MASTERARBEIT | MASTER'S THESIS

Titel | Title

Neural Mechanisms of Anosognosia in Stroke Patients with Left- or Right-Hemisphere Damage

verfasst von | submitted by

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angestrebter akademischer Grad | in partial fulfilment of the requirements for the degree of

Master of Science (MSc)

Wien | Vienna, 2024

Studienkennzahl lt. Studienblatt | Degree programme code as it appears on the student record sheet:	UA 066 840
Studienrichtung lt. Studienblatt | Degree programme as it appears on the student record sheet:	Masterstudium Psychologie
Betreut von | Supervisor:	Dipl.-Psych. Dr. Jennifer Randerath

Abstract

Anosognosia, or impaired insight, significantly affects rehabilitation and therapeutic outcomes while providing insights into the neural foundations of self-referential processes. Previous research has largely overlooked the role of left-hemispheric lesions and specific impairments, such as aphasia and apraxia, in this phenomenon. This study investigates the neural mechanisms underlying anosognosia using voxel-based lesion-symptom mapping in 125 patients with hemispheric lesions. Discrepancy scores, based on self- and external assessments, assessed impaired insight for motor (hemiplegia/hemiparesis), language (aphasia), and tool-use (apraxia) deficits. The analysis revealed significant associations between impaired insight and cortical, subcortical, and white matter regions in the left hemisphere. Specifically, the temporal pole, basal ganglia, and insula were significantly associated with all three domains in the left hemisphere group. These regions are considered neural hubs that play a key role in integrating and transmitting self-referential information. No significant associations were observed in the right hemisphere possibly due to the subacute stage of most patients, which limited the number of anosognosia cases. This finding suggests potential hemispheric differences in the temporal and functional dynamics of anosognosia. As one of the first studies to examine anosognosia in language and tool-use deficits, the results highlight the involvement of shared neural structures across different types of impaired insight and support the existence of a shared metacognitive network for self-referential processes.

Zusammenfassung

Anosognosie, also eine verringerte Krankheitseinsicht, beeinflusst die Rehabilitation und therapeutische Ergebnisse erheblich und erlaubt Einblicke in die neuronalen Grundlagen selbstreferenzieller Prozesse. Die Forschung zur Anosognosie hat die Rolle linkshemisphärischer Läsionen und spezifischer Beeinträchtigungen wie Aphasie und Apraxie bei diesem Phänomen weitgehend vernachlässigt. Diese Studie untersucht folglich die neuronalen Mechanismen, die Anosognosie zugrunde liegen. Dazu wurde bei 125 Patienten mit links- oder rechtshemisphärischen Läsionen eine voxelbasierte Läsions-Symptom-Kartierung (voxel-based lesion-symptom mapping) durchgeführt. Diskrepanzwerte, basierend auf Selbst- und Fremdeinschätzung, erfassten das eingeschränkte Krankheitsbewusstsein bei motorischen Defiziten (Hemiplegie/Hemiparese), Sprachstörungen (Aphasie) und Störungen des Werkzeuggebrauchs (Apraxie). Die Analyse zeigte signifikante Assoziationen zwischen eingeschränktem Krankheitsbewusstsein und kortikalen, subkortikalen und weißen Substanzregionen in der linken Hemisphäre, wobei der Temporallappenpol, die Basalganglien und die Insula in der Gruppe der linken Hemisphäre signifikant mit allen drei Domänen assoziiert waren. Diese Regionen gelten als neuronale Knotenpunkte, die eine Schlüsselrolle bei der Integration und Übertragung selbstreferenzieller Informationen spielen. In der rechten Hemisphäre wurden keine signifikanten Assoziationen beobachtet, möglicherweise weil die meisten Patienten im subakuten Stadium waren, was zu einer geringeren Anzahl von Anosognosie-Fällen führte. Dieses Ergebnis deutet auf mögliche hemisphärische Unterschiede in den zeitlichen und funktionalen Dynamiken von Anosognosie hin. Als eine der ersten Studien, die Anosognosie bei Sprach- und Werkzeuggebrauchsstörungen untersucht, unterstreichen die Ergebnisse die Beteiligung gemeinsamer neuronaler Strukturen über verschiedene Arten eingeschränkten Krankheitsbewusstseins hinweg und unterstützen die Existenz eines gemeinsamen metakognitiven Netzwerks für selbstreferenzielle Prozesse.

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Introduction

Definition

The term anosognosia is derived from the ancient Greek words α (a; meaning "without"), νόσος (nosos; meaning "disease"), and γνῶσις (gnōsis; meaning "knowledge"), and refers to the lack of awareness of one's own illness (Langer & Levine, 2014). Although the phenomenon was already mentioned by the stoic philosopher Seneca, who described the case of a blind woman unaware of her impairment (Gainotti, 2019), it gained more attention in the 19th century through the physicians Anton (1899) and von Monakow (1885), who examined clinical cases where patients suffering from cortical blindness or cortical deafness showed no awareness of their current impaired states. The neologism anosognosia was then coined by the Polish-French neurologist Joseph Babinski (1914), who observed the phenomenon in two patients with a right cerebral stroke and a resulting left hemiplegia, suffering from an unawareness of their deficits (for a translation see Langer & Levine, 2014). Despite their serious condition the patients showed a complete unawareness of their existing paralysis, while apparently maintaining their intellectual capacities.

As described in Gauggel (2016), the term nowadays encompasses a broader concept, as it can also be applied to the failure to recognize partial disorders, since the complete unawareness of one’s own illness or deficit is quite rare and typically occurs only in the acute stage of brain damage, Patients often overestimate their abilities and claim to have no limitations or problems in their daily lives. They frequently display an affect that does not match their current situation, appearing indifferent and unconcerned (Gauggel, 2016). Synonyms for anosognosia, therefore, often include terms such as "unawareness of impairments," "unawareness of illness," "lack of insight into impairments," or "impaired self-awareness" (Prigatano, 2010). Hereafter, these terms will be used interchangeably.

