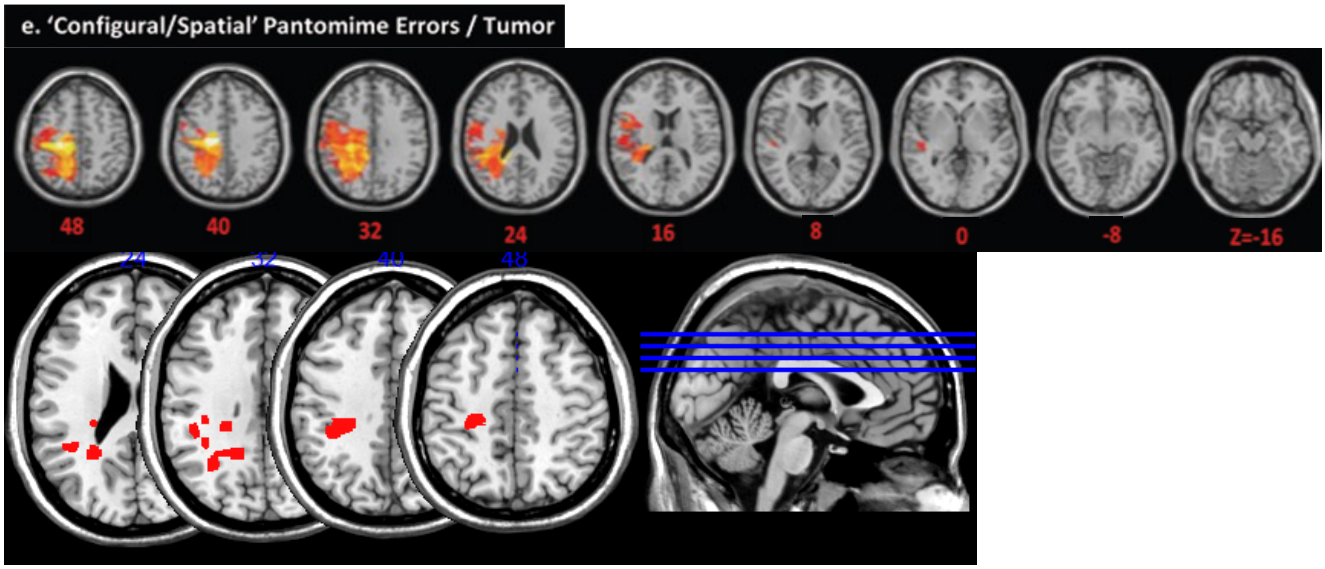


Figure 2(a) The top half of the image is a modified image of the lesion overlay plot for configural/spatial pantomime errors in patients with stroke in the study by Manuel et al., 2013, the highest overlap is depicted in the color yellow. The modification was done to reverse the R-L flip in the original image. The bottom half of the image depicts the reconstructed lesion image for the area of most overlap.

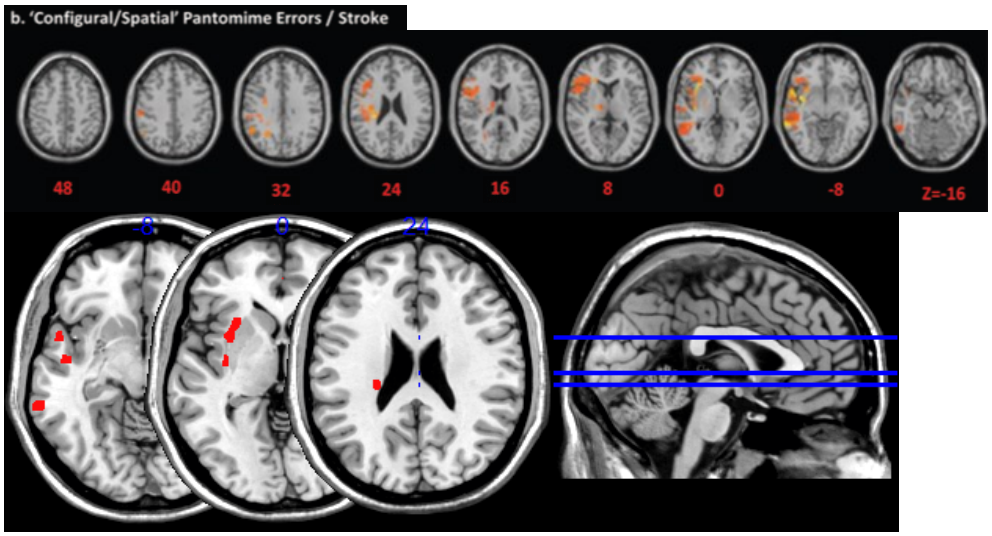


Figure 2(b) The top half of the image is modified lesion overlay plot for configural/spatial pantomime errors in patients with tumor taken from the study by Manuel et al., 2013, the highest overlap is depicted in the color yellow. The modification was to reverse the L-R flip in the paper. The bottom half of the image depicts the reconstructed lesion image for the volume of maximum overlap

Subtype 2: Creating an overlay plot for studies with individual patient images

When a paper contained lesion images of each patient, we created a lesion overlay plot to find the region of maximum overlap of lesions. First, we reconstructed the images from individual patients using the draw function in MRIcron and saved the individual images. Following this, we opened another template, and selected the overlay option, which then imported the individual patient lesion and superimposed the lesions to highlight the region of highest overlap. To ensure visibility of the regions of contrast between high and low overlap we selected an appropriate color scheme and contrast statistic.

As an example we consider the overlay plot constructed for the study by Ietswaart et al. (2001). This study explored the disconnection of the dorsal and ventral streams that may lead to symptoms of Ideomotor Apraxia, included ten patients who had a vascular lesion in the left hemisphere. Of the ten, scans were available for 9 of the patients. These images had a right-left flip like the first image considered. A careful examination of the representation of the scans in these studies suggests that the scans are on two axial planes. As this study did not specify neuroanatomical landmarks or axial planes to locate the lesion, we used the breadth of the ventricles and depth of the sulci visible as reference points. The lesion locations were diverse, some appeared to be focal, others were widespread. Figure 3a, 3b and 3c show outcomes of the each of these steps.

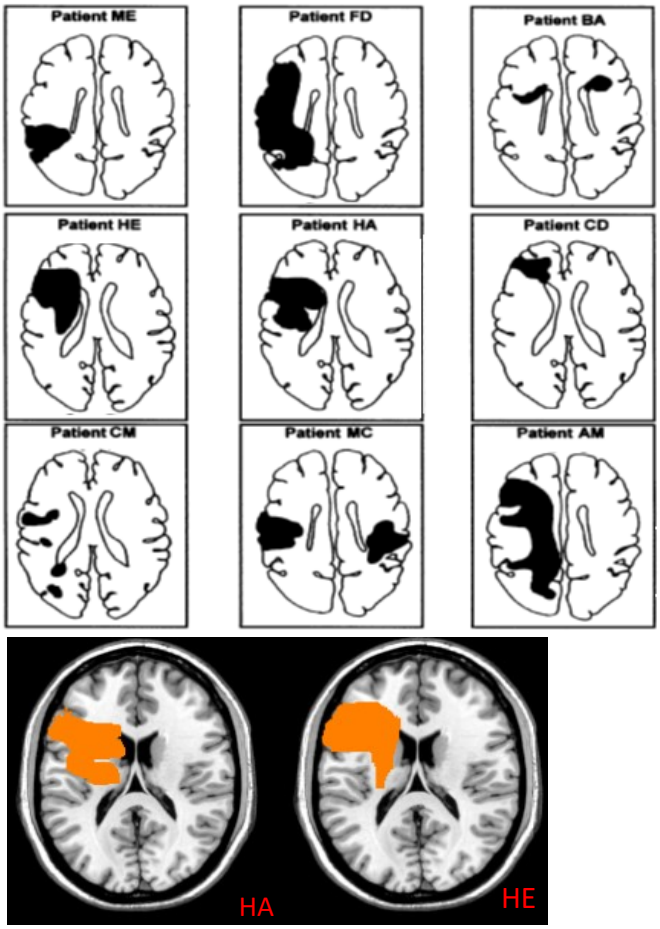


Figure 3a. The top half of the image is a modification of the individual lesions presented in the original study by Ietswaart et al., (2001). The bottom half of the image has two examples of the reconstruction of the lesion images: for patient HA on the left in orange and for patient CD in orange on the right.

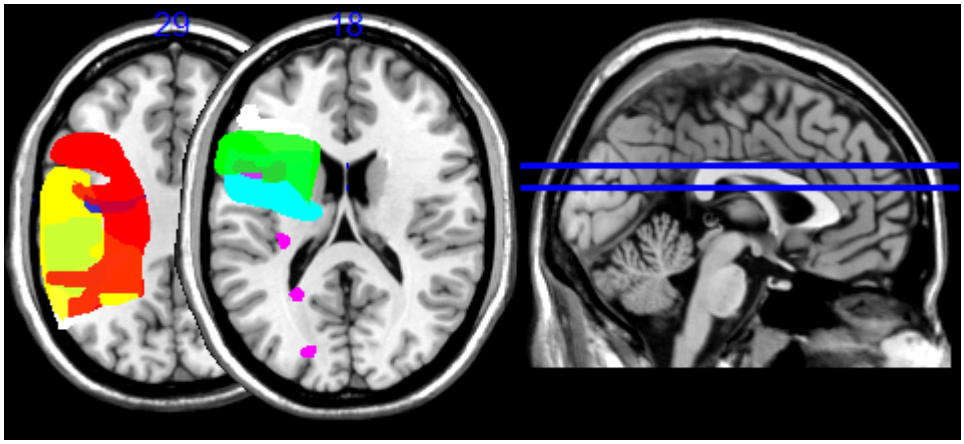


Figure 3b. A multi-slice view of individual lesions overlay. The different colours are selected to highlight the individual lesions

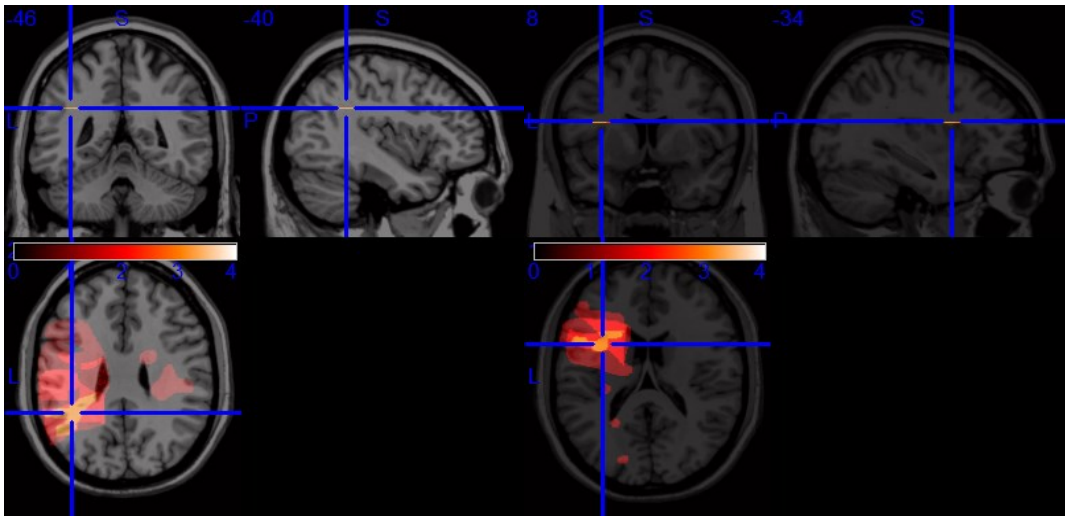


Figure 3c. An overlay plot which presents a gradation of the area of the highest overlap when individual patient lesions are superimposed. As can be noted on the index in the images, the faint red colours show the least overlap, the brighter areas show the highest overlap.

Subtype 3: Reconstruction of volume of subtraction plots between patients with and without Ideomotor Apraxia

Lesion subtraction is a type of voxel-wise analysis where the lesion overlap of patients without a deficit is subtracted from those of lesion overlap maps of patients with the cognitive deficit. Such that only the region of lesions belonging exclusively to the cognitive/behavioral impairment of interest can be deducted. It is a descriptive method. For this example, we consider the paper by Buxbaum et al. (2005), in which 44 patients were studied to test the hypothesis about deficient inferior parietal representations which present as symptoms of Ideomotor Apraxia. Lesioned regions between patients with Ideomotor Apraxia and Left-Hemisphere Cerebro-Vascular Accidents were overlaid. In such cases, the region of relatively higher lesions in our group of interest, i.e, Ideomotor Apraxia indicated by a colour index under the original image were reconstructed on MRIcron after recognizing the closest approximation for the axial slice. We used the size of the ventricles and the intensity of sulci and gyri visible for guidance. Figure 4 shows the original image in the paper alongside the reconstruction.

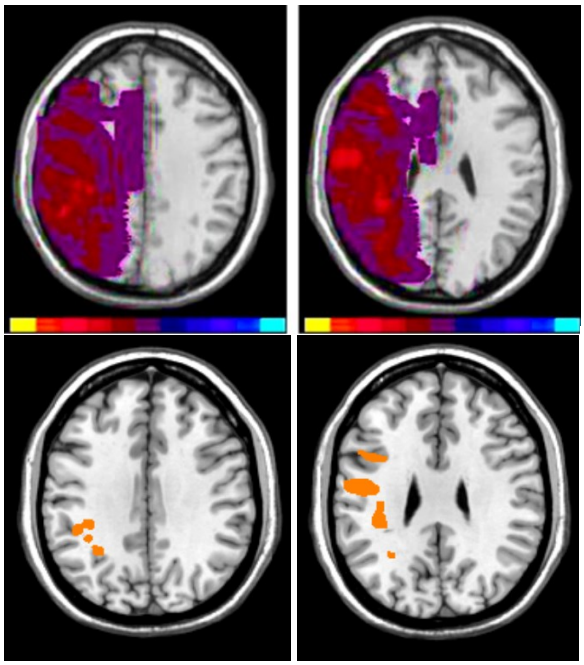


Figure 4. The top half of the image is a modification of subtraction overlay from original study by Buxbaum at al., (2005). The modification was done to address the L-R flip in the original image. The original image was constructed on the ch2 template in MRIcro. The colour index suggests that the brighter shades indicate relatively more lesions in the Ideomotor Apraxia group. The bottom half of the image is the reconstruction corresponding to the available images in the original study using MRIcron.

2.2.1. Extraction of Coordinates

Once we had the region of maximum overlap in each of the studies in our database, we used the toggle cross hair function of MRIcron to recognise the approximate coordinates for the region of maximum overlap. As elaborated above, these were based on lesions either replicated from the study or created from individual images from the study. Enabling the toggle cross hair function displays MNI (Montreal Neurological Institute) coordinates. We attempted to extract one coordinate per maximum overlay, however, depending on the anatomical location/s of lesions, some studies prompted the extraction of multiple coordinates. If we use Figure 3c. as an example, we extracted two coordinates, i.e, -34 8 18; -40 -46 29, keeping in mind the neurologically favoured Right-Anterior-Superior convention.

We acknowledge that the heterogeneity of the lesion representations in our database are not optimal. It is noted that different studies followed different templates for reconstruction such as De Armond et al., (1989) or templates from the U.C Davis reconstruction workbook. Different studies had different criteria for overlap grouping, some studies grouped highest over lesions based on 75-100% overlap (Mutha, 2017) others on 85-100% (Haaland at al., 2000). We only had access to lesion information on specific slices as chosen by the authors of the papers. However, as our goal was to use an approach that allowed us to converge structural neuroimaging data, we had to make several decisions to ensure that we could reconstruct this data on to a uniform template and reconstruct the lesions on axial planes with as much

neuroanatomical accuracy as possible. We will discuss these issues in more detail in the subsequent chapters.

2.3 ALE Meta-Analysis

We used GingerALE version 3.0.2 to perform a quantitative meta-analyses using the coordinates extracted in the MNI space. GingerALE assesses the convergence between activation foci from different experiments. ALE seeks to refute the null-hypothesis that the foci of experiments are spread uniformly throughout the brain (Eickhoff at al., 2012).

Recent modifications in the GingerALE algorithm allow organization of foci by subject groups rather than organization by experiments. This is suggested to be more conservative and appropriate for analyses using Activation Likelihood Estimation(ALE) (Turkeltaub et al.,2012). GingerALE results are driven by the dataset's foci and how they are grouped. GingerALE prescribes a format for writing specifying foci in a .txt file.