Another common distinction made in the context of anosognosia is whether there is implicit or explicit (partial) knowledge of one’s own limitations. Studies (Fotopoulou et al., 2010; Mograbi & Morris, 2013; Nardone et al., 2008) have demonstrated the phenomenon of implicit awareness in patients with reduced insight into their illness. In these cases, patients may demonstrate little to no awareness of their condition when directly questioned, yet their behavior or decision-making

indicates an implicit knowledge of it. According to Gauggel (2016), implicit awareness is present when there are indirect verbal expressions or non-verbal behaviors that suggest the patient has some awareness of the existence of a disorder or disability. In contrast, explicit awareness is when the patient can provide a detailed account of their deficits during a conversation.

Other concepts that describe similar phenomena to anosognosia include the term "anosodiaphoria," introduced by Babinski (1914), which describes a milder form of anosognosia where patients, after a stroke, are aware of their paralysis but remain indifferent to it. Another related concept is Sigmund Freud's (1894) concept of denial (“Verleugnung”), which describes an unconscious defense mechanism where a person denies or ignores unpleasant realities to avoid emotional pain. Weinstein and Kahn (1955) introduced the concept of “denial of illness” to describe the adaptive, active and motivated response of individuals aimed at reducing anxiety and distress when confronted with an illness or disability. Similarly, Schachter (1990) employed the term “unawareness of deficit” to characterize the phenomenon wherein patients are unable to recognize the presence of a clear illness or disability. In the ICD 11 anosognosia is described under the code MB21.2 as “a lack of awareness or failure to recognize one’s own illness, symptoms, or functional deficits, considered to be an aspect of the illness” (World Health Organization, 2019).

Nowadays anosognosia has been observed in a variety of neuropsychological syndromes, such as neglect (Appelros et al., 2002, 2007), aphasia (Lebrun, 1987), apraxia (Buchmann et al., 2020; Scandola et al., 2021), hemianopsia (Celesia et al., 1997), as well as in neurodegenerative diseases such as Alzheimer’s disease (Cacciamani et al., 2021), in mild cognitive impairment (Mondragón et al., 2019), Parkinson’s disease (Maier et al., 2012) and in frontotemporal dementia (Rosen, 2011). The phenomenon of a lack of insight into one’s own illness or deficit has also been the focus of various psychiatric disorders such as psychosis and schizophrenia (Amador & David, 2004), bipolar disorder (Peralta & Cuesta, 1998) and obsessive-compulsive disorder (Thirioux et al., 2020). For example, patients suffering from anorexia nervosa perceive their body image as distorted, believing they are overweight even when they are significantly underweight. Although they are aware of the negative health consequences associated with their restrictive calorie intake, they are unable to fully integrate this knowledge (Gauggel, 2016).

If one's own impairments and the associated limitations are not (fully) recognized, this has a negative impact on therapeutic success (Hartman-Maeir et al., 2002, 2003; Ownsworth & Clare, 2006). If the patient is unable to adequately recognize their problems, they will not see any reason for potential rehabilitation or compensation measures and will exhibit reduced intrinsic motivation. This impaired illness insight thus affects not only the therapy itself but also other factors such as family life and professional reintegration (Gauggel, 2016).

A study by Vossel et al. (2013) investigated a group of patients who had neglect or neglect-related visual impairments following a right hemispheric stroke. It was found that anosognosia was the strongest predictor for limitations in daily activities. If the patient is unaware of their limitations, they cannot account for them in everyday tasks.

A prospective study by Pedersen and colleagues (1996) demonstrated that stroke patients with anosognosia had lower scores on the Barthel Index, a reduced likelihood of achieving independent living following rehabilitation, and that anosognosia was a strong predictor of mortality. These findings highlight the significant impact of anosognosia on individuals, showing how it markedly reduces their quality of life across various dimensions.

Distinction from Denial

As early as 1914, the neurologist Henry Meige commented on Babinski's paper on anosognosia: “Is it resignation, a wish to hide from himself or others a defect that afflicts him? It is possible, in certain cases; but in others one is faced with a true psychopathological problem” (Langer & Levine, 2014, p. 7). With this insight, he captured an important aspect—namely, whether and how one can distinguish the lack of recognition of one's own illness from the phenomenon of denial.

In his comprehensive book about anosognosia, Gauggel (2016) proposes a clear distinction between denial and anosognosia, whereas Fotopoulou and Besharati (2023) argue for a more integrative perspective. Gauggel defines denial of an illness or impairment in the clinical context as a psychological coping mechanism aimed at self-protection, attempting to reduce extreme negative emotions. In contrast, reduced awareness of one's deficits, or anosognosia, is primarily caused by damage to specific brain areas necessary for self-reflection and self-perception.

Fotopoulou and Besharati (2023) suggest that Babinski's ideas, questioning whether anosognosia is motivated by self-esteem or whether it is a genuine condition, represent a classic form of dualism. They propose a more integrative approach, drawing on a variety of studies (Davies et al., 2005; Levine, 1990; Levine et al., 1991; Marcel et al., 2004; Ramachandran, 1995; Vuilleumier, 2004) that link combinations of top-down and bottom-up factors, as well as emotional and cognitive elements. An example of such an integrative approach is the two-factor theory proposed by Davies and colleagues (2005), where: (1) the abnormal belief arises due to impairments in perception, and (2) there is a failure in higher-order cognitive processes responsible for belief evaluation, preventing the individual from rejecting the implausible belief.

The fact that anosognosic patients can still exhibit forms of implicit awareness supports the notion that they can unconsciously process some knowledge about their deficits, even while actively denying or ignoring them. Several case reports describe patients making indirect comments about their deficits, as if their "facade" briefly slips. Consider the intriguing case reported by Ramachandran (1995), where a patient who actively denied her paralysis received caloric vestibular stimulation, temporarily alleviating her symptoms completely. Not only did she acknowledge that her arm was paralyzed, something she had previously denied, but she could also estimate how long her arm had been paralyzed ('several days'). Eight hours later, she was again actively denying any issues with her arm but could still recall the caloric stimulation. Although this is just one case, it offers valuable insights into the complex dynamic interactions between the inability to access unconsciously stored information that is nonetheless perceived at some level.

These observations align with the perspective of Fotopoulou and Besharati (2023), who aim to demonstrate that awareness should be understood as emerging from the dynamic interplay of multiple converging processes, rather than being attributed to a single unitary module that is either damaged (leading to anosognosia proper) or intact (as in denial). This integrative view moves beyond the traditional dualistic approach, suggesting that awareness involves complex interactions between cognitive and emotional processes.