It uses the subject information from each foci group to calculate the Full-Width Half-Maximum (FWHM) of the Gaussian Function using methods described by Eickhoff at al., 2009. These probabilities are combined to generate a modeled activation (MA) map for each experiment. The MA maps are calculated by finding the union or maximum across individual focuses's Gaussian. GingerALE treats coordinates as centers of probability distribution, the "true" location of each activation is modelled by the 3-D Gaussian curve. Each of the foci (coordinates) are replaced with a curve which then shows the likelihood of activation within each voxel. In our case the activation peaks would indicate the points of maximum overlap of lesions. The final ALE image is a union of all the MA maps (Eickhoff at al., 2009; Turkeltaub at al., 2012). The voxel wise ALE scores are generated within a mask that uses the convergence across experiments at each gray matter voxel.

The ALE meta-analysis procedure follows three steps.

i. ALE and Testing Significance: Activation Likelihood Values for each voxel across the whole brain is computed and tested to determine the null distribution of the ALE statistic at each voxel.
ii. Thresholding: GingerALE uses the P-Value from the previous step and computes the threshold for the ALE image. At this stage, depending on the methodology and assumptions made, a threshold can be assigned such that any voxel that has P-value image over the threshold is set to 0. The software recommends using conservative

thresholds such as p<0.001 or 0.0001, or the use of False Discovery Rate. However, as these methods are not optimal, GingerALE has two other thresholding algorithms, Family-wise error (FWE) and cluster level inference. These algorithms simulate random data sets using similar characteristics as the data input. The FWE corrected threshold is set such that no more than a specified fraction of distribution exceeds that value; these thresholds are more conservative so 5% of random studies is recommended (p<.05).

iii. Cluster Analysis: For the cluster level inference, GingerALE finds adjacent volumes above the set threshold and tracks the distribution of the value, p<0.001 as a cluster forming threshold and 0.05 for cluster level inference are recommended. The cluster statistics include volume, bounds, weighted center, and the locations and values at peaks within the region. The cluster statistics also include a table of the number of activations from each foci group that fall in the cluster.

All images produced by GingerALE are in the NIfTI format. We performed a single dataset analysis using the cluster level inference in the MNI-coordinate space with a cluster level of 0.05, threshold permutation of 5000 and uncorrected p-value of 0.001, we used a conservative small mask size. The minimum chosen cluster size was set at 840mm^3.

The data we used in the GingerALE input file is presented in Table 5. GingerALE requires a .txt file in which the x, y and z coordinates separated by a space are written under the name of the author, year of publication and the number of subjects in the study on consecutive. If a study had two groups, they were mentioned separately and treated as two studies. All non-coordinate data is entered with a //. GingerALE allows us to specify the reference space as the first line in the input document. We specified that our coordinates were in the MNI space. GingerALE also checks that the reference space matches the foci space and makes changes if needed.

Using the information from our database presented earlier, we created another table to specify the number of patients with Ideomotor Apraxia for whom the imaging data was available. We carefully cross checked this information to avoid errors in our analysis. At this stage, we chose to exclude two studies from the database.

We excluded the study by Platz et al. (1995), as it had images for just one patient. The other study by Basso et al. (1980) represented localized lesions using gridlines divided into 60 columns antereo-posteriorly. Compared to the other studies in the database, we could not

estimate the lesion demarcations on the axial plane, considering the lesion reconstruction is based on approximations, we decided to err on the side of caution and exclude the coordinates from this study for the meta-analysis.

2.4 BCB Toolkit

The final part of our analysis was to run the clusters derived from the meta-analysis through the Brain Connectivity & Behaviour (BCB) toolkit v.4.0.0 (http://www.brainconnectivitybehaviour.eu), to create probabilistic maps of the structural disconnections of clusters derived from our regions of interest. For the purpose of our study, we used the Tractotron and Disconnectome map functions of the toolkit, which are available as standalone versions and allow us to study the impact of lesions.

Tractotron provides a probability and proportion of disconnection for almost all known tracts. The tractotron maps lesions from each of the clusters onto tractography reconstructions of white matter pathways obtained from a group of healthy controls (Rojkova et al., BSF 2015). The severity of the disconnection is then quantified by measuring the probability of the tract to be disconnected. (Thiebaut de Schotten et al., 2014). The results from the analysis are exported as excel files.

Disconnectome maps are generated by using a set of 10 healthy controls' (Rojkova et al., BSF 2015) diffusion weighted imaging datasets to track fibres passing through each lesion. For each participant tractography is estimated as indicated by de Schotten. (Thiebaut de Schotten et al., 2011). Patients' lesions in the MNI152 space are registered to control native space using affine and diffeomorphic deformations (Klein et al., 2009; Avants et al., 2011) and subsequently used as seed for the tractography in Trackvis (Wang et al., 2007). Tractographies from the lesions are transformed in visitation maps (Thiebaut de Schotten et al. 2011), binarised and brought to the MNI152 space using the inverse of precedent deformations.

Finally, a percentage overlap map is produced by summing at each point in MNI space the normalized visitation map of each healthy subject. Hence, in the resulting disconnectome map, the value in each voxel takes into account the inter-individual variability of tract reconstructions in controls, and indicates a probability of disconnection from 0 to 100% for a given lesion (Thiebaut de Schotten et al. 2015). The lesion file output from GingerALE was used to generate the disconnectome map.

RESULTS

5.1 Lesion Mapping and Coordinate Extraction

We extracted 34 coordinates (foci for meta-analysis) after reconstructing lesion maps from the 23 structural neuroimaging studies on Ideomotor Apraxia. There were 541 patients across the studies. This information was used to create a Ginger ALE input file to derive clusters with maximum lesion overlap. All the reconstructed lesion images focusing on the coordinates can be found in the Appendix. From two of the papers in the database, we derived two sets of coordinates based on the sub-groups in the paper. These are entered as different "experiments" in GingerALE, we had a total of 25 entries for the meta-analysis. These are recorded in Table 3.

Table 3: Coordinates extracted from studies in the final database.

N	Article	MNI Coordinate(s)	No. of Patients	N	Article	MNI Coordinate(s)	No. of Patients
1.	Mutha, 2017	-48, -21, 12	12	**14.**	Giroud, 1995	0 11 20	8
2.	Bolognini, 2015	-35-21,26	6	**15.**	Agostoni, 1983	-29 -12 1	7
3.	Sunderland, 2013	-54 -34 24				18 -14 1	
		-30 1 22		**16.**	Jax, 2006	-47 -39 24	15
		-13 -90 1	8	**17.**	Alexander, 1992	-39 6 23	28
4.	Manuel, 2013	-67 -41 -8				-49 -51 26	
		-53 6 -8		**18.**	Motomura, 1989	-31 -38 24	
		-30 12 0	81			-27 14 16	5
5.	Manuel, 2013	-34 -33 40	69	**19.**	Basso, 1987	-39 11 18	
6.	Mutha, 2010	-47 1 19	9			-44 -7 16	26
7.	Buxbaum, 2007	-48 -49 27	16	**20.**	Kertes, 1984	-26 -5 26	9
8.	Ambrosoni, 2006	-49 15 -13		**21.**	Buxbaum, 2002	-43 -12 37	
		-55 -11 40	11			-52 -50 -2	7
9.	Buxbaum, 2005	-49 -10 30		**22.**	Evans, 2016	-32 -14 25	8
		-40 -39 34	44	**23.**	Haaland, 2000	-55 20 20	41
10.	Buxbaum, 2005	-47 -38 51	13	**24.**	Haaland, 2000	-52 32 20	41
11.	Ietswaart, 2001	-34 8 18		**25.**	Hermsdorfer, 1996	-27 0 17	20
		-40 -46 29	9				
12.	Haaland, 1999	-39 -15 4	10				
13.	Rushworth, 1997	-35 -17 12	9				

5.2 Meta-Analysis

The random-effects inference from GingerALE is based on the above-chance convergence between different studies. Results were corrected for multiple comparisons using the false discovery rate (FDR) as is standard in GingerALE. While setting thresholds for the cluster analysis we used uncorrected P<0.001 cluster-forming threshold and 0.01 for cluster-level inference. For analyses using FDR, a recommended cluster size is included in the statistics. This volume is calculated using the false discovery rate and the total volume above the threshold. The resulting minimum volume will remove any cluster that was smaller than the allowed false positives, leaving clusters that should contain true positives. We used a conservative mask size.

Two significant clusters were found at the chosen minimum cluster threshold of 840mm^3, both clusters were located in the left hemisphere. Cluster 1 of 2096 mm^3 was located from MNI coordinates -44, -6, 14 to -24, 14, 26 with 2 peaks and a maximum ALE value of 0.0156 at -38, 8, 20. This cluster was located in the frontal and sub-lobar region. Cluster 2 of 1728 mm^3 was located from coordinates -52, -54, 22 to -32, -30, 42 with 4 peaks and a maximum ALE value of 0.0166 at -48, -50, 26. This cluster was located in the parietal, temporal and sub lobar regions. These clusters are visualized in figure 5.

As the BCB toolkit presents its output on an MNI 152 template, we use this template to visualize all our results.

Table 4: Cluster-wise results of meta-analysis

Cluster	X	Y	Z	ALE	P	Z	Hemisphere	Lobe	Gyri
1	-38	8	20	0.0153983	3.92E-07	4.9391923	Left	Frontal Sub-Lobar	Sub-Gyral, Extranuclear, Insular, Pre-Central Gyrus
1	-28	0	18	0.0123438	5.49E-06	4.3968425	Left		
2	-48	-50	26	0.0165501	1.29E-07	5.152435	Left	Temporal	
2	-40	-40	34	0.0109108	1.65E-05	4.1513586	Left	Parietal	Inferior Parietal Lobule, Supramarginal Gyrus, Sub-Gyral, Superior Temporal Gyrus, Insular
2	-34	-34	40	0.0101553	3.36E-05	3.9859002	Left	Parietal	
2	-48	-38	24	0.0091153	1.27E-04	3.6591754	Left	Sub lobar	

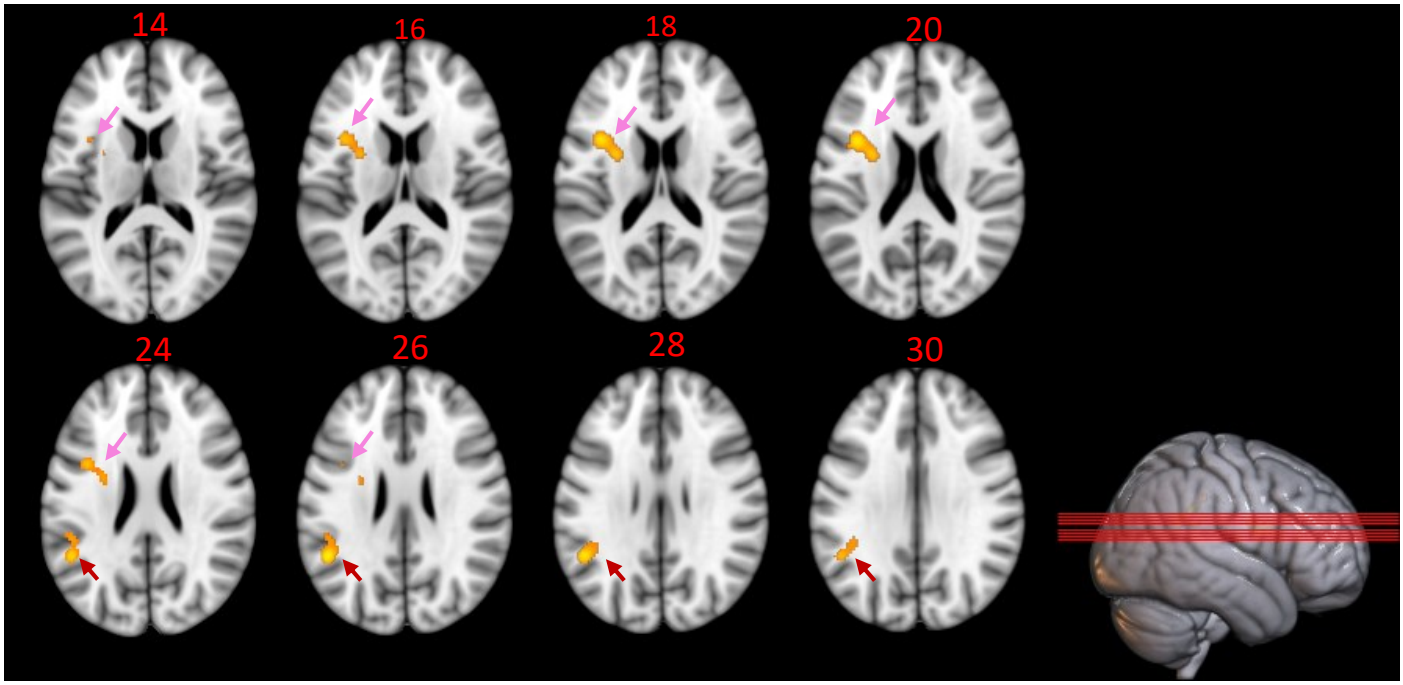


Figure 5: Axial view of selected slices with both clusters from the meta-analysis visualized on a MNI152 template in MicroGL. The numbers above the slice are the respective coordinate of the z axis. The pink arrows indicate the anterior cluster, the red allows indicate the posterior cluster.

5.3. Tractotron and Disconnectome Map

The probability of white matter disconnections for the clusters related to the maximum overlap of lesions extracted from our database was estimated. The software uses a normalized MNI 152 template to analyze the white matter disconnections, we use this template to visualize our results. For each tract, the software uses a probability between 1-0 to quantify the disconnection. This allows us to draw an inference about the impact of a lesion. A tract is considered to be involved when the probability of involvement for voxels in the tract is more than 50% (Fulon et al., 2018). 15 tracts were revealed to have a disconnection probability of over 0.5. Table 5 provides a summary of the probability of disconnection associated with white matter tracts. To be comprehensive we include the probability of all tracts higher than 0. Only the involvement of significant tracts (over 50% or 0.5) is discussed in the next section. Figure 6 shows the white matter tracts with disconnection probabilities in the analysis.

Table 5: List of tracts with probability of disconnection above .5 (50%)

N	Tract	Probability
1	Arcuate Long Segment Left	1.00
2	Arcuate Posterior Segment Left	1.00
3	Cortico Spinal Left	1.00
4	Frontal Aslant Tract Left	1.00
5	Pons Left	1.00
6	Superior Londgitudinal Fasciculus II Left	1.00
7	Superior Londgitudinal Fasciculus III Left	1.00
8	Fronto Striatal Left	0.98
9	Corpus callosum	0.9
10	Anterior Thalamic Projections Left	0.9
11	Frontal Inferior longitudinal Left	0.87
12	Arcuate Anterior Segment Left	0.8
13	Fronto Insular tract4 Left	0.78
14	Fronto Insular tract3 Left	0.68
15	Frontal Commissural	0.6
16	Handsup U tract Left	0.38
17	Handinf U tract Left	0.26
18	Fronto Insular tract5 Left	0.22

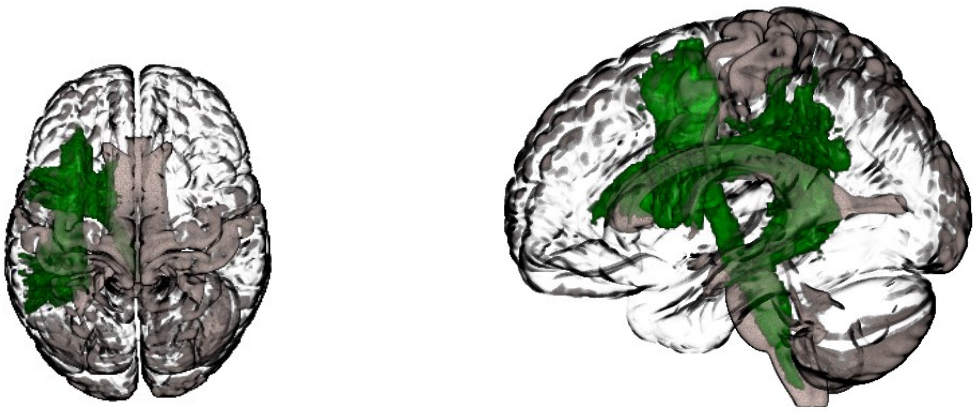


Figure 6: Visualization of the tracts in the left hemisphere with disconnection probabilities significant to Ideomotor Apraxia from the study using a glass brain rendering in MicroGL. The tracts with disconnection probabilities are represented in green. Some important neuroanatomical landmarks are coloured gray.