Prevalence and Prognosis

Accurately assessing the prevalence of anosognosia is challenging for several reasons, and specific epidemiological studies on this topic are currently lacking. Firstly, the clinical picture of anosognosia is ambiguous due to its multifaceted nature, vague definition, and frequent comorbidity with various neurological, neuropsychological, neurodegenerative, and psychiatric disorders (Gauggel, 2016). Additionally, certain groups of patients, such as those with language deficits or left hemispheric lesions, are often excluded from studies (Orfei et al., 2007), making comprehensive assessment difficult. Moreover, there is high variability in the diagnostic approaches used to evaluate anosognosia.

Another factor is the variability in the frequency of anosognosia depending on the time of measurement. For instance, Vocat et al. (2010) demonstrated in their study of 58 strokepatients with hemiplegia, all of whom had suffered a right-hemisphere stroke, that the frequency of anosognosia was 32% in the hyperacute phase (three days after stroke), decreased to 18% in the subacute phase (after one week), and affected only 5% of patients in the chronic phase (approximately six months later). However, all these results regarding the occurrence over time relate only to patients with right-hemisphere lesions. Research on the course of anosognosia following left-hemisphere lesions is currently quite limited. A case report by Cocchini et al. (2002) showed that a patient with primarily left-hemisphere lesions still exhibited anosognosia for hemiplegia even after one year. Hartman-Maeir et al. (2001) found that one month after stroke, the prevalence of anosognosia for hemiplegia was similar in patients with left-hemisphere lesions (24%) and right-hemisphere lesions (28%).

Despite these challenges, studies exist that assess the prevalence of anosognosia. In his book, Gauggel (2016) summarizes several of these studies and estimates that at least 30% of patients with right-hemisphere damage exhibit impaired illness insight during the acute phase. However, this proportion decreases significantly in the post-acute and chronic phases for the patients with right-hemipshere damage, confirming the findings of the aforementioned study by Vocat et al. (2010). Additionally, the course of the illness shows that lack of insight into the condition can either gradually resolve, intensify, or persist over time.

Jehkonen et al. (2000) demonstrated in a study involving 49 patients with right-hemisphere brain damagethat anosognosia for hemiparesis, neglect, and general unawareness of illness can be double-dissociated. Moreover, they found that anosognosia for hemiparesis and general unawareness of illness were predictors of poor functional outcomes 12 months post-stroke. Notably, at this 12-month mark, none of the patients continued to display anosognosia for hemiparesis or general unawareness of illness, though reduced awareness of neglect persisted in some cases.

An additional factor to consider is that stroke patients experiencing forms of unawareness may verbally recognize their symptoms and show progress in this acknowledgment through therapy; however, these improvements often do not translate into behavioral adjustments. For example, a stroke patient with neglect may verbally acknowledge their deficits during a therapy session but then fail to adjust their behavior accordingly, such as colliding with objects due to an inability to compensate for visual neglect (Cocchini et al., 2010; Gauggel, 2016; Marcel et al., 2004; Nimmo-Smith, 2005).

These observations highlight that unawareness of illness is a highly dynamic phenomenon, marked by temporal fluctuations and variability in both severity (domain-general or domain-specific), form (implicit or explicit), and lesion location (left- or right-hemisphere).

Theoretical Frameworks of Anosognosia

There are numerous theoretical models that attempt to explain the underlying deficits responsible for anosognosia. The diversity of these models reflects the complexity of the clinical picture. It has been noted that in anosognosia, thinking about oneself, the ability for self-reflection, self-perception (self-monitoring), and the general self-concept are impaired to some extent (Gauggel, 2016). Fundamentally, perceiving, accurately assessing, and flexibly modifying one's own abilities is a complex task that requires the integration of multiple information sources. This process requires not only a realistic image of one's abilities but also a continuous updating of this image. The belief that one can move one's own arm is based on experiential knowledge and an associated representation of one's capabilities ("I can

move my arm in this situation"). This assessment, and thus any future prediction, relies solely on an internal model and not on afferent feedback (Goldenberg, 2007).

Patients who suddenly experience a limitation of their abilities due to a stroke face the challenge of processing the significant discrepancy between their self-assessment ("I can move my arm at any time") and the new reality ("My arm cannot be moved"). One possible explanation for anosognosia could be that affected individuals cannot immediately overcome this discrepancy and cannot integrate the new information into their existing self-concept. Supporting this notion is the fact that anosognosia, in most cases, is not a permanent phenomenon but occurs predominantly in the acute and post-acute phases following the event (Vocat et al., 2010).

A similar conclusion is also drawn from Fotopoulou and Besharati who concluded that anosognosia is “best explained as a disconnection between how one expects the body to feel in a first-person perspective (emotionally mine and under my control) and how one perceives the body counterfactually” (Fotopoulou & Besharati, 2023, p. 140). Additionally, Fotopoulou (2014, 2015) argues that Anosognosia arises from an aberrant dynamic interplay between three facets of body perception, namely exteroceptive signals, interoceptive signals and signals from social and third-person perspectives. These failures to integrate various forms of perception could explain the different manifestations of anosognosia as a clinical condition. One might accurately integrate the visual feedback that one’s hand is paralyzed, but still rely on an outdated proprioceptive prediction involving a fully functioning hand or vice versa. This is also in line with the results of Besharati et al. (2014), who found that brain areas commonly damaged in anosognosia for hemiplegia (insular and striatal regions) weaken the accuracy of interoceptive signals, which then result in flawed inferences about the self and difficulties in integrating new information and updating premorbid beliefs about the bodily state.

Other models that theorize about the primary causes of anosognosia and adopt a more modular approach include the "Dissociable Interactions and Conscious Experience" model (DICE model) developed by Schacter (1990). In this model, a "conscious awareness system" (CAS) is responsible for integrating various perceptions and, through a connection to the executive system, influences action planning and execution. A disruption of the CAS leads to a domain-overarching

deficit, while a disruption of individual modules results in a domain-specific deficit. Levine (1990) developed a model in which realistic illness awareness must gradually develop. He explains that detecting blindness is not like discovering something by seeing it; rather, it resembles a diagnostic process where one notes data and infers the most plausible explanation. One learns about one's blindness not through introspection and examination of the sensory content of consciousness, but through a process of self-diagnosis. Other models proposed to explain reduced illness awareness include the "Disconnection Hypothesis" by Geschwind (1965), the Feed-Forward Hypothesis by Heilman (1991), the Feedback Hypothesis by Frith et al. (2000) and the Awareness Model by Stuss et al. (2001).