We superimposed the output from both analyses so we can take a look at the significant clusters in the study relative to some of the white matter tracts with varying probability of disconnection in the study.

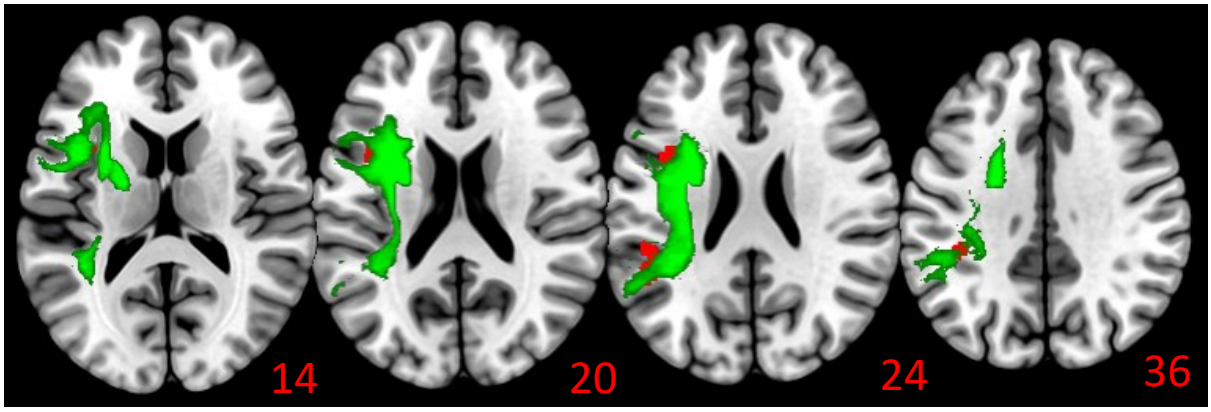


Figure 7: Selected Axial slices of superimposed cluster images and white matter tracts with disconnection probabilities. The clusters are coloured in red while the white matter tracts with disconnection probabilities between the two clusters are indicated in green.

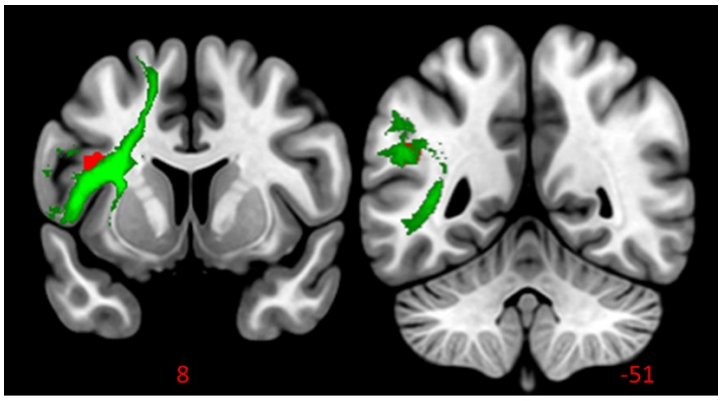


Figure 8: Selected coronal slices of superimposed cluster and white matter tracts with disconnection probabilities. The images are selected to highlight the anterior and posterior cluster from the meta-analysis. The clusters are coloured in red while the white matter tracts with disconnection probabilities

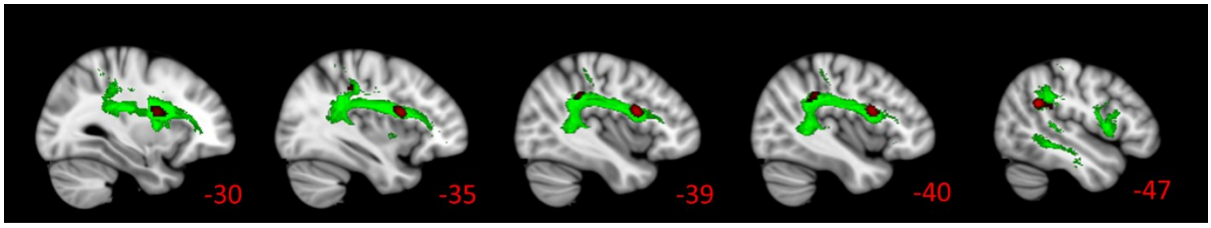


Figure 9: Selected sagittal view slices of superimposed cluster images and white matter tracts with disconnection probabilities. The clusters are coloured in red while the white matter tracts with disconnection probabilities between the two clusters are indicated in green.

We performed the tractotron analysis and generated disconnectome maps using separate files of the clusters revealed by the GingerALE, this gives us a clear visualization of the tracts associated with both the clusters revealed in the meta-analysis. Selected slices showing this are shown in figure 10.

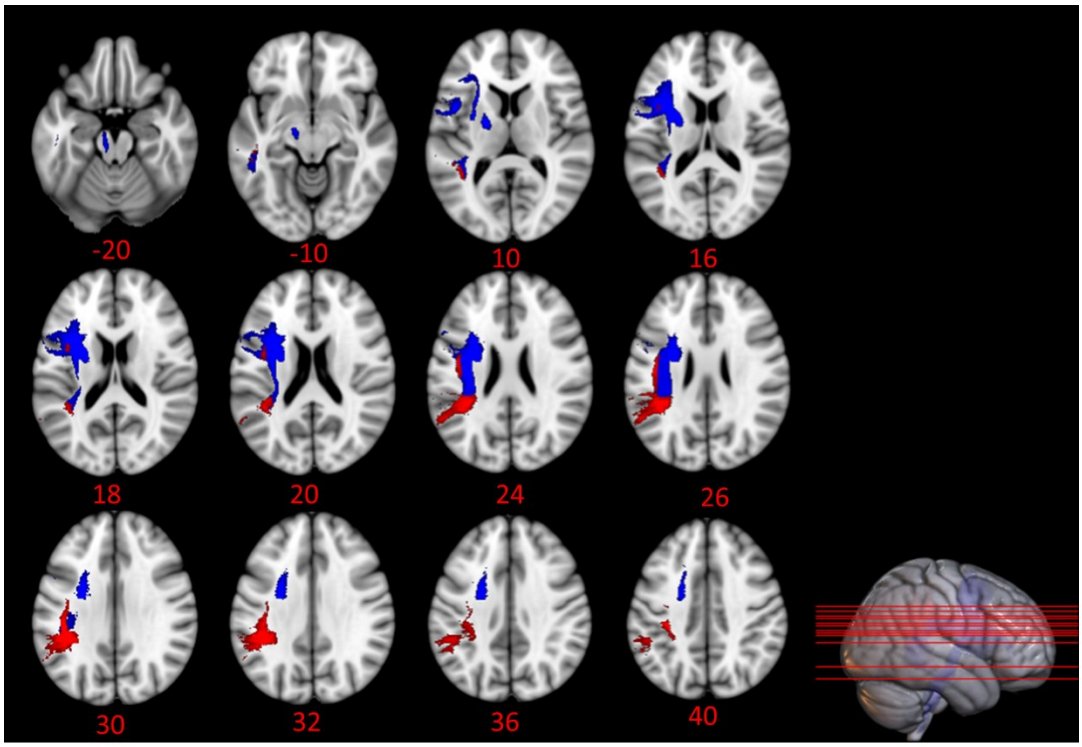


Figure 10: Selected axial slices of white matter tracts with disconnection probabilities. The tracts coloured blue are associated with Cluster 1, the tracts that are coloured red and associated to Cluster 2.

Table 6: List of tracts with probability of disconnection above .5 (50%) from analysis of Individual Clusters.

Tract	Cluster 1 (Anterior)	Cluster 2 (Posterior)
Anterior Thalamic Projections Left	0.9	0
Arcuate Anterior Segment Left	0.66	0.8
Arcuate Long Segment Left	0.9	1.00
Arcuate Posterior Segment Left	0	1.00
Corpus callosum	0.9	0.76
Cortico Spinal Left	1.00	0
Frontal Aslant Tract Left	1.00	0
Frontal Commissural	0.6	0
Frontal Inferior longitudinal Left	0.87	0
Fronto Insular tract3 Left	0.68	0
Fronto Insular tract4 Left	0.78	0
Fronto Striatal Left	0.98	0
Pons Left	1.00	0
Superior Londgitudinal Fasciculus III Left	1.00	1.00
Superior Londgitudinal Fasciculus II Left	0.92	1.00

GENERAL DISCUSSION

In this study, we propose a cumulative approach to studying the neural correlates of Ideomotor Apraxia. Through a systematic literature review, we narrowed down a set of 25 structural neuroimaging studies that used heterogeneous templates to report lesions associated with Ideomotor Apraxia. The novelty of our study is the proposition of a method that could potentially allow studying various sources of data to further our understanding of the pathophysiology of various neurological conditions. We used a 3-D lesion reconstruction software, MRIcron for mapping lesions reported in the 25 studies. A meta-analysis of the coordinates from these papers revealed an approximately medial-anterior and a lateral-posterior cluster. Broadly speaking, this corresponds to the involvement of fronto-parieto-temporal damage in Ideomotor Apraxia.

Both clusters had contributions from 6 papers each from the database. Two of these papers contributing one coordinate each to either clusters (Ietswaart et al., 2001, Alexander et al., 1992). That is not to say that the significant coordinates from one cluster were excluded in the other, but that the coordinates that made more statistically significant contributions after implementing our rather conservative threshold in each of the clusters are listed.

In the papers contributing to the first cluster, were studies involved in studying tool use and studying dissociation between the simple and complex movements in apraxia. Patients in these studies had frontal cortical lesions (Basso et al., 1987; Sunderland et al., 2013), lesions of dorsolateral frontal lobe, frontal pre-motor cortex, the most anterior paraventricular white matter around and above the frontal horn, head of caudate nucleus, putamen, lesions in the pre-rolandic and post-rolandic gyri from the sylvian fissure, the white matter deep to rolandic cortex (Basso et al., 1987; Alexander et al., 1992), lesions of the superior and inferior parietal lobe including the supramarginal gyrus and angular gyri (Sunderland et al., Ietswaart et al., 2001; Kertesz et al., 1984; Alexander et al., 1992), motor association cortex (Ietswaart et al., 2001 Alexander et al., 1992) One of the papers reported an unusual lesion location in the left inferior temporo-occipital and small splenial infarction caused by left posterior cerebral artery occlusion. (Kertesz, 1984).

From these papers, for cluster one the significant contributing lesions (activation peaks) were located in the frontal lobe (60.3%) and sublobar areas (39.7%). Distributions of gyral lesion locations were seen in sub-gyral (59.2%), extra nuclear (36.6%), insular (3.1%) and pre-central gyrus (1.1%).

The papers contributing to the second cluster included lesions in the inferior, parietal and temporal areas. Lesions included left inferior parietal region (Manuel et al., 2013; Buxbaum., 2005; Buxbaum, 2007; Jax, 2006) supramarginal and angular gyri (Manuel at al., Alexander et al., 1992), posterior superior temporal lobe (Buxbaum 2005., Buxbaum 2007., Alexander et al., 1992), One of the paper also reported lesions in the occipitotemporal area (Buxbaum, 2007) and the temporal isthamus (Alexander et al., 1992).

Cluster two had significant contributing lesions in the parietal lobe (55.6%), temporal lobe (35.6%) and sublobar regions (7.9%). Significant lesions were located in the inferior parietal lobule (30.1%), supramarginal gyrus (25%), sub-gyral (19%), superior temporal gyrus (18.1%) and insular gyrus (7.9%).

These results suggest a cortical and a subcortical involvement in our subset of studies on Ideomotor Apraxia. Congruent to our analysis, ample evidence supports the involvement of damage to inferior parietal lobule and associated supramarginal gyrus and pre-central gyrus in deficient praxis and by extension in relation to ideomotor Apraxia (Wheaton & Halett, 2007; Buxbaum, 2001). Our findings seem consistent with Heilman's model that emphasizes the importance of frontal and parietal cortex as well as the view that subcortical parietal damage to connecting fibres play a role in Ideomotor Apraxia (Heilman et al., 1982; Geshwind, 1965). Several EEG and fMRI studies with healthy subjects have also established evidence for a coherent network in self-paced movements that involve a parietal-premotor-motor network. (Moll et al.,2000; Wheaton et al., 2005) Ideomotor Apraxia deficits have additionally been attributed to a fronto-parieto-temporo network with separate dorsal and central white matter connections. (Goldenberg, 2009)

As such our findings remain congruent with literature that focus on large and small lesions attributed to Ideomotor Apraxia, however, they also reveal significant contribution from lesions of subcortical structures and white matter tracts, which have been a point of disagreement in literature. (Leiguarda, 2000; Haaland et al., 2000).

The results from the disconnectome allow a more dynamic understanding of the clusters from the meta-analysis as we have a clearer indication of the lesions in the white matter tracts of the sub-lobar regions

The disconnectome maps reveal the highest probability (1 or 100%) for white matter disconnection in the Left Arcurate Segment, Cortico spinal tract, frontal aslant tract, pons, and

superior longitudinal fasciculi. These tracts connect the temporal and inferior parietal areas to the frontal cortex. Fronto Striatal Left, Corpus callosum, Anterior Thalamic Projections Left, Frontal Inferior Longitudinal Left, Arcuate Anterior Segment Left have been had between 80%-90% disconnection probabilities. These fibre tracts are noted to be structures that connect posterior structures to anterior regions and consist of lateral pathways and consist of frontal interlobal association tracts (Rojkova et al., 2015). Increased left inferior fronto-striatal activation are observed during error monitoring (Criaud et al., 2020); the anterior thalamic projections receive projections from sub-thalamic nuclei and connect to anterior structures like orbitofrontal cortex; the inferior longitudinal fasciculus are long range associative pathways connecting occipital and tempero-occipital areas to the anterior temporal regions; the anterior arcuate segment is a lateral pathway connecting inferior parietal cortex and broca's area. (Catani et al., 2005).

The lesion data in our studies comes from hospitalized patients in clinical studies, some, with co-morbid motor deficits which might explain the involvement of cortico-spinal tract in our finding, however, where possible, we used subtraction overlays where patients with identical damage without ideomotor apraxia are used as control from which we were able to derive lesions belonging specifically to the pathophysiology of Ideomotor Apraxia.

Probabilities of disconnection between 60%-78% were noted for Fronto Insular tract4 Left Fronto Insular tract3 and Left Frontal Commissural. The fronto-insular tracts link respectively the pars orbitalis or BA47, the pars triangularis or BA45 (Rojkova et al., 2015). The insular gyrus is found to contribute to both clusters of lesions located in the meta-analysis. The insula has been associated to connecting the fronto-parietal mirror neuron system to the limbic system, apparently connecting and perhaps plays a role in gesture imitation (Iacoboni & Dapretto, 2006). Parcellations superior and anterior to the insula have recently been noted as a subdivision of the region classically located as Brodmann Area (BA) 44, as an area of debated necessity to transitive gestures (O'Neal at al., 2021). The frontal commissural pathway is a small fibre bundle closely located to the corpus callosum, the damage associated to the pathway could perhaps be an extension of lesions to the corpus callosum.

When the anterior and posterior clusters are analysed separately using the tractotron and disconnectome, we find that white matter tracts with the highest probability common between the two clusters are Arcuate Anterior Segment Left, Arcuate Long Segment Left, Corpus callosum, Superior Longitudinal Fasciculus III Left and the Superior Longitudinal Fasciculus

II Left. We can infer that these results suggest a disconnection of these tracts between the anterior and posterior cluster. Except for the corpus callosum, these are ipsilateral fibres connecting frontal, temporal and parietal areas. The Arcurate Anterior Segment connects the inferior parietal lobe to Broca's Area. The Superior Longitudinal Fasciculus II connects the supramarginal gyrus with the dorsal precentral gyrus and the caudal middle frontal gyrus and the Superior Longitudinal Fasiculus III connects the inferior frontal gyrus with the ventral pre-central gyrus. These findings re-emphasize the central role of the inferior parietal lobe in Ideomotor Apraxia. These fasciculi have been associated with the angular gyrus projecting towards the frontal gyri and tempero-parietal junction connecting the inferior frontal gyrus respectively (Thiebaut de Schotten et al., 2011; Janelle et al., 2022).