Hemispheric Dominance

In his seminal paper on anosognosia, Babinski proposed the hypothesis that anosognosia might be specific to lesions of the right hemisphere, a question that has since become central to research on the condition (Langer & Levine, 2014). He posed this question because the two patients he reported exhibited hemiplegia following right-hemispheric brain damage. The assumption that impaired illness awareness primarily results from right-hemispheric lesions subsequently dominated scientific literature. Often, study designs excluded individuals with left-hemispheric lesions, partly because most diagnostic procedures were based on interviews and the majority of people have left-hemispheric language dominance. Consequently, Weinstein and Kahn (1955) argued that this linguistic asymmetry could introduce bias, as individuals with impaired language comprehension and production have limited ability to adequately communicate their lack of illness awareness.

Studies by Gilmore et al. (1992), Carpenter et al. (1995), and Durkin et al. (1994) addressed this question using the intracarotid sodium amobarbital procedure (Wada test). This procedure involves injecting a barbiturate that temporarily anesthetizes either the right or left hemisphere, allowing clinicians to assess the functions of the non-anesthetized hemisphere. After the anesthesia wore off, patients were asked if they noticed any deficits or impairments. These studies found that most patients did not recall any impairments after right hemisphere anesthesia, whereas after left hemisphere anesthesia, most could recall their specific impairments during the anesthesia.

Although these results seem to support the assumption that anosognosia primarily results from right-hemispheric lesions, such interpretations should be approached with caution. Complete hemispheric anesthesia is not comparable to specific lesions, and other factors might play a role. Moreover, Cocchini et al. (2009) demonstrated using a nonverbal test that anosognosia for motor deficits can also occur after left brain damage. Similarly, impaired insight into language deficits was found after left hemisphere damage (Cocchini et al., 2010), and anosognosia in apraxia has been reported (Buchmann et al., 2018). These findings suggest that the right-hemispheric dominance observed in the literature might be an artifact arising from methodological biases, such as assessment methods or the exclusion of certain patient groups, rather than a result of underlying neural mechanisms.

Neuropsychological Assessment of Anosognosia

Assessing whether anosognosia is present in a clinical context can be carried out using various tests. A patient's lack of illness awareness can have significant consequences for potential rehabilitation and intervention measures (Gauggel, 2016). Due to the multifaceted nature of anosognosia, its distinction from other phenomena like denial (Freud, 1894) and denial of illness (Weinstein & Kahn, 1955), and the differentiation between explicit and implicit anosognosia, there is no "gold standard" for assessing an impaired awareness of deficits. A review by Nurmi and Jehkonen (2014) found 41 different methods used to detect anosognosia after a stroke. Similar findings were reported by Ruijter et al. (2020), who identified 49 different test procedures to assess anosognosia in dementia patients. Despite this multitude of measurement methods, they can be broadly categorized into three groups: 1. clinical rating, 2. discrepancy between patient and informant, and 3. discrepancy between patient's self-assessment and actual performance.

Clinical Rating

In clinical rating, the clinician assesses whether and to what extent anosognosia is present. This can be done using non-standardized questions and observations, as was common in the early literature on anosognosia (Babinski, 1914; von Monakow, 1885), or through standardized questionnaires, which is the prevalent practice today. One of the first tests was developed by Cutting (1978), where the clinician asks the patient a series of questions regarding their motor deficits to detect anosognosia and

other associated phenomena (e.g., anosodiaphoria). Another questionnaire is the Bisiach Scale (Bisiach et al., 1986), which categorizes the patient's responses during the clinical interview on a 4-point Likert scale to distinguish between different severity levels. The scoring is as follows:

- **0**: The disorder is spontaneously reported or mentioned by the patient following a general question about their complaints.
- **1**: The disorder is reported only following a specific question about the strength of the patient's left limbs.
- **2**: The disorder is acknowledged only after its demonstration through routine techniques of neurological examination.
- **3**: No acknowledgement of the disorder can be obtained.

The Bisiach Scale is frequently used due to its simplicity and general efficiency but is not without limitations. For instance, it does not distinguish between nonverbal or implicit anosognosia and verbal or explicit anosognosia (Jenkinson et al., 2011). Other similar methods to assess explicit anosognosia include the PCRS by Prigatano et al. (1998), the Anosognosia Questionnaire by Starkstein et al. (1992), and the Anosognosia for Hemiplegia Questionnaire by Feinberg et al. (2000).

Beyond assessing explicit or verbal anosognosia, methods have evolved to determine the presence of implicit or nonverbal anosognosia. Ramachandran (1995) used an experimental design where patients with hemiplegia chose between a unimanual task (e.g., stacking a set of blocks) or a bimanual task (e.g., tying a shoelace). The reward (e.g., money) for successfully completing the bimanual task was higher. Since completing the bimanual task is impossible for patients with hemiplegia, choosing it indicates implicit anosognosia. Such designs for assessing implicit anosognosia have gained traction in recent years. Fotopoulou et al. (2008) used the rubber hand illusion (Botvinick & Cohen, 1998) to reveal differences in motor intention between hemiplegic patients with and without anosognosia. Another procedure, similar to Ramachandran's design, is the Bimanual Task (Cocchini et al., 2010) where patients solve tasks best performed with two hands. The study demonstrated a dissociation between explicit and implicit anosognosia in some patients, suggesting that anosognosia is a multifaceted phenomenon (Prigatano, 2010).

Discrepancy Between Patient and Informant

Another method to detect anosognosia is by determining a discrepancy score between the patient and an informant, usually a family member, caregiver, or clinician. It is crucial that the informant has sufficient insight into the patient's abilities due to regular interaction, enabling a realistic assessment. Potential biases in external assessments by close individuals (Hackett et al., 2020) and caregivers (De Wit et al., 2024) should also be considered. If the patient overestimates their abilities, reporting no or few problems, while the informant notes significant limitations, this results in an elevated discrepancy score. Exceeding a predefined threshold indicates the presence of anosognosia. This approach is found in the Awareness Questionnaire (Sherer et al., 1998), the Catherine Bergego Scale (Azouvi, 1996), and a test by Vossel et al. (2012) for anosognosia in neglect.

Notably, the Visual-Analogue Test for Anosognosia (VATA) exists for detecting anosognosia in various domains: motor deficits (VATA-M; Della Sala et al., 2009), language problems or aphasia (VATA-L; Cocchini, et al., 2010) , apraxia (Buchmann et al., 2018), and activities of daily living (Della Sala et al., 2022). An advantage of the VATA tests lies in their ease of administration. Each situation, whose severity the patient assesses, includes a question (e.g., "Do you have difficulty washing your hands?") accompanied by an image (e.g., a person washing their hands). This simplifies application and allows testing of patients with language impairments (Cocchini et al., 2010), who are often excluded due to test design (Orfei et al., 2007).

Discrepancy Between Patient's Self-Assessment and Actual Performance

An additional way to assess anosognosia is by evaluating the discrepancy between the patient's retrospective assessment of their performance in a neuropsychological test and their actual test results. A significant discrepancy—where the patient overestimates their performance—can indicate possible anosognosia. A Self-Appraisal Discrepancy (SAD; Tondelli et al., 2018) score can be calculated for each test. This approach is mainly used with patients who have neurodegenerative diseases like dementia, Alzheimer's, or mild cognitive impairment (Ruijter et al., 2020), as seen in studies by Antoine et al. (2013) or Anderson and Tranel (1989).

However, the results of these scores should be interpreted with caution, since an accurate performance assessment in healthy subjects may not be a realistic baseline assumption (Leicht et al., 2010), and self-ratings can be affected by mood or personality-related variables (Clare et al., 2005).

Overall, there are several different approaches to assessing anosognosia for various pathological syndromes. Ideally, implementing multiple methods would provide valuable insight into the different facets and severity of anosognosia. However, given the high ecological cost, it's important to consider the individual situation (e.g., Does the patient have a caregiver with likely unbiased insight into their abilities? Does the clinician have experience in assessing and dealing with anosognosia? Can the disorder be captured by a valid test and compared with the patient's subjective evaluation?).

Neural Correlates of Anosognosia

Due to its multifaceted etiology, advancements in methodology and varying application, anosognosia has been linked to various brain regions and associated networks. The vast majority of literature deals with neural correlates of anosognosia for motor deficits, such as hemiplegia or hemiparesis. A meta-analysis from Pia et al. (2004) showed that the occurrence of anosognosia is not dependent on a specific brain region, but is rather caused by a combination of cortical (frontal, parietal or temporal) and subcortical structures, with the highest for lesions involving a combination of frontal and parietal structures.

Anosognosia did also occur when only subcortical areas were damaged, most frequently the thalamus, basal ganglia and the insula. A study by Karnath et al. (2005) showed that the right posterior insula was significantly more damaged in patients with hemiplegia/hemiparesis and anosognosia than with solely hemiplegia/hemiparesis. The authors argue that the posterior insula might play a role in integrating different input signals related to self-awareness. There have been several other studies (Berti et al., 2005; Fotopoulou et al., 2010; Kletenik et al., 2023; Klingbeil et al., 2020; Orfei et al., 2007; Pacella et al., 2019; Starkstein et al., 2010; Vocat et al., 2010) that have linked anosognosia with the (anterior) insula cortex. Neuroscientific studies have shown that the anterior insula cortex (AIC) can be linked to perception and subjective representation of proprioception and viscerception

(Craig, 2009; Critchley et al., 2004; Farrer et al., 2003; Farrer & Frith, 2002; Tsakiris et al., 2007), the perception of sensation and movements (Craig, 2002, 2011; Mutschler et al., 2007) and subjective expectations (Preuschoff et al., 2008; Seymour et al., 2004).

The role of the insula can be linked to the free-energy principle proposed by Karl Friston (Barrós-Loscertales, 2018; Friston, 2010), where the human brain strives to minimize a quantity called “free energy”, by predicting sensory inputs beforehand to reduce the difference between those predictions and actual sensory inputs, thereby maintaining homeostasis. Here the insula could be regarded as one of the key areas for integrating interoceptive predictions (Barrett & Simmons, 2015). Therefore, a hypothesis for anosognosia could be that, when damaged, the insula is unable to adequately integrate those aberrant sensory inputs (e.g. paralysis after a stroke), resulting in a divergent perception of reality (e.g. my arm is totally fine).

Another distinct region that has been linked with anosognosia is the anterior cingulate cortex (ACC). Several studies (Ham et al., 2014; Kletenik et al., 2023; Moro et al., 2011, 2016; Pacella et al., 2019; Vocat et al., 2010; Vossel et al., 2012) showed that damage to the ACC is linked to the occurrence of anosognosia. The ACC is involved in many different functions (Medford & Critchley, 2010; Paus et al., 1998) such as mediating cognitive influences on emotion (Stevens et al., 2011), modifying responses to challenging cognitive and physical states (Gasquoine, 2013) and updating of beliefs and internal models (Kolling et al., 2016). The literature has demonstrated a strong co-activity between the AIC and the ACC in a variety of tasks (Medford & Critchley, 2010; Taylor et al., 2009). This leads to the hypothesis that the AIC is responsible for afferent representations of bodily signals, while the ACC uses these representations to initiate behavior in response to these signals (Craig, 2009; Heimer & Van Hoesen, 2006).

Another area that shows a strong connection with the ACC is the supplementary motor cortex (SMA; Goldberg, 1985). Here it was shown that the ACC is modulating the activity of the SMA, especially in tasks that require the integration of cognitive and motor functions during coordinated unimanual motor behavior (Asemi et al., 2015), and that the ACC serves as a modulator, suppressing intrinsically favored coordination tendencies (Wenderoth et al., 2005). Given that damage to the SMA has been linked to anosognosia (Berti et al., 2005; Fotopoulou et al., 2010;

Kletenik et al., 2023; Pacella et al., 2019; Pia et al., 2004; Vocat et al., 2010; Vossel et al., 2012) and that SMA is linked to the coordination of temporal action sequences (Gerloff et al., 1997) and the initiation of internally generated movements (Halsband et al., 1994; Roland et al., 1980), impairment in this area could explain the failure in anosognosia to successfully adapt to the new circumstances caused by an injury or disease.