Broadly speaking, the largest disconnection probabilities are located in fibre tracts associated to some lateral temporal-posterior parietal-inferior parietal and subcortico-frontal connections, these are in accordance to a recent study that attempted to find a praxis subnetwork. This study assessed a 101 patients with left hemisphere stroke for the ability to perform meaningful gestures including pantomime of tool use and communicative gestures. They used diffusion tensor imaging and fractional anisotropy topographies to study white matter disconnections and connected Ideomotor Apraxia to a pathology of a densely connected network of white matter tracts in frontal, temporal and parietal networks (Rosenzopf et al., 2021).

These findings are consistent with recent findings that Ideomotor Apraxia may arise in part from the disconnection of the conceptual representation in the temporal lobes from skilled action production of the inferior parietal lobe. Disconnections between the temporal and parietal lobe are also related to tool use gesture errors, which was a frequent measure of Ideomotor Apraxia in the papers we considered (Garcea at al., 2020). These studies taken together also correspond to the suggestion that a Parietal-Inferior-to Superior Tract divided between the supramarginal gyrus, angular gyrus and the superior parietal lobe might prevent the transfer of information about visual orientation of objects to prevent efficient selection of behaviour may contribute to the deficits in Apraxia (Catani et al., 2017).

This evidence is in anatomical accordance with cortical lesion data in apraxia patients, and suggests that praxis is not defined best by discrete areas of activation but rather by dynamic relationships across multiple areas (Wheaton & Hallett, 2007). The findings of disconnections short and long fibre connections in our study agree with a recent, reassuring trend in literature

to identify sub-networks associated to praxis instead of focusing on delineated localised lesions (O'Neal et al., 2021).

As with most studies that use pre-existing literature, we were limited in access to information that was filtered and processed by the authors according to the aims of their studies. The outcome of our study is also limited by the tasks used in the studies to differentiate between patients with and without apraxia (ideomotor). The use of different neuroanatomical atlases in our data source also means that our reconstruction may have excluded certain coordinates at the border of different anatomical labels. However, this is a general limitation of lesion mapping methods (Moore, 2015).

Our method of controlling this variability was limited to ensuring the use of the phrase Ideomotor Apraxia in the studies that we selected into our database and using conservative thresholds and masks in our analyses. In our study we focus only on the disconnections in the left hemisphere, however, considering the possibility of the involvement of commissural pathways, possible evidence from right hemisphere and bilateral lesions might be considered on other studies.

We did not control for age or the time elapsed between stroke and obtaining the lesion imaging data some of the deviations in our observation from literature might also be a function of plasticity or re-organization of brain associated with old age, or rehabilitation after stroke.

For lesion mapping, we could only access the slices that were presented in the study, most studies followed the Damasio and Damasio (1898) template but some other templates were also used. However, despite these considerations, our findings were able to demonstrate a possibility of reconciling neuroimaging data from various data sources. We recognise that several of our trade offs were not optimal, however, the novelty of our study was to propose a method that would allow the integration of heterogeneous findings from literature using a cumulative approach. We hope that in an inclusive and more accessible research environment, access to all lesion mapping data from original studies would allow for more precision and inclusion of a broader range of studies. This kind of an integration could also facilitate exploration of different models of Ideomotor Apraxia.

CONCLUSION

In this study we used a systematic literature review of papers on Ideomotor Apraxia in patients with unilateral, left brain damage as a result of stroke or tumors. We screened a total of 318 papers from which we created a database of 25 papers. Each of these papers had structural neuroimaging data including CT and or MRI scans and lesions related to the brain damage. We extracted the coordinates of the regions with maximum overlap of lesions in each of the papers and derived clusters using a Ginger ALE meta-analysis. Our analysis revealed a medial-anterior cluster corresponding to the frontal lobe and a lateral-posterior cluster in the parietal and temporal lobes. Both clusters included lesions of the subcortical area. These clusters were analysed using a brain behaviour connectivity toolkit to create disconnectome maps of white matter tracts with the highest probability of disconnection associated with these clusters. This revealed highest disconnection probabilities of long range and short fibers connecting the parietal, temporal and frontal lobes. Our findings are consistent with new trends in the literature on the praxis network. Through our study, we proposed a method to use heterogeneous structural neuroimaging data from a variety of clinical studies to derive a comprehensive understanding of the anatomy associated with Ideomotor Apraxia.

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APPENDIX

Total Number of Studies: 23

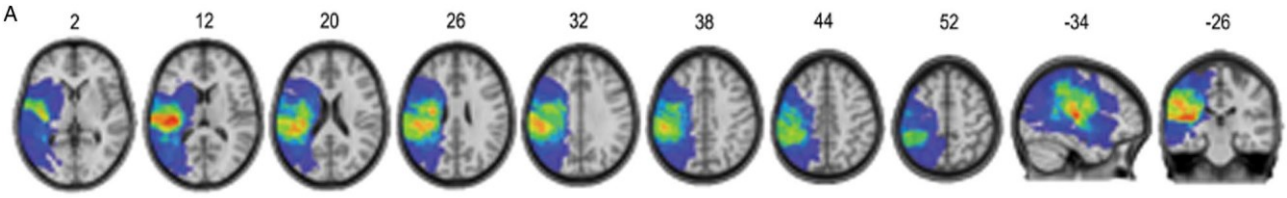
Note: The original images are from the papers in the database which

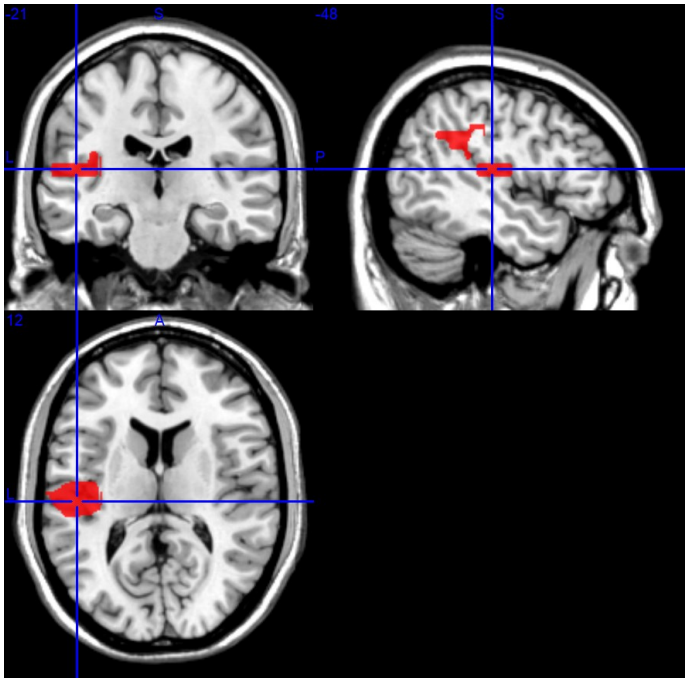
The Subject number refers to the number of subjects for whom the imaging data is available.

1. //Mutha, 2017: Healthy, Nonapraxic Vs. Apraxic

//Subjects=12

Coordinate(s): -48 -21 12

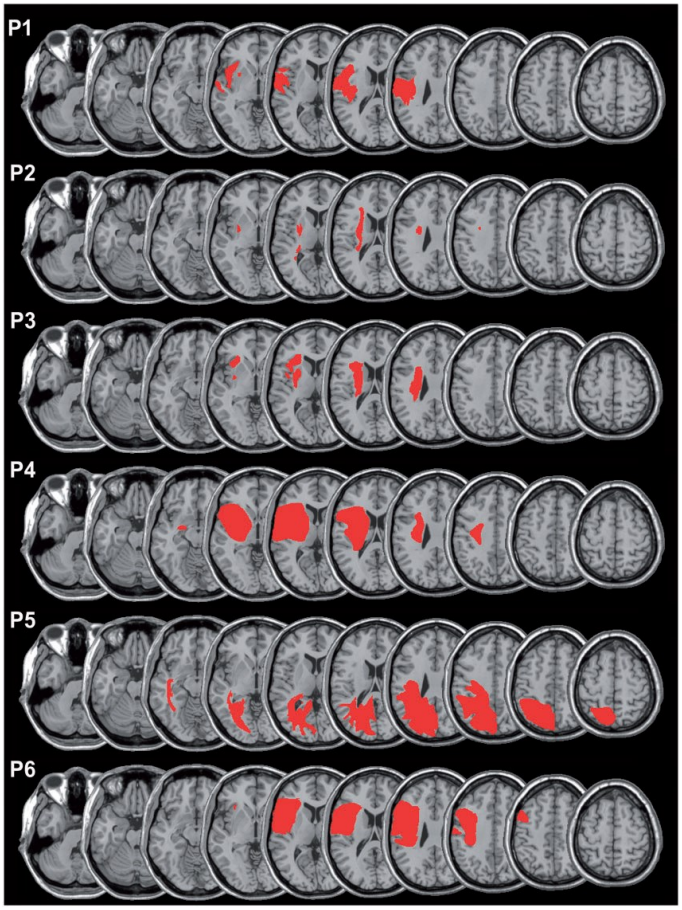


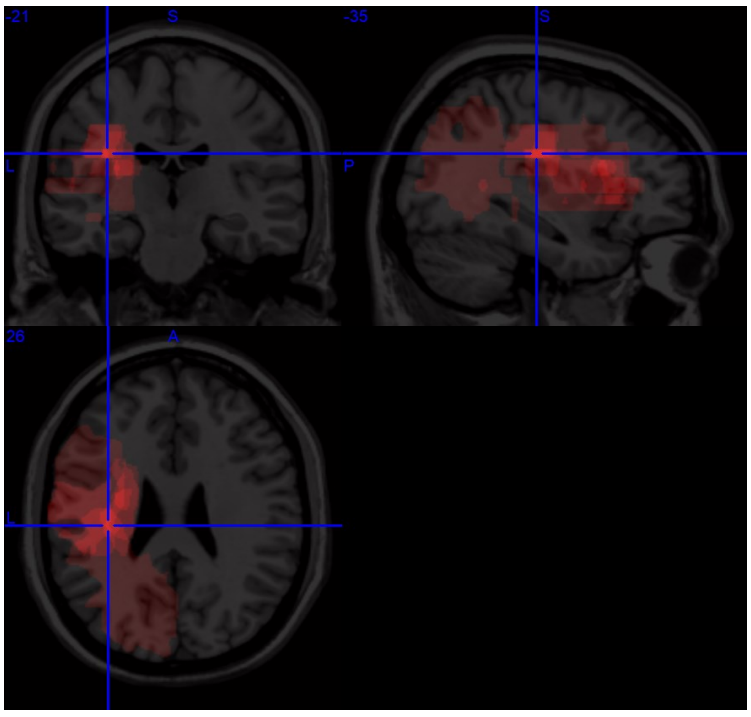


2. //Bolognini, 2015: Healthy Vs. Apraxia

//Subjects=6

-35 -21 26





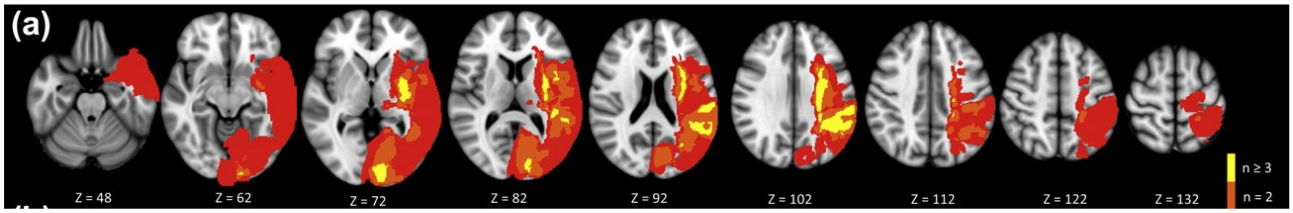
3. //Sunderland, 2013

//Subjects=8

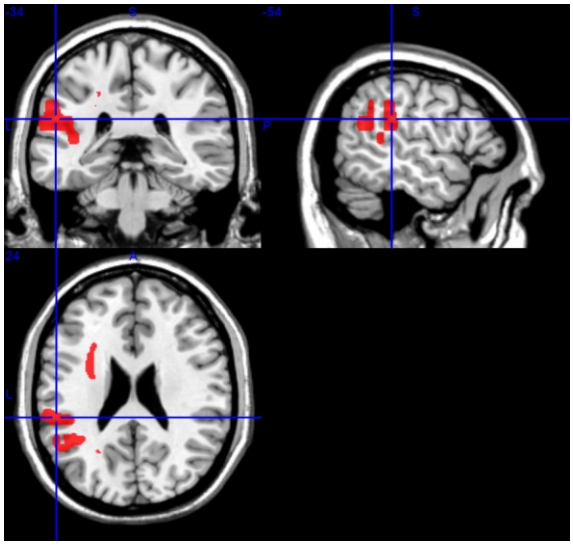
-54 -34 24

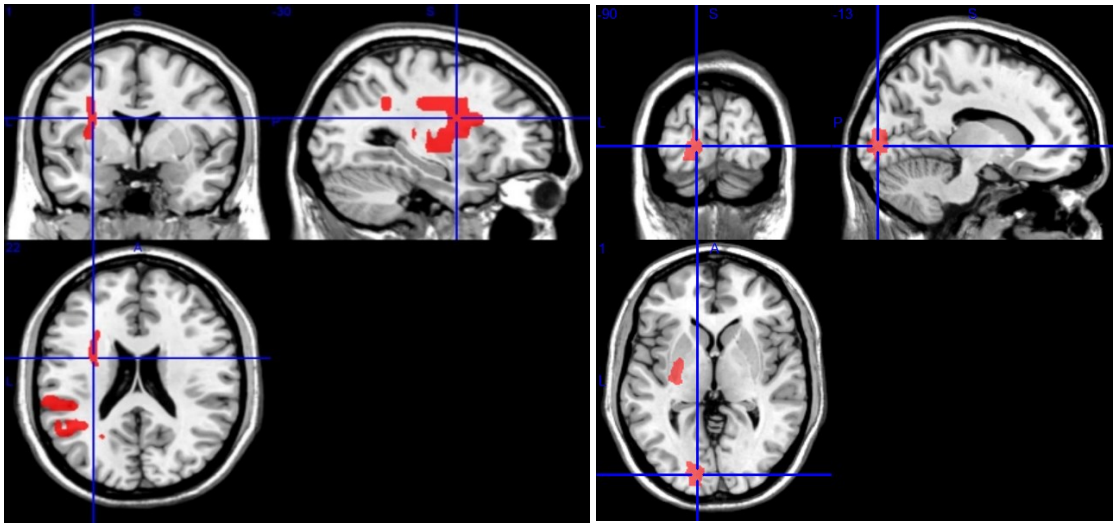
-30 1 22

-13 -90 1



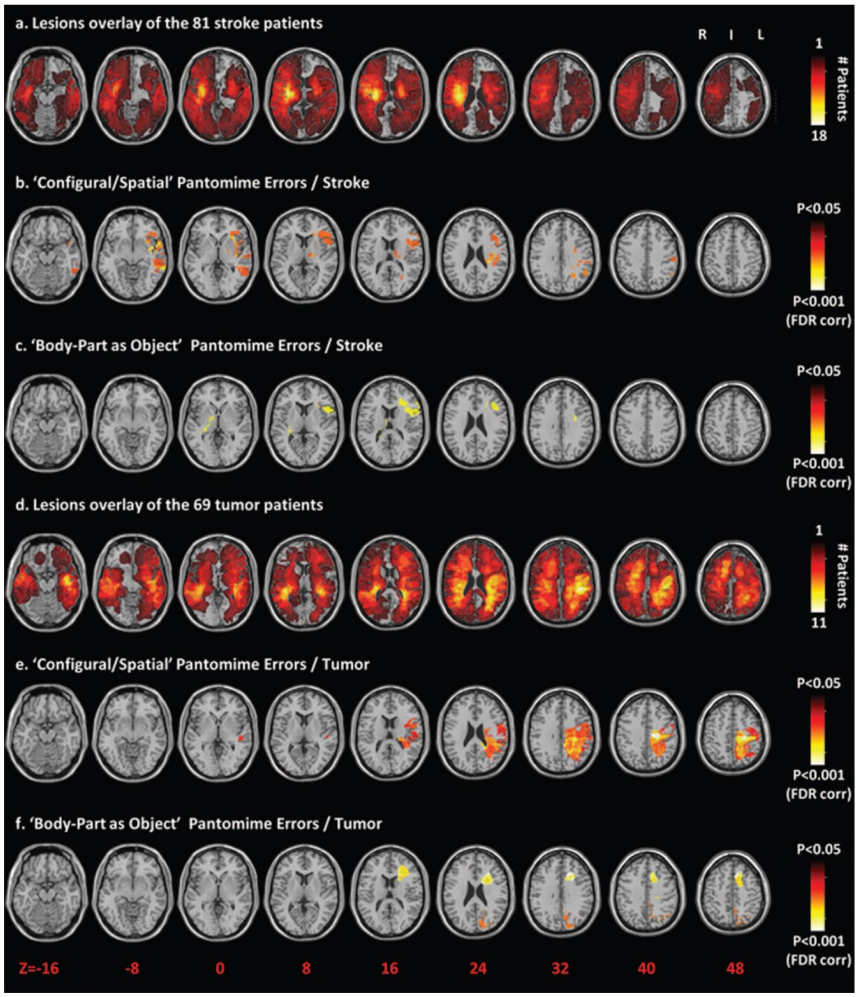
Note: R is L.