These aforementioned brain areas primarily indicate a failure in integrating various sensory inputs through a bottom-up pathway, but limitations in the verification of such information, as well as the top-down controlled regulation, also seem to be partially impaired in anosognosia. Especially in damaged structures involving the vast fronto-parietal cortex, anosognosia has also been shown (Berti et al., 2005; Fotopoulou et al., 2010; Hartman-Maeir et al., 2001; Moro et al., 2011, 2016; Orfei et al., 2007; Pia et al., 2004; Ramachandran, 1995, 1996; Starkstein et al., 1992, 2010; Vocat et al., 2010; Vossel et al., 2012).

Other subcortical regions that have been associated with anosognosia besides the already mentioned are the amygdala (Pacella et al., 2019; Pia et al., 2004; Vocat et al., 2010), the basal ganglia (Fotopoulou et al., 2010; Moro et al., 2011, 2016; Pia et al., 2004; Romano et al., 2014), the hippocampus (Berlingeri et al., 2015; Klingbeil et al., 2020; Pacella et al., 2019; Vocat et al., 2010) and the thalamus (Karussis et al., 2000; Orfei et al., 2007; Pia et al., 2004). The literature illustrates that the occurrence of anosognosia does not depend on lesions in specific brain areas. Therefore, it seems plausible that anosognosia is less a disorder of individual modules and more a result of disconnection within multimodal networks that encompass cortical and subcortical regions.

A trend that has established itself in recent years in clinical neuropsychology, addressing this assumption, is the application of network analyses based on lesion data (Foulon et al., 2018; Fox, 2018; Thiebaut de Schotten et al., 2015). In addition to this approach, there is also a growing trend to examine clinical neuropsychological disorders through aberrant large-scale network activities, using fMRI (Calhoun et al., 2014) or resting-state fMRI (van den Heuvel & Hulshoff Pol, 2010) techniques. This approach enhances the informational gain achievable through lesion data. Recent studies have shown that there seems to be abnormal activity in the default mode network (DMN) in patients with memory deficits and anosognosia than in patients

only with the deficit (Berlingeri et al., 2015; Mondragón et al., 2019). A study from Klingbeil et al. (2020) could show that in anosognosia for hemiplegia (AHP) a network involving the right posterior hippocampus (i.e. diaschisis) is impaired. Pacella et al. (2019) could show that in AHP three neural systems contribute to AHP, namely the premotor loop (i.e. frontal aslant and fronto-striatal connections between the striatum, the preSMA and the inferior frontal gyrus), posterior parts of the limbic network (i.e. cingulum connections between the amygdala, the hippocampus and the cingulate gyrus) and the ventral attentional network (i.e. SLF III connections between temporo-parietal junction and ventral frontal cortex). A study from Monai et al. (2020) revealed similar findings. Patients with AHP showed aberrant connections in regions of different cognitive networks, such as the default, ventral, attention and cingulo-opercular network. An abnormal activity in the fronto-parietal control network in a group of patients with anosognosia for traumatic brain injury could also be supported by a study from Ham et al. (2014). Furthermore, Kletenik et al. (2023) could show domain specific networks for anosognosia in visual and motor deficits. Visual anosognosia was associated with lesions connected to the visual association cortex and posterior cingulate, while motor anosognosia was characterized by lesions connected with the insula, supplementary motor area and the anterior cingulate. Lesions independent of modality were more connected to the hippocampus and precuneus. Another trend that has gained increasing interest is the study of anosognosia in memory-related disorders, such as Alzheimer's disease (Andrade & Pacella, 2024; Antoine et al., 2019; Hallam et al., 2020; Tondelli et al., 2024) and mild cognitive impairment (Vannini et al., 2017). Findings suggest that anosognosia in these disorders is often associated with an aberrant connectivity profile, particularly involving central hub regions, when compared to patients without impaired illness insight.

All these new findings suggest that anosognosia involves aberrant activity in the multimodal integration of internal, bodily, self-referential, and external perspectives, that can be differentiated regarding the unawareness of different illnesses.

The just mentioned literature mainly focuses on anosognosia for motor deficits (such as hemiplegia, hemiparesis) and anosognosia for memory deficits (such as MCI, dementia, Alzheimer). Neural correlates for anosognosia in aphasia (Lebrun, 1987) have largely not been investigated. This is partially due to the exclusion of

patients with left brain damage in studies (Orfei et al., 2007) and the strong incidence of aphasia in left-brain damaged patients (Scarpa et al., 1987), in whom speech is predominantly left-hemisphere dominant (Corballis, 2014). The commonly used interview style for diagnosing anosognosia makes it difficult to detect in patients with language problems (Cocchini et al., 2010). Since apraxia has also been commonly associated with left brain damage (Buxbaum & Randerath, 2018; Park, 2017) and linked with aphasia (Goldenberg, 2013) the same sparse literature about neural correlates for anosognosia in apraxia exists. But recent findings suggest that apraxia (and its different forms) also involves a high correlated system between different cortical and subcortical networks (Kusch et al., 2018; Rosenzopf et al., 2022), especially in the fronto-parietal network.

Study Aim

The aim of this study is to investigate the neural correlates of anosognosia in motor deficits (hemiplegia, hemiparesis), language deficits (aphasia), and common tool-use disorder (apraxia) to gain a deeper understanding of the pathophysiology of these conditions. Given the limited literature on the neural correlates of anosognosia in aphasia and apraxia, this study provides novel insights into the manifestation of anosognosia across different clinical contexts. Additionally, the investigation allows for a comparison of the various forms of anosognosia to identify potential neural similarities and/or differences.

Main Questions of Research

The following hypotheses refer to an impaired insight for the following disorders: namely, motor deficits, language deficits (aphasia), and impairments in common tool-use deficits (apraxia).

Are lesions in specific brain areas associated with the occurrence of an impaired insight into motor deficits?

- H0 (1.1): An impaired insight into motor impairments is not associated with lesions in the left or right hemispheric areas:
    - (Anterior) Insula
    - Supplementary Motor Area

    - Fronto-Temporo-Parietal Cortex
    - Anterior Cingulate cortex

- H1 (1.1): An impaired insight for motor impairments is associated with lesions in the left or right hemispheric areas:
    - (Anterior) Insula
    - Supplementary Motor Area
    - Fronto-Temporo-Parietal Cortex
    - Anterior Cingulate Cortex

Are lesions in specific brain areas associated with the occurrence of an impaired insight into common tool-use abilities (apraxia)?

- H0 (1.2): An impaired insight for common tool-use abilities (apraxia) is not associated with lesions in the left hemispheric areas:
    - (Anterior) Insula
    - Supplementary Motor Area
    - Fronto-Temporo-Parietal Cortex
    - Anterior Cingulate Cortex
- H1 (1.2): An impaired insight for common tool-use abilities (apraxia) is associated with lesions in the left hemispheric areas:
    - (Anterior) Insula
    - Supplementary Motor Area
    - Fronto-Temporo-Parietal Cortex
    - Anterior Cingulate Cortex

Are lesions in specific brain areas associated with the occurrence of an impaired insight into language related deficits (aphasia)?

- H0 (1.3): An impaired insight for language abilities (aphasia) is not associated with lesions in the left hemispheric areas:
    - (Anterior) Insula

    - Supplementary Motor Area
    - Fronto-Temporo-Parietal Cortex
    - Anterior Cingulate Cortex
- H1 (1.3): An impaired insight for language abilities (aphasia) is associated with lesions in the left hemispheric areas:
    - (Anterior) Insula
    - Supplementary Motor Area
    - Fronto-Temporo-Parietal Cortex
    - Anterior Cingulate Cortex

Exploratory Research Questions

In addition to the focused examination of specific regions, where extensive research allows for specific hypothesis formulation, many other cortical, subcortical, and white matter tracts may be associated with impaired awareness of illness based on the abundant literature. Therefore, the subsequent analysis will adopt an exploratory approach to identify additional connections and associated brain areas related to impaired awareness of illness.

Methods

This study is part of a larger research project focused on motor cognition, led by Prof. Dr. Randerath. The participants were recruited from the Kliniken Schmieder in Konstanz. All participants in this study confirmed their voluntary participation in advance by signing a consent form. In this form, they also agreed to have their personal data and medical findings stored and processed in anonymized form. The participants were able to withdraw from the study at any time without providing a reason and without any disadvantages resulting from their withdrawal.

Participants were excluded from the study if one or more of the following criteria applied:

- Individuals with bilateral hemisphere involvement
- Individuals with cerebellar lesions

- Individuals with brainstem lesions
- Individuals with additional neurological (pre-)conditions
- Individuals with psychiatric (pre-)conditions
- Individuals without normal or "corrected to normal" vision
- Individuals in rehabilitation phases A/B (only patients in phases C/D were included)
- Individuals with excessive alcohol consumption
- Individuals over the age of 80

Study Design

The study design is a correlational observational study with a cross-sectional design. The mapped lesion data of the participants will be tested for correlations with the behavioral test results of the individual scores.

Clinical Sample

The study consists of 125 patients with a unilateral stroke, of whom 58 are female and 67 are male. 56 suffered from a left hemispheric lesion, and 69 from a right hemispheric lesional stroke. The average time between the stroke (i.e., the lesion event), the imaging of the lesion, and the behavioral testing is 68 days, with a median of 43 days. Most patients were thus in the sub-acute or post-acute phase at the time of testing. All participants are native German speakers or have sufficient German language proficiency. Since the two samples with either a left- or right-hemispheric lesion are analyzed separately, the data will be treated independently in subsequent analyses.

Measuring Instruments

Anosognosia is assessed using the "*Visual-Analogue Test Assessing Anosognosia*" (VATA). For linguistic deficits (aphasia), the VATA-L (Cocchini et al., 2010; German version: Buchmann & Randerath, 2020a) is used. For apraxia, the VATA-NAT (Buchmann et al., 2018; German version: Buchmann & Randerath, 2020b) is applied, and for motor deficits, the VATA-M (Della Sala et al., 2009; German version: Buchmann & Randerath, 2020c) is utilized. The participants all used the translated German version of the test. All tests demonstrate satisfactory test-retest reliability (>.90; Buchmann et al., 2018; Cocchini, Gregg, et al., 2010; Della Sala et al., 2009). Additionally, the VATA-M showed a high Cronbach's alpha (α=.94;

Della Sala et al., 2009), and the VATA-NAT exhibited high interrater reliability (.83; Buchmann et al., 2020) and high internal consistency (.85). The VATA is used because it is the only test that assesses anosognosia in apraxia and facilitates the inclusion of patients with language deficits. The VATA tests all work by determining the previously described discrepancy score. The patient assesses their abilities, while an informant provides an external assessment. The external evaluation is then subtracted from the self-assessment. If the value is positive, the patient overestimates their abilities. The higher the value, the more the patient overestimates themselves. If the value is negative, the patient underestimates their abilities. The lower the value, the more the patient underestimates themselves. The tests have cut-offs that differentiate the severity of anosognosia (mild, moderate, severe). This allows for an efficient determination of whether the patient is over- or underestimating their abilities and to what extent. Due to the rather small sample size, discrepancy values were used instead of the standard cut-off values for anosognosia, resulting in greater variance.

Lesion Mapping Procedure

No original brain scans were created for this study. Instead, CT or MRI scans provided by the patients were used to analyze lesion images. Since this study is part of a broader research project examining various aspects, the lesions were already outlined. The program SPM 8 (Functional Imaging Laboratory, 2009), along with the Clusterize Toolbox (Clas et al., 2012; de Haan et al., 2015), was used to outline the lesion areas. After outlining, the lesions were saved as VOI (Volume of Interest) files.

Voxelwise Statistical Lesion-Behavior Mapping Analyses

To relate the behavioral data to the specific lesion locations of the patients, a voxelwise statistical lesion-behavior mapping (VLSM) analysis was conducted. For this analysis, the program NiiStat (NITRC, 2018) was used. NiiStat consists of a series of scripts that can be executed in MATLAB (The MathWorks, 2024). The core idea is to perform a statistical test for each voxel, assessing its status (lesion/no lesion) in relation to the corresponding behavioral value (de Haan & Karnath, 2018). This univariate analysis assumes a directed relationship, meaning that lesions in specific brain areas are associated with lower performance in behavioral measures.

Due to the nature of mass-univariate analysis, which involves conducting a vast number of independent statistical tests across thousands of voxels, the probability of reporting false effects, known as familywise error rates, increases (Karnath et al., 2018). NiiStat allows users to control for these error rates using different correction methods. One method employed in this study is controlling the false discovery rate (FDR; Benjamini & Hochberg, 1995), which manages the proportion of falsely identified significant voxels (false positives) among all voxels declared significant.