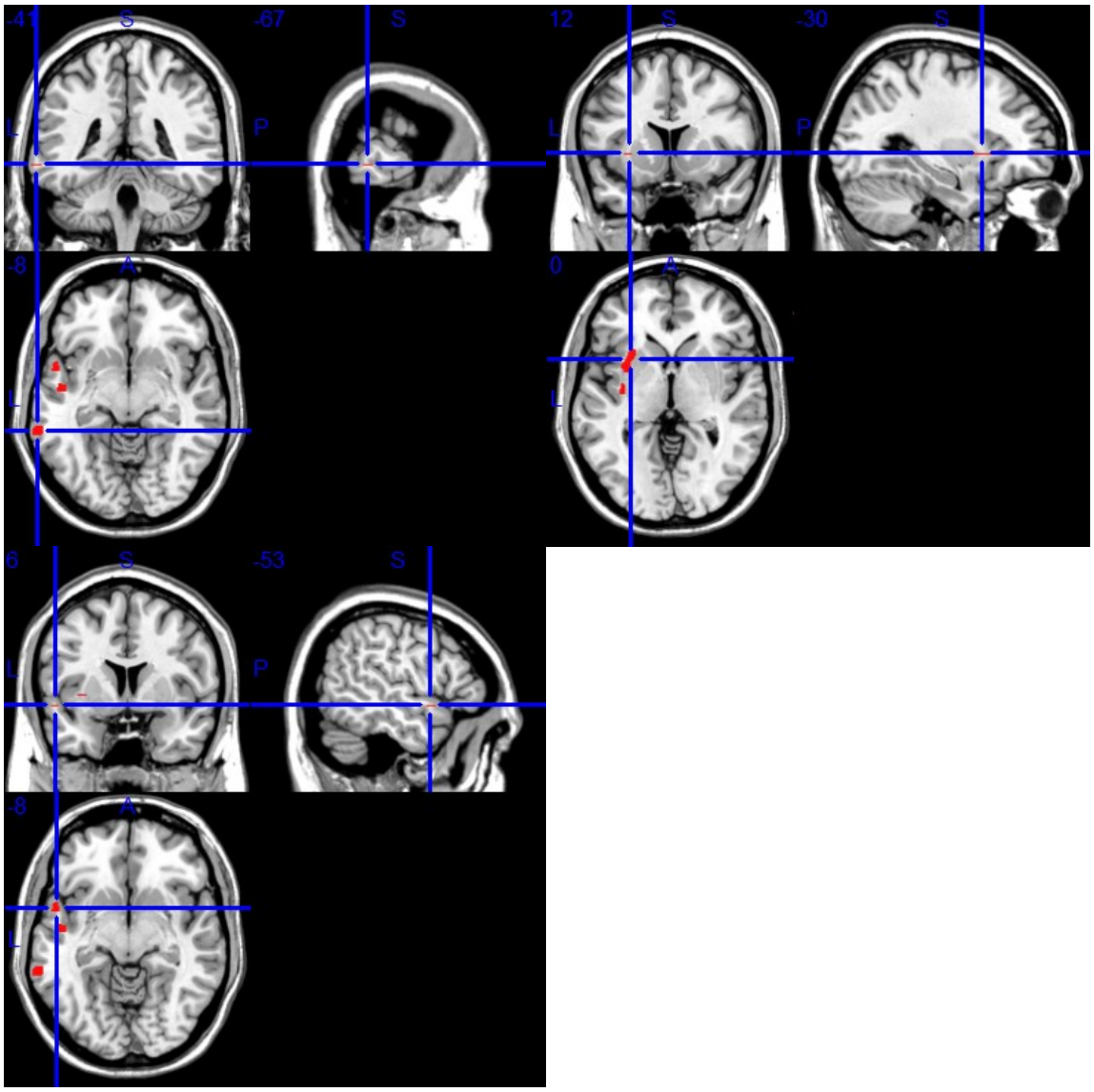


4. //Manuel, 2013

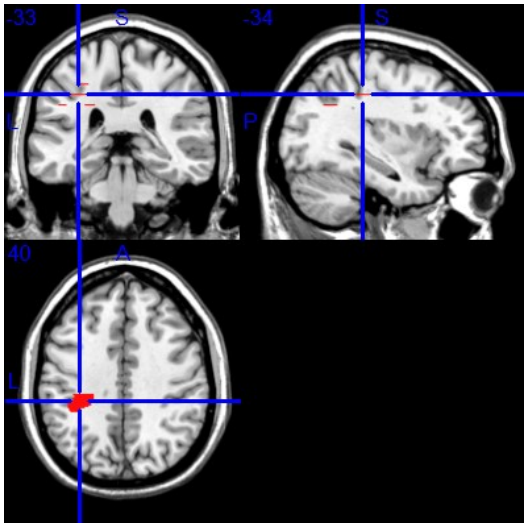
Stroke Pantomime Error: Patients: 81; Coordinates: -67 -41 -8; -53 6 -8 ; -30 12 0;
Tumor Pantomime Error: Patients 69; Coordinates: -34 -33 40



Stroke:



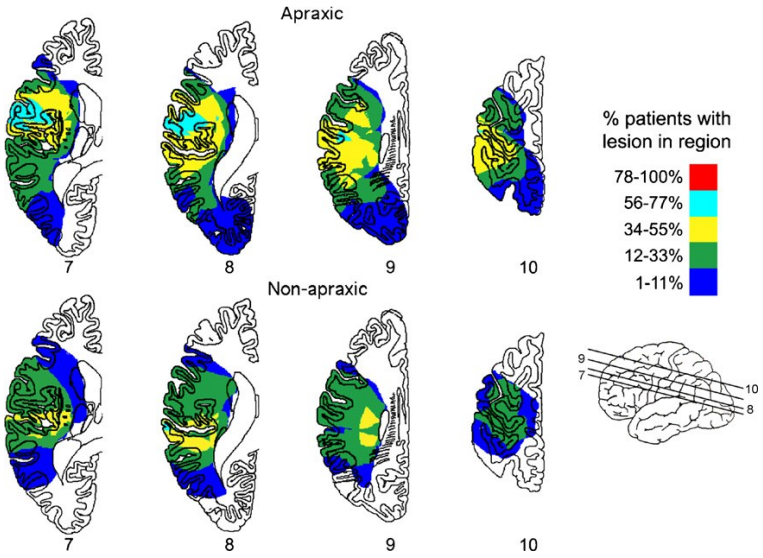
Tumor:

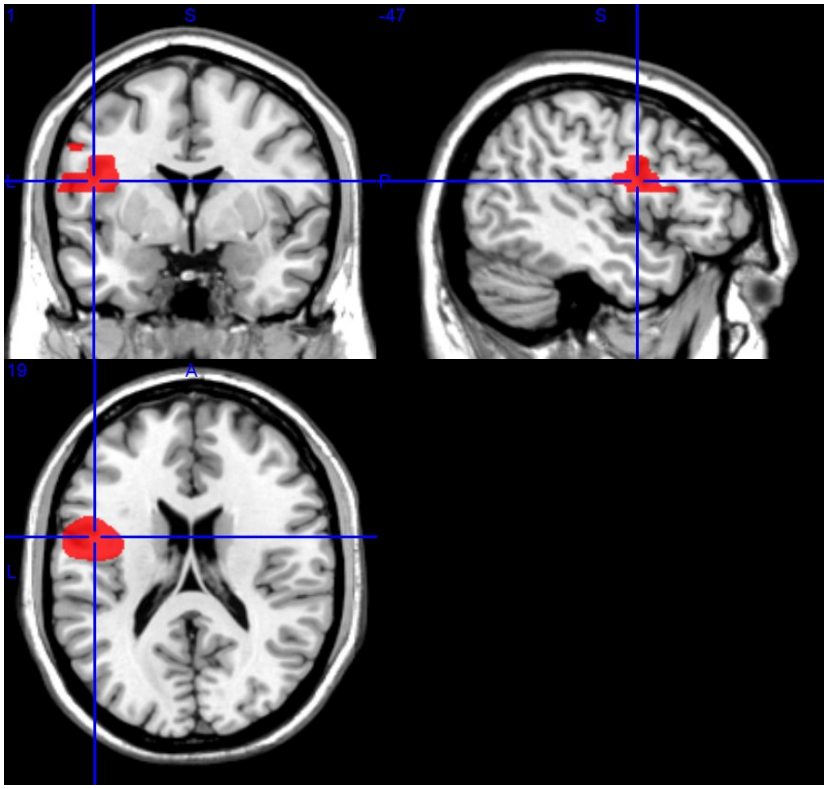


5. //Mutha, 2010

//Subjects=9

-47 1 19

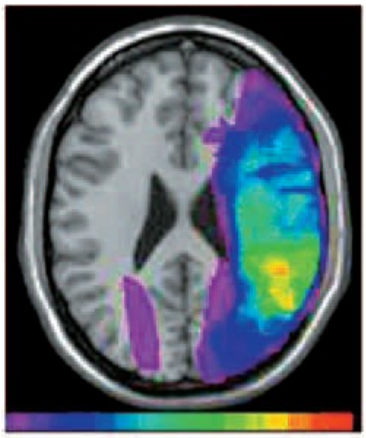


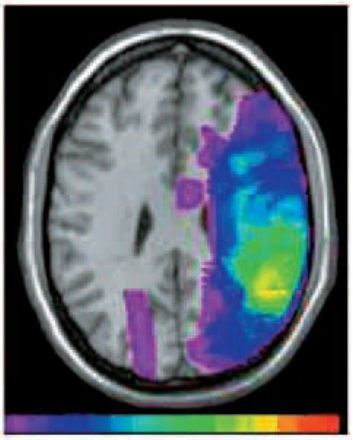


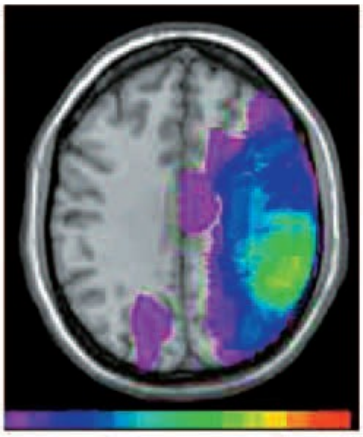
6. //Buxbaum, 2007

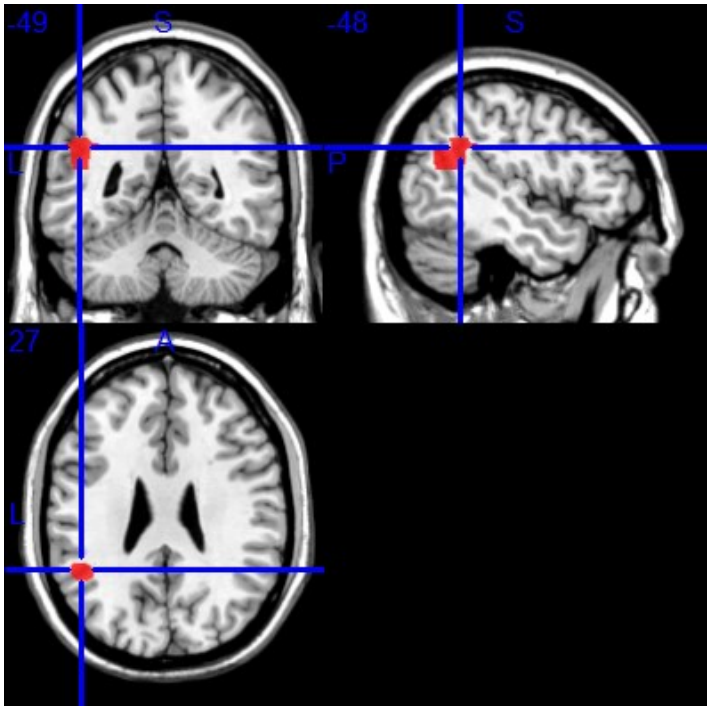
//Subjects=16

-48 -49 27







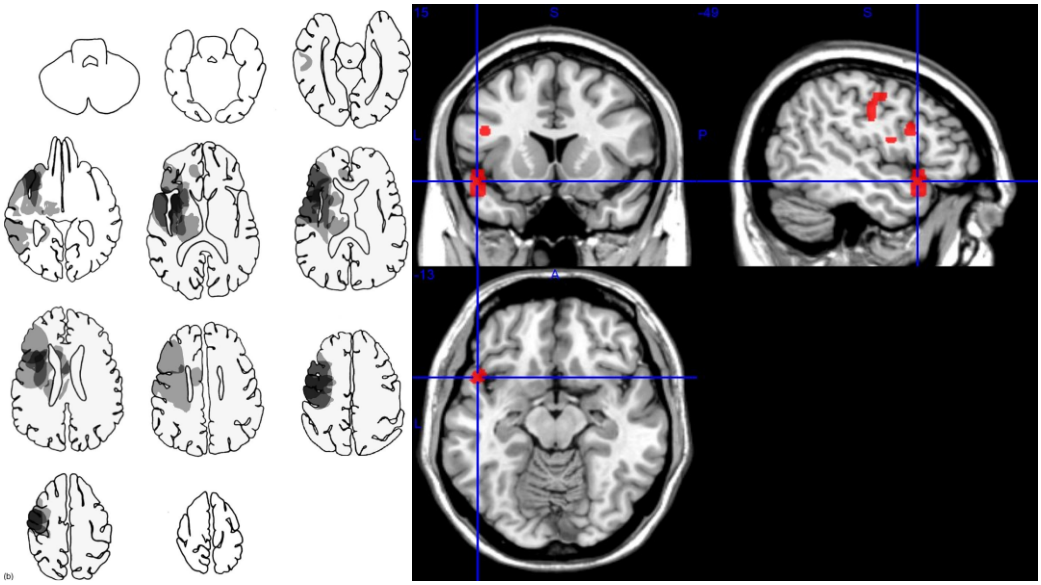


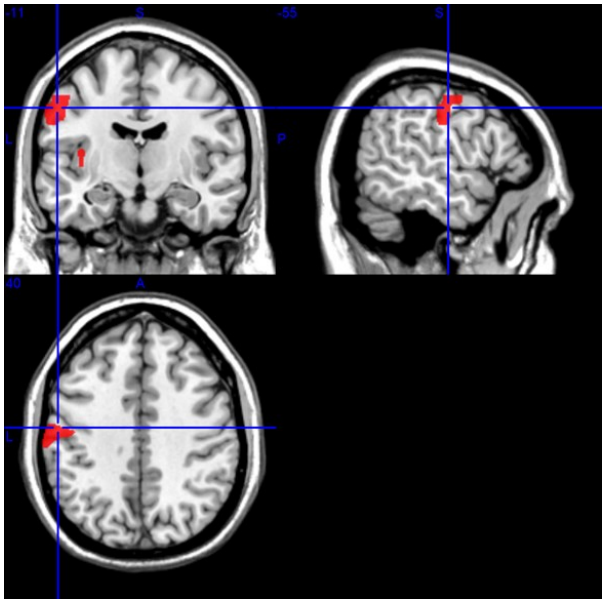
7. //Ambrosoni, 2006

//Subjects=11

-49 15 -13

-55 -11 40



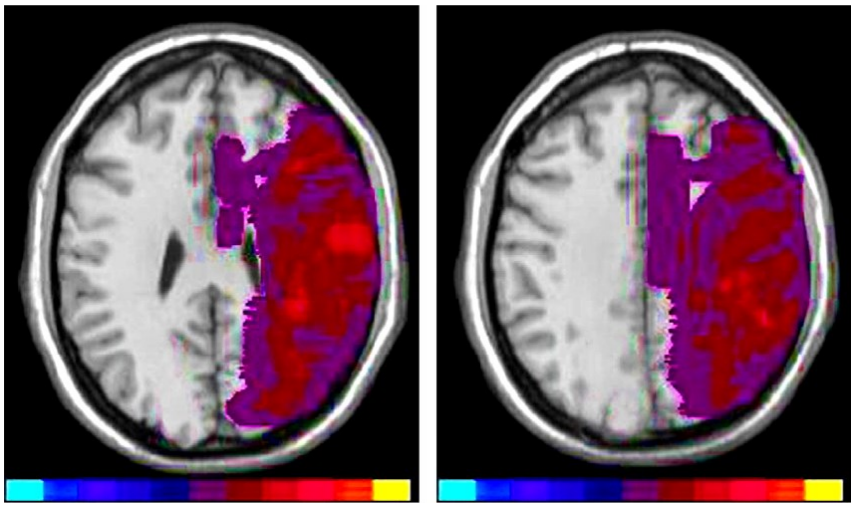


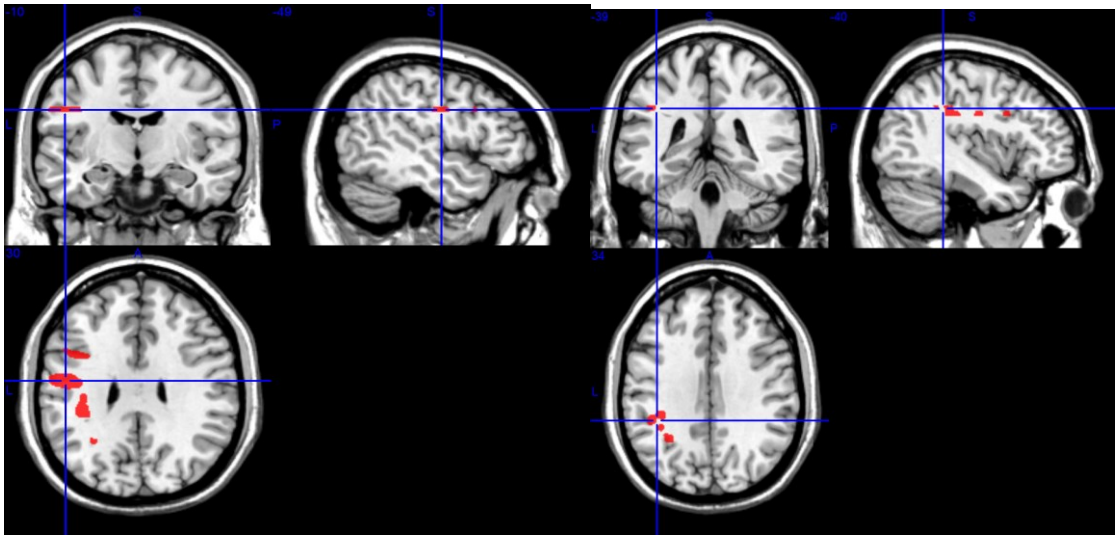
8. //Buxbaum, 2005: Apraxia Vs Non Apraxic

//Subjects=36

-49 -10 30

-40 -39 34

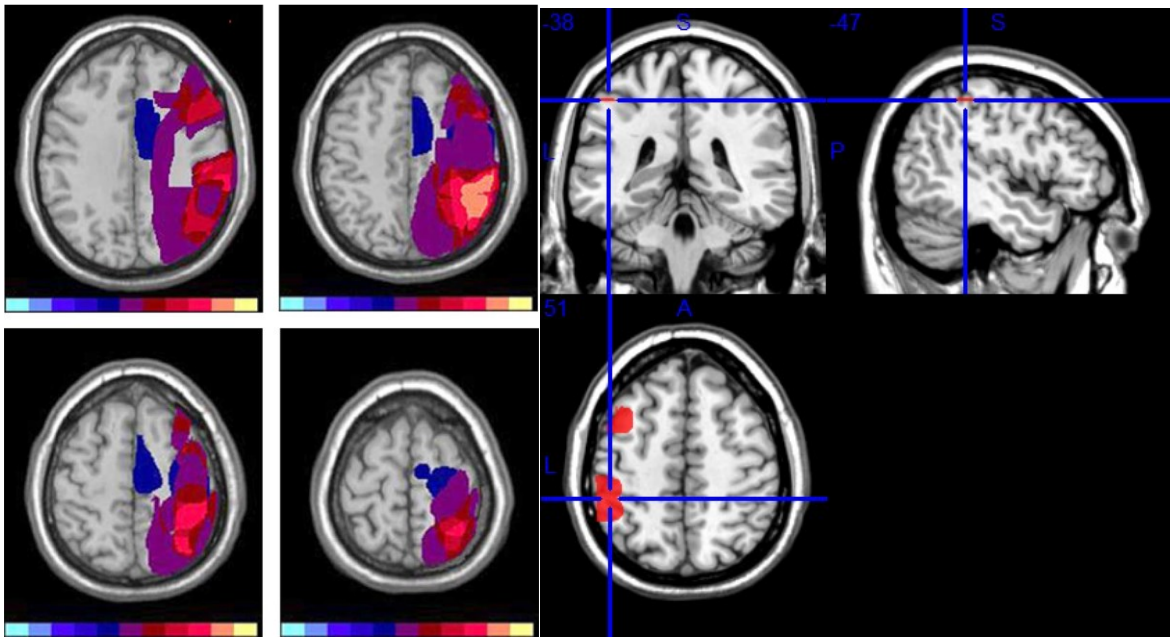




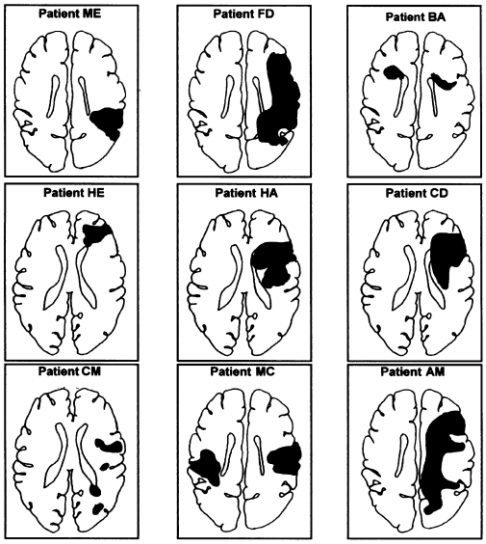
9. //Buxbaum, 2005

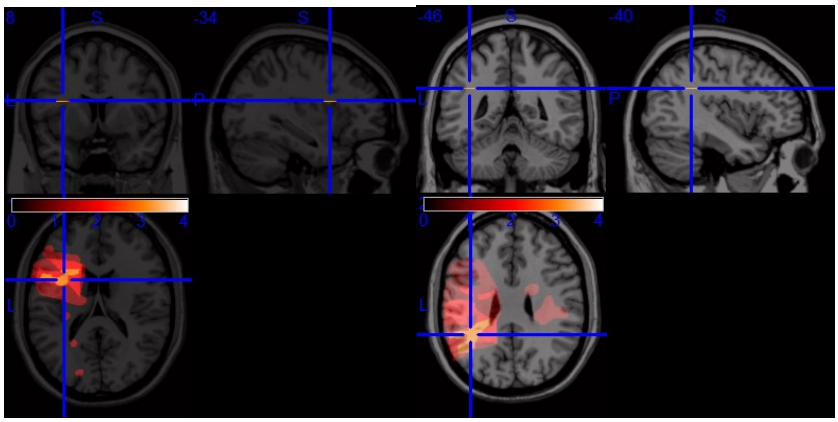
//Subjects=13

-47 -38 51

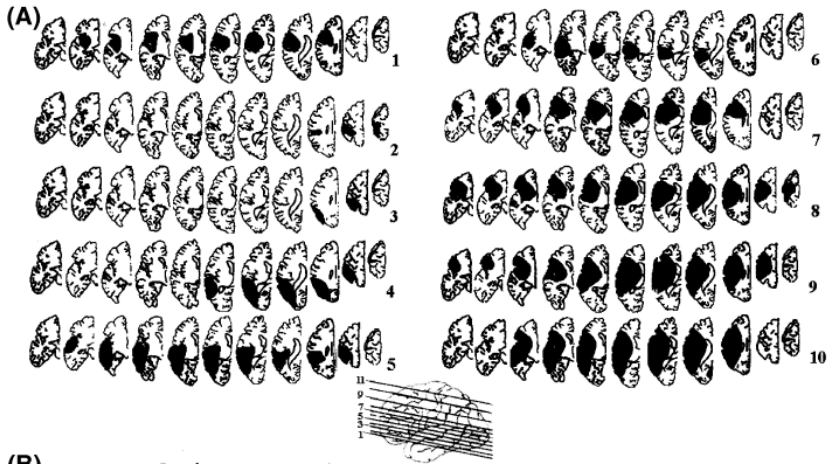


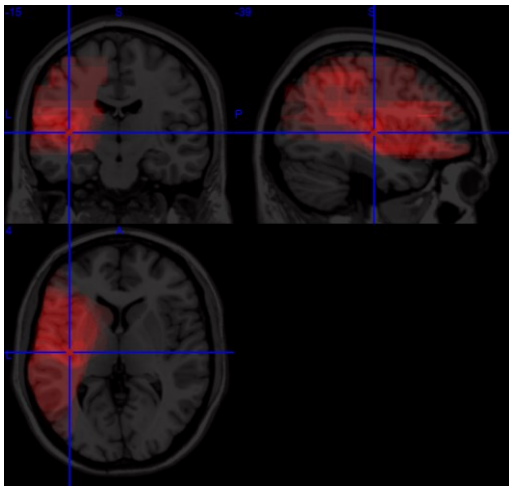
10. //Ietswaart, 2001
//Subjects=9
-34 8 18
-40 -46 29



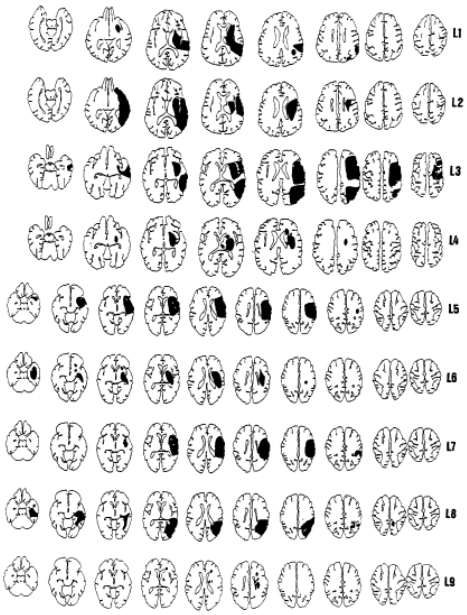


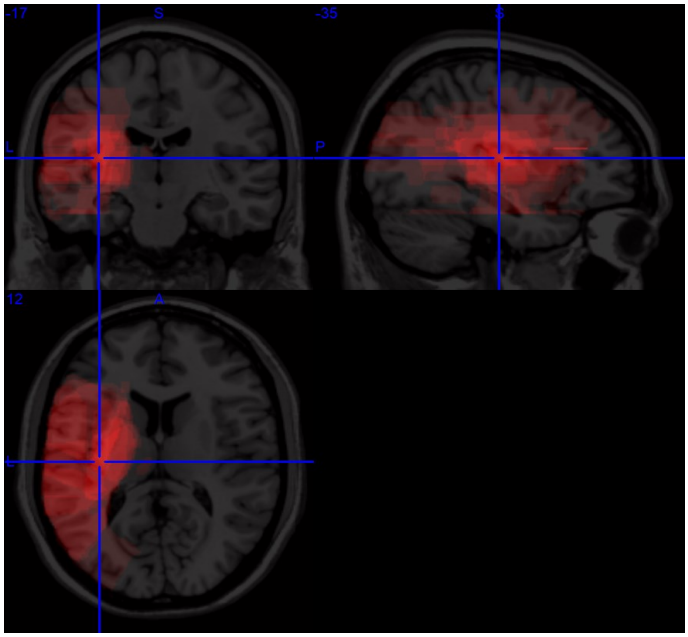
11. //Haaland, 1999
//Subjects=10
-39 -15 4





12. //Rushworth, 1997
//Subjects=9
-35 -17 12

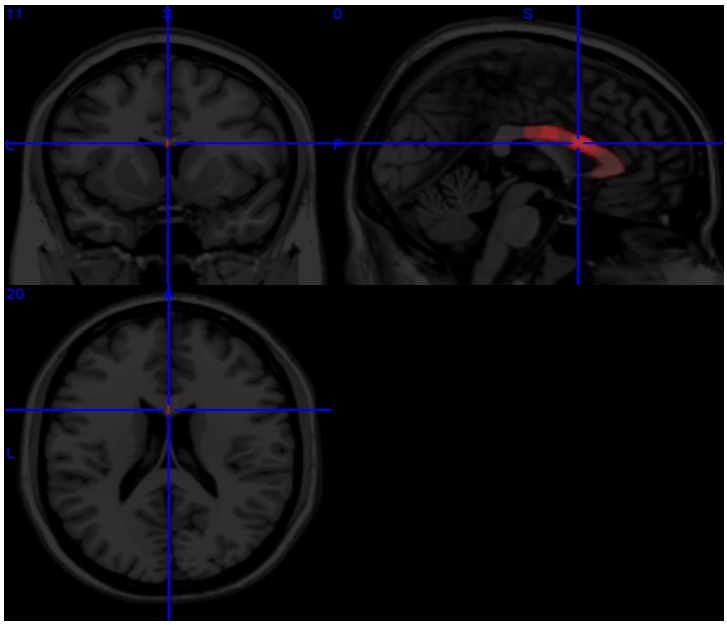




13. //Giroud, 1995
//Subjects=8
0 11 20

Table 1 Clinical and MRI features of callosal infarction

Patients	*Left tactile anomia*	*Left ideomotor apraxia*	*Left agraphia*	*Left visual anomia*	*Left hemideafness*	*Constructive apraxia*	*Left tactile alexia*	*Alien hand*	*Frontal gait disorders*	*MRI features*
1	0	0	0	0	0	0	0	0	+	
2	0	0	0	0	0	0	0	0	+	
3	0	+	0	0	0	+	0	0	+	
4	0	+	0	0	0	+	0	0	0	
5	0	+	+	0	+	+	0	0	0	
6	0	+	+	0	0	+	0	0	0	
7	+	+	+	0	0	+	+	+	0	
8	0	+	+	0	0	+	0	+	0	



14. //Agostoni, 1983
//Subjects=7
-29 -12 1
18 -14 1

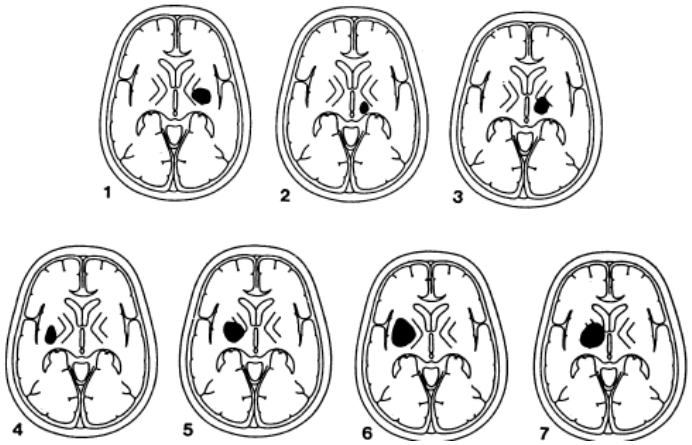
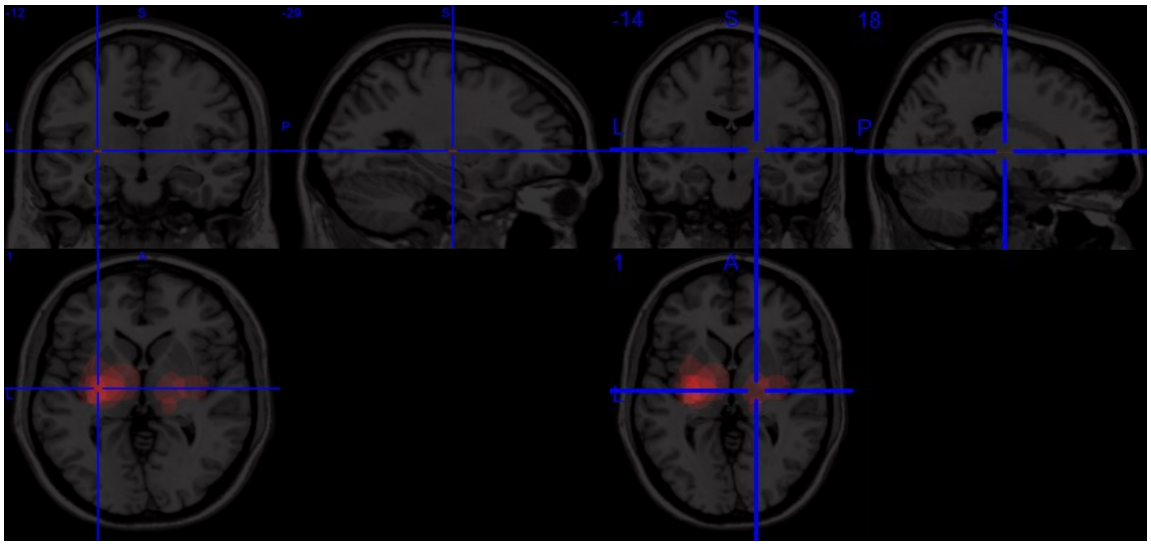


Fig 1 *Schematic representation of the lesion in CT scans.*



15. //Jax, 2006
//Subjects=15
-47 -39 24

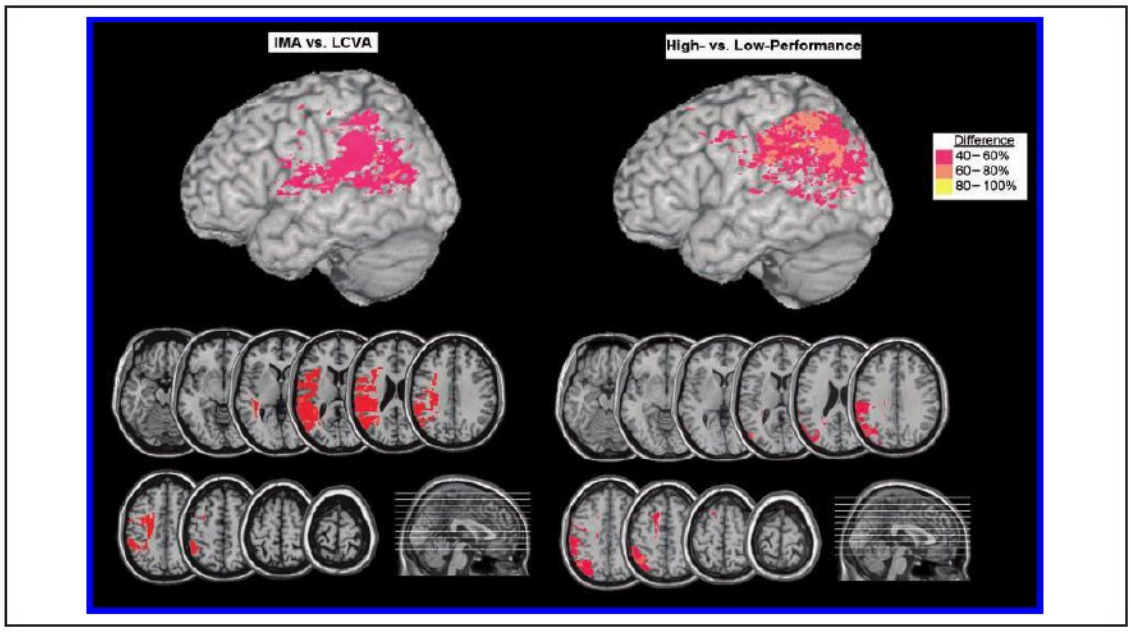
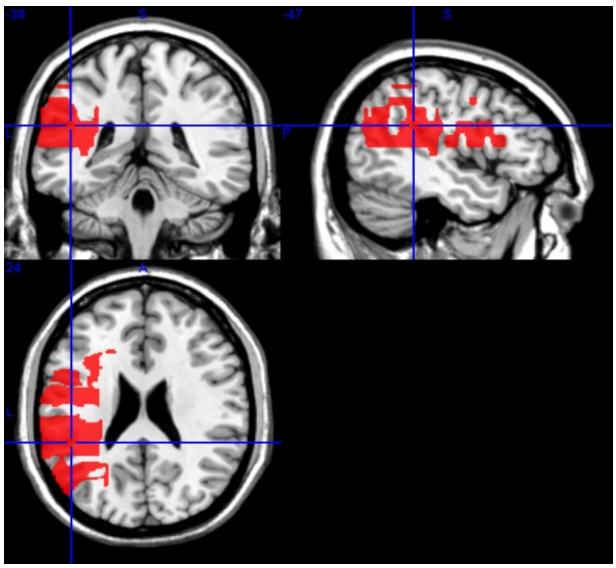


Figure 5. Results of lesion subtraction analysis comparing the IMA and LCVA groups (left) as well as the groups with low and high movement production scores (right). Colored voxels indicate areas where the percentage of participants with damage to a given voxel was greater in the IMA than LCVA group (left) or low-performance than high-performance group (right). For clarity, we only plot voxels where the percentage



16. //Alexander, 1992
//Subjects=28
-39 6 23
-49 -51 26

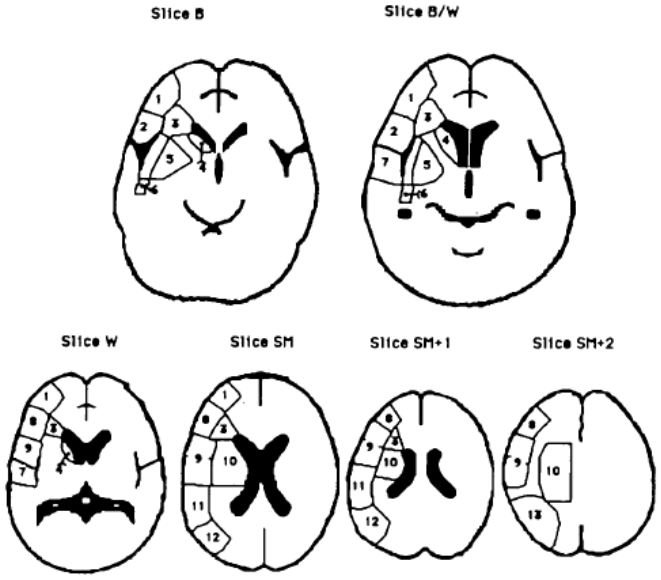


FIG. 1. Schematic representation of brain regions rated for lesion site studies. Numbers refer to regions listed in Tables 5A,B.

TABLE 5A. BRAIN REGIONS RATED FOR ANTERIOR AND CENTRAL CASES

Rolandic cortex: all lesion in the prerolandic and postrolandic gyri from the sylvian fissure to the highest CT slice (9).

Motor association cortex:
(*a*) All lesion in Broca's area, i.e. the opercular and triangular gyri (2).
(*b*) Dorsolateral frontal lobe anterior to the prerolandic gyrus at CT slices above Broca's area (8).

Frontal premotor cortex (1).

The white matter deep to rolandic cortex and motor association cortex including the anterior two-thirds of the paraventricular white matter (10).

The inferior parietal lobule including the anterior supramarginal gyrus (11).

Deep structures:
(*a*) The most anterior paraventricular white matter around and above the frontal horn (3).
(*b*) Head of caudate nucleus (4).
(*c*) Putamen (5).

Numbers in parentheses identify areas on Fig. 1.

TABLE 5B. BRAIN REGIONS RATED FOR POSTERIOR CASES

Rolandic cortex: all lesions in the prerolandic and postrolandic gyri from the sylvian fissure to the highest CT slice (9).

Inferior parietal lobule including:
(*a*) Supramarginal gyrus (11).
(*b*) Angular gyrus (12).

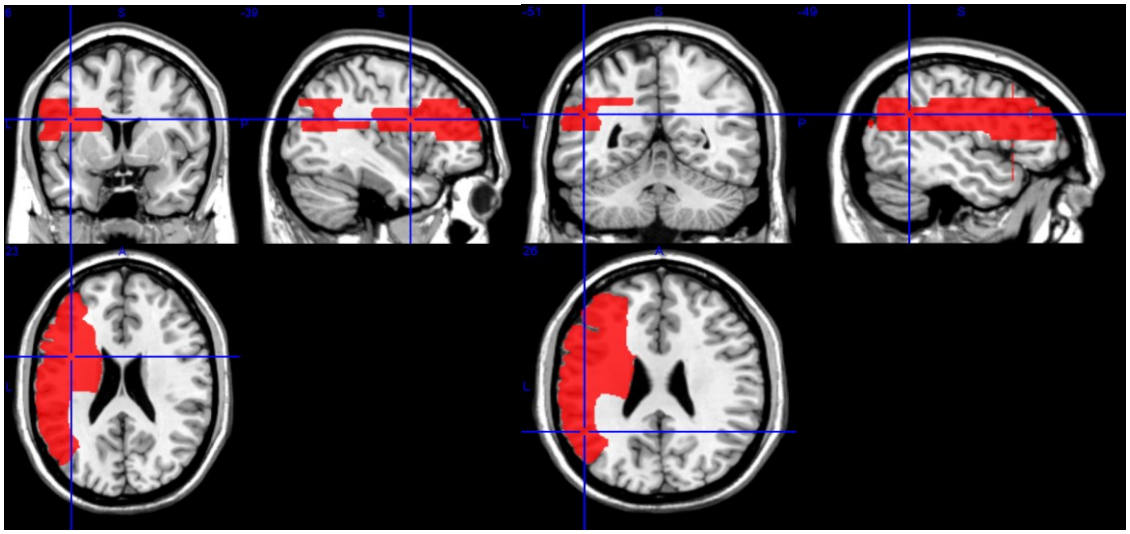
Superior temporal gyrus (7).

The white matter deep to rolandic cortex and inferior parietal cortex including the anterior two-thirds of the paraventricular white matter (10).

The temporal isthmus (6).

The superior parietal lobule (13).

Numbers in parentheses identify areas on Fig. 1.


S
-39
S
-51
S
-49
S
P
P
L
L
23
A
26
A
L
L

17. //Motomura, 1989
//Subjects=5
-31 -38 24
-27 14 16

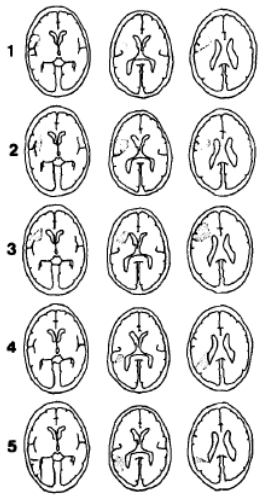
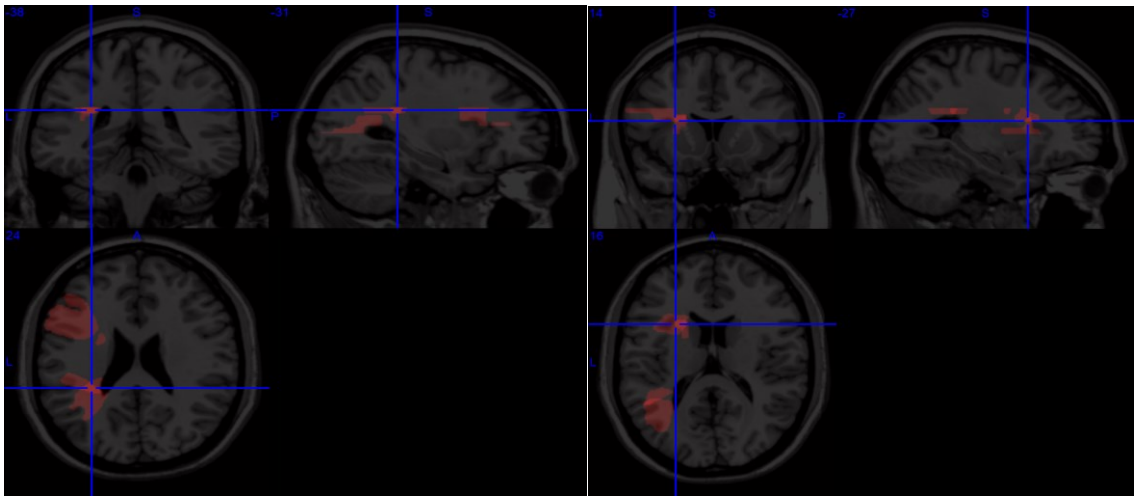


FIGURE 5 Lesions of Cases who Failed to Master Luria's Motor Sequence Test Within Six Trials. Note that case 4 and 5 had nonfrontal lobe lesions.

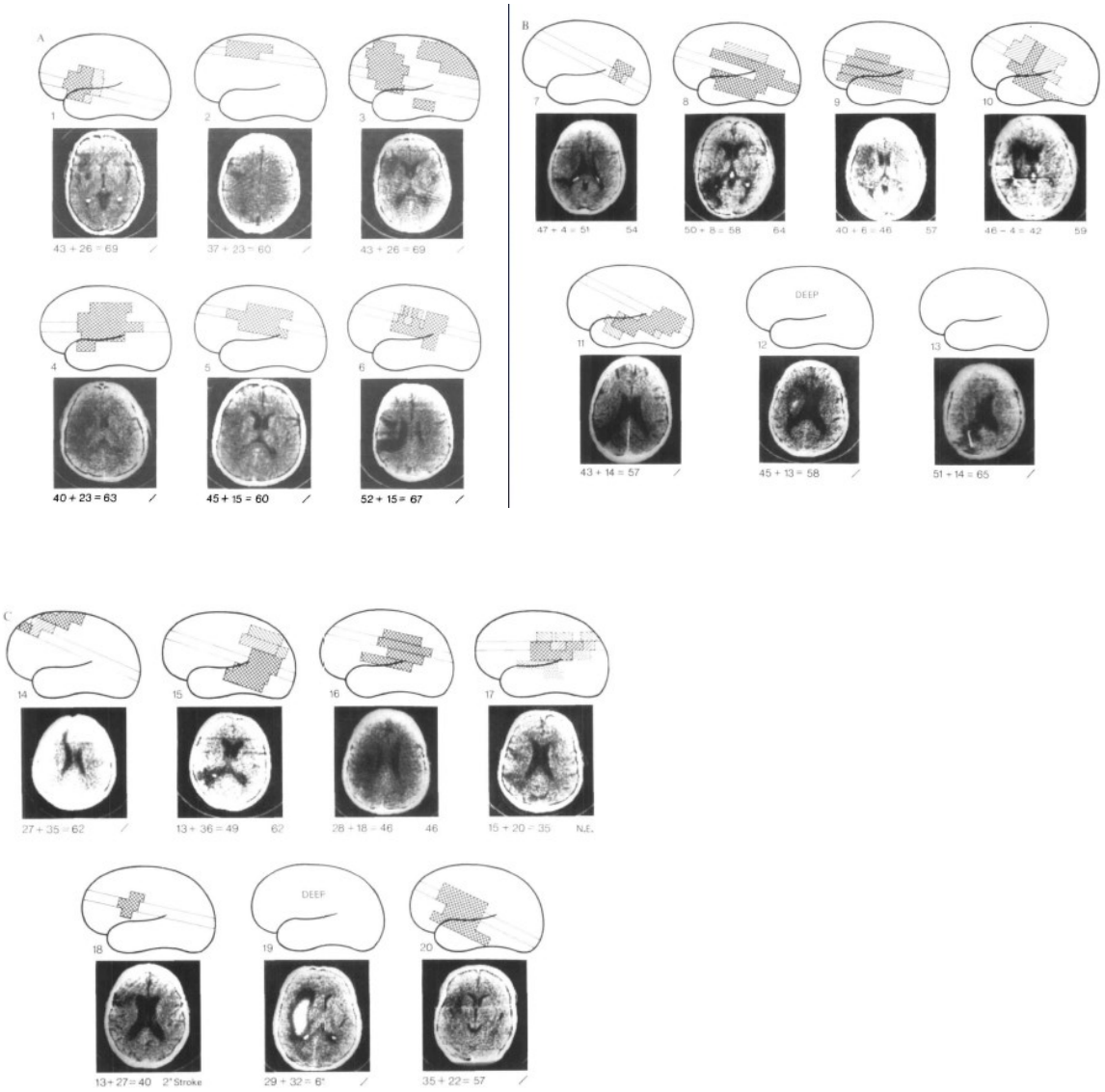


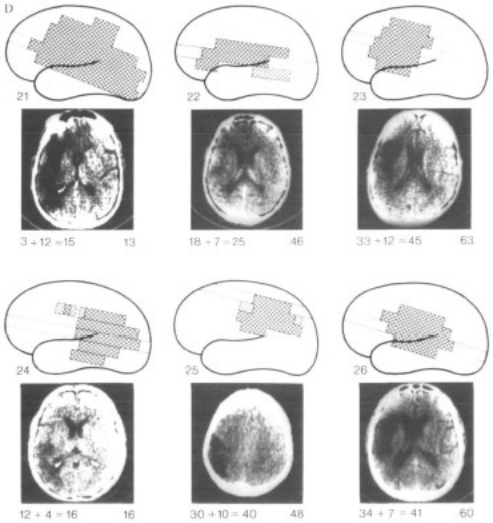
18. //Basso, 1987

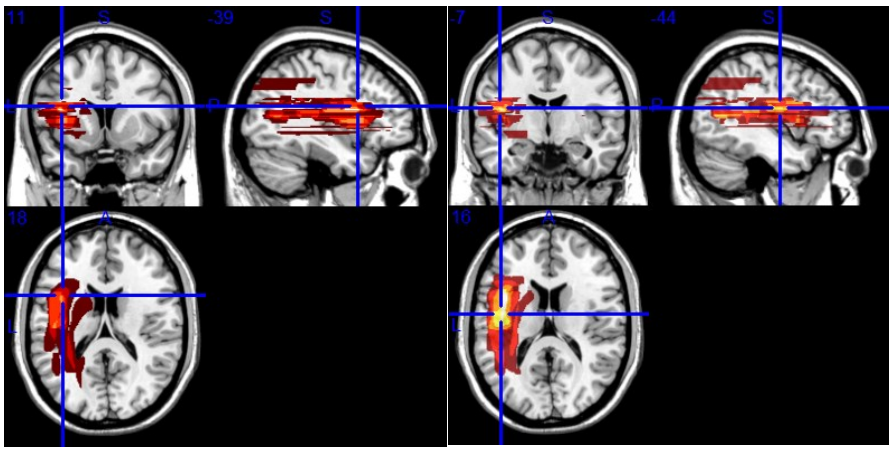
//Subjects=26

-39 11 18

-44 -7 16




D
21
22
23
3 +12 =15
13
18 + 7 = 25
46
33 +12 = 45
63
24
25
26
12 + 4 = 16
16
30 +10 = 40
48
34 + 7 = 41
60


11
S
-39
S
18
A
-7
S
-44
S
16
A

18. //Basso, 1987

//Subjects=6

Bilateral Ideomotor Images

Note: [As we considered unilateral studies in our studies, these bilateral lesions were mapped but not included in the analysis]

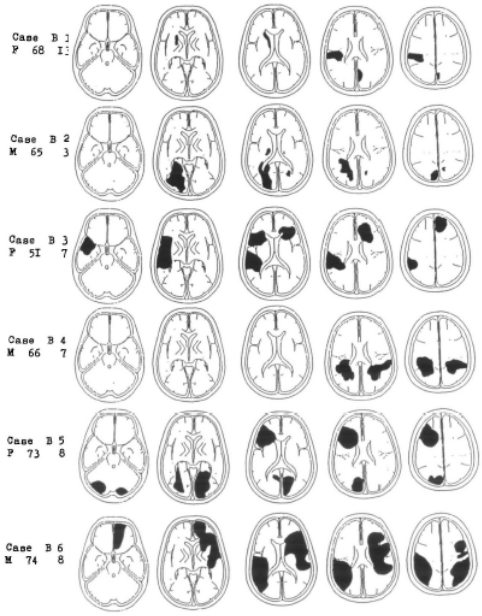
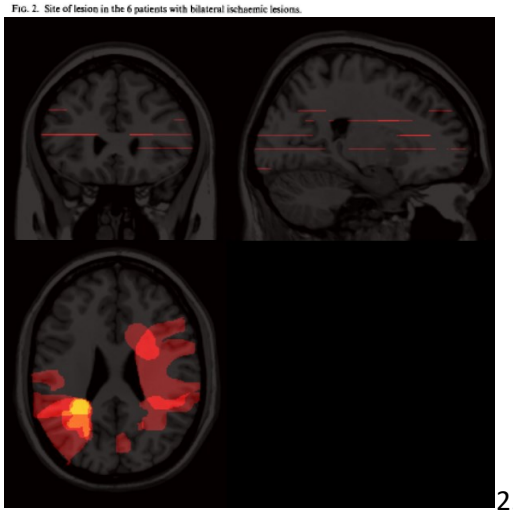
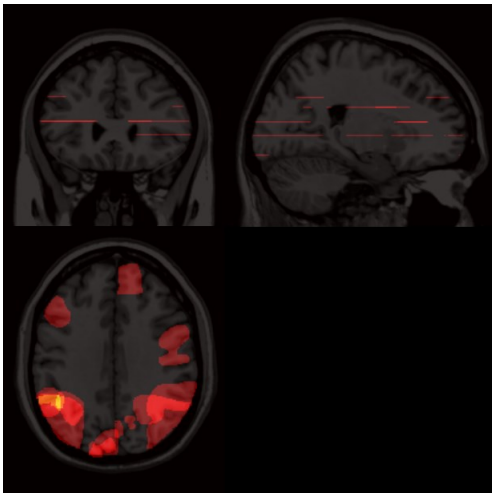
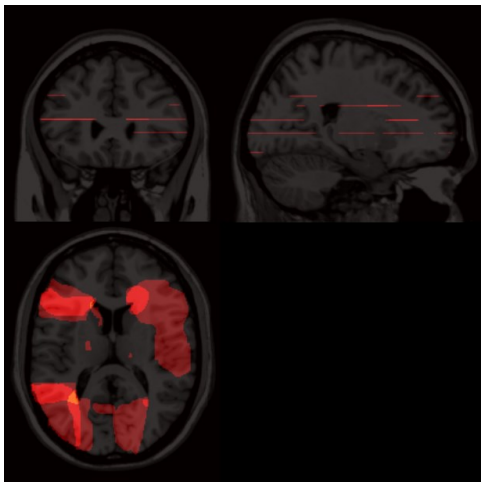


FIG. 2. Site of lesion in the 6 patients with bilateral ischaemic lesions.

1. 

2. 

3. 

19. //Kertes, 1984
//Subjects=9
-26 -5 26

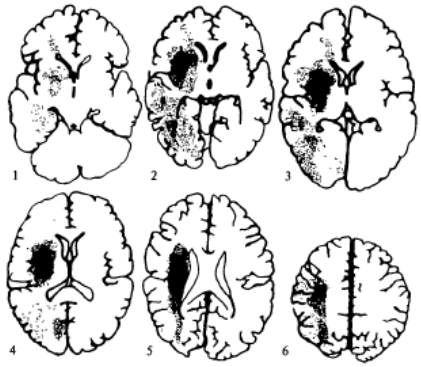
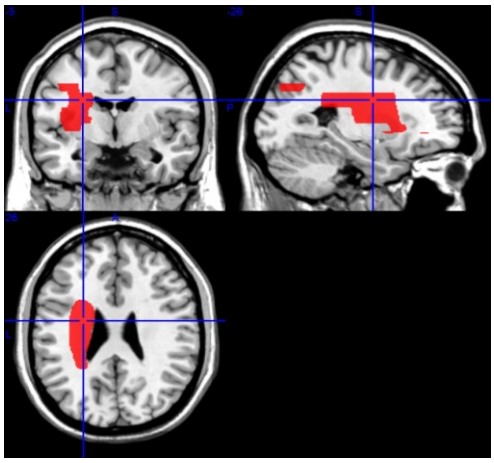
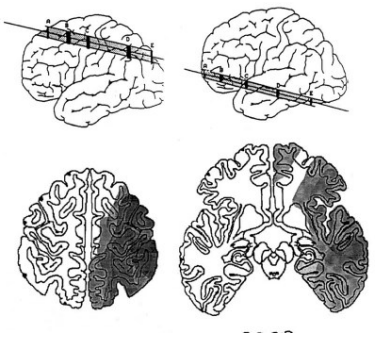


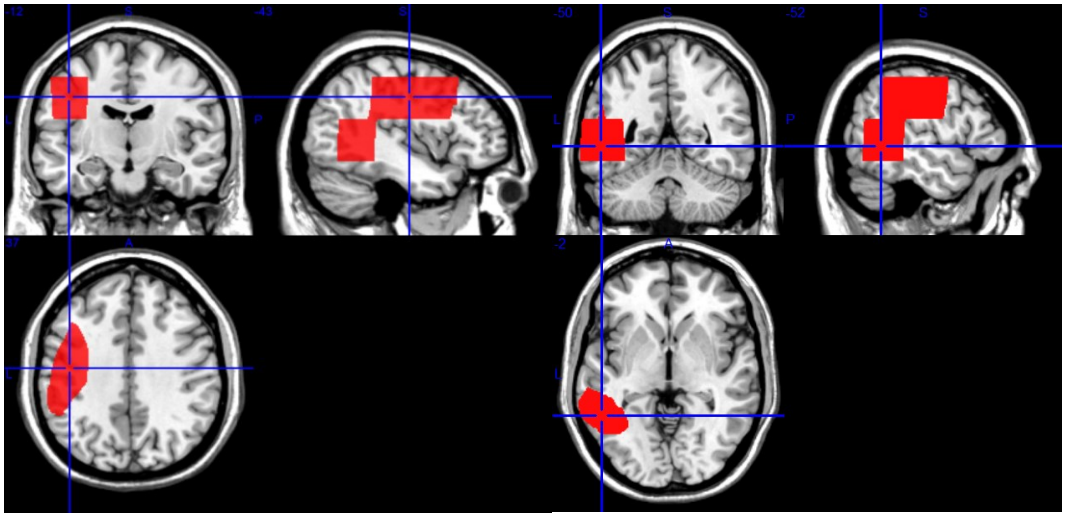
FIG. 1. Superimposed CT scan abnormalities for 9 cases of small lesions and severe apraxia. The lower cuts have lower numbers.



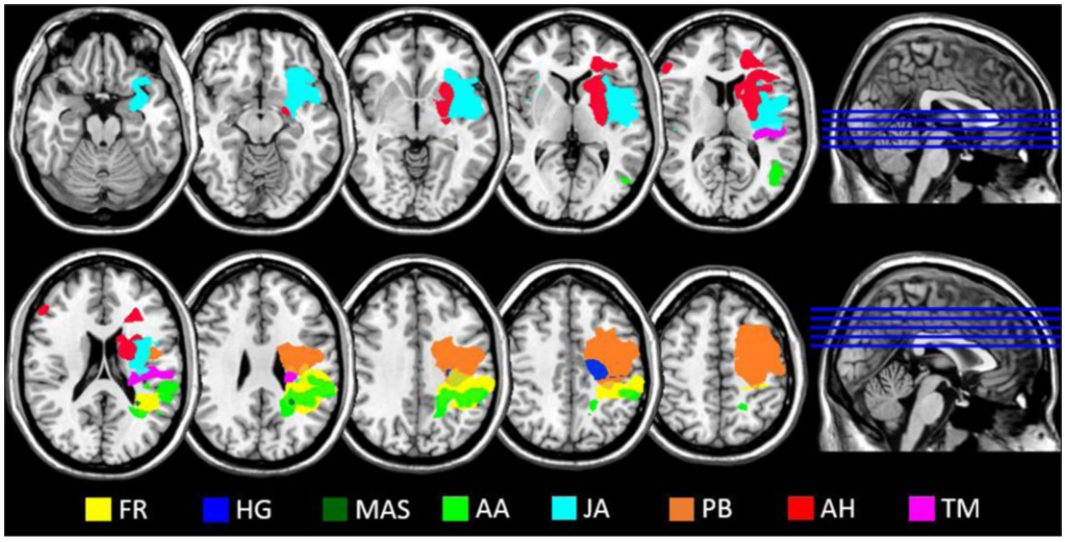
20. //Buxbaum, 2002
//Subjects=7

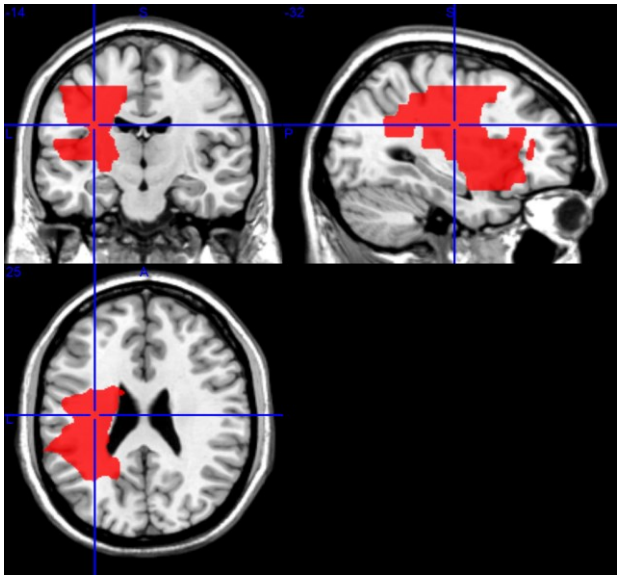
-43 -12 37
-52 -50 -2
Another coordinate for the inferior area



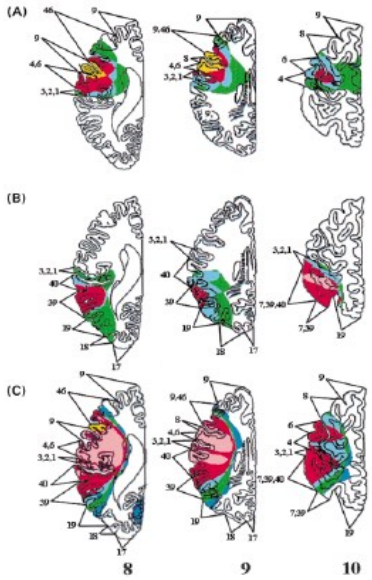


21. //Evans, 2016
//Subjects=8;
-32 -14 25

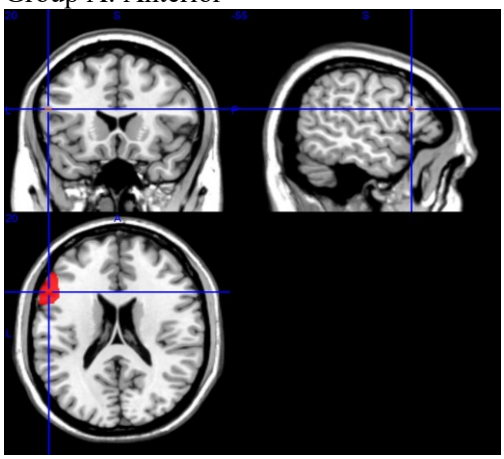




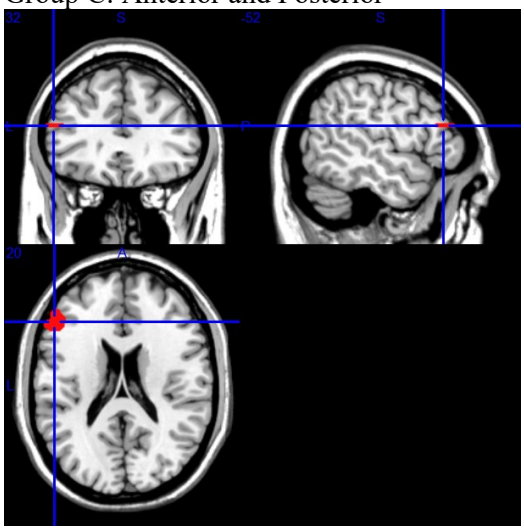
22. //Haaland, 2000
//Subjects=41
-55 20 20
-52 32 20



Group A: Anterior



Group C: Anterior and Posterior



23. //Hermsdorfer, 1996
//Subjects=20
-27 0 17