NiiStat also offers the option to deskew the data and regress for lesion volume. Regressing lesion volume is particularly helpful when patients have lesions covering extensive brain regions. Large brain lesions that span multiple areas are usually associated with severe impairments across various neurological and neuropsychological functions (Kimberg et al., 2007). This complexity complicates the precise identification of specific brain regions linked to particular neuropsychological impairments. By selecting this option, the behavioral data are adjusted for variability described by the overall lesion volume. NiiStat describes the procedure as computing the total lesion volume for each individual, regressing this volume against each behavioral variable, and basing the subsequent analysis on the residual variability of the behavior (NiiStat, 2020).

Another helpful tool offered by NiiStat is deskewing the data. VLSM utilizes a general linear model, which assumes that the behavioral data are normally distributed. In clinical populations, this assumption is often violated, typically resulting in a negatively skewed distribution. Patients without deficits tend to perform near the maximum level, while those with deficits show poorer and more variable performance (Karnath et al., 2019). Deskewing the data helps meet the assumptions required for conducting a t-test. If the data are significantly skewed (skewness > 1.96), a square or square-root transformation is applied (NiiStat, 2020).

Unless otherwise stated, the options to deskew the data and regress for lesion volume were consistently applied in the analysis. The minimum overlay, defined as the percentage of participants required to show a lesion in a given area, was set at a threshold of at least 10% of the patients included in the analysis. This threshold aligns with the overlap criterion established by Karnath and Sperber (2017). The corrected p-value threshold determining statistical significance was set at 0.05.

For the behavioral scores, the reported discrepancy values were categorized as either overestimations or underestimations by the patient. Each analysis was performed separately for these groups. Additionally, the discrepancy scores were transformed into corresponding percentage values. Because NiiStat interprets lower behavioral scores as indicative of greater impairment, we transformed the discrepancy values so that a perfect self-assessment (discrepancy value = 0) corresponds to 100%, indicating no impairment. The maximum discrepancy value observed (whether it reflects overestimation or underestimation) was set to 0%, representing the highest level of impairment in self-awareness. After conducting the analysis, NiiStat generates a folder containing various files. Some of these files are in the ".nii" format, referring to the Neuroimaging Informatics Technology Initiative (NIfTI), which is a format used to store and display brain image-related data. If the VLSM identifies significant voxels that survive thresholding, NiiStat outputs a topography plot of all significant voxels. It also produces a topography plot of the z-transformed voxel-based results for all voxels included in the statistical analysis (Baldo et al., 2022), along with a text file containing results, the minimum and maximum z-values, and additional MATLAB-generated commands. This comprehensive topography plot allows setting manual z-score thresholds with specified minimum and maximum values, thereby including only voxels with a high association to the behavioral score. Even though this approach is descriptive, it still permits drawing some conclusions from the lesion data. If no significant voxels are found, meaning the voxels did not survive thresholding, this descriptive approach is also employed. The specific minimum and maximum z-values, along with their corresponding p-values, are reported in the analysis section.

Lesion Data Imaging

For visual representation and interpretation, the program MRIcroGL (Rorden, 2022) was used. MRIcroGL allows for the visualization and interpretation of the NIfTI files generated by NiiStat. The files were overlaid onto the "MNI152" standard brain template (Fonov et al., 2009, 2011) to identify significant voxels in the VLSM analysis. To capture the affected brain areas, two atlases were employed: the Automated Anatomical Labeling (AAL; Rolls et al., 2020) atlas for cortical and subcortical regions, and the Natbrainlab white matter tractography atlas (de Schotten et al., 2011) for white matter tracts.

MRIcroGL offers an option to 'Generate Cluster Table,' which provides detailed information about clusters and links impaired brain regions to the cortical and subcortical areas of the AAL atlas. This feature was utilized to generate clusters of significant regions by applying a threshold intensity of 40 and a minimum cluster size of 32 mm^3. This cluster size corresponds directly to the size of the associated voxels, meaning that a cluster needed to contain at least 32 significant voxels to be reported and included in the analysis. Since this function could not be applied to the Natbrainlab atlas for white matter tracts, the associated tracts were manually registered. Including these two atlases enabled the association of all significant voxels with either a cortical or subcortical structure or a white matter tract.

Results

Descriptive Statistics of Sample and Results of the Discrepancy Values

Table 1 provides an overview of how patients overestimated and underestimated their abilities compared to the ratings by an informant.

Table 1

Overview of the prediction outcome of all the discrepancy tests

		Total	Over	Under	Accurate
LBD	VATA-L	56 (100%)	30 (53.57%)	18 (32.14%)	8 (14.29%)
	VATA-M	56 (100%)	35 (62.5%)	14 (25%)	7 (12.5%)
	VATA-NAT	56 (100%)	25 (44.64%)	23 (41.07%)	8 (14.29%)
RBD	VATA-M	69 (100%)	42 (60.87%)	17 (24.64%)	10 (14.49%)

Note. Description of how many of the patients either over-, underestimated or accurately estimated their abilities compared to the evaluation of an informant. An accurate estimation equals a discrepancy of 0.

In all groups, patients tended to overestimate their abilities rather than underestimate them. The smallest group comprised those who accurately rated their abilities compared to the informant (discrepancy value of 0). Table 2 presents the descriptive statistics for both underestimation and overestimation separately, since in the analysis both groups are treated separately as well. It is noteworthy that accurate

predictions (discrepancy value of 0, representing 100% accuracy) are included in both overestimation and underestimation groups for analysis purposes. The described Barthel Index is an instrument for assessing patients' daily living skills, evaluating their ability to perform 10 basic activities of daily life (Mahoney & Barthel, 1965).

Table 2

Descriptive Characteristics of the Patient Sample with Left- and Right-Hemispheric Lesions

Left-Hemispheric Lesion				
	Total Sample	Female		Male
Gender	56	24 (42.86%)		32 (57.14%)
	Mittelwert	Median	SD	Min – Max
Age	60.2	63.5	13.08	30 – 79
Barthel Index [a]	58.53	60	19.21	25 - 90
	High	Middle		Low
Education Level [b]	19 (33.93%)	32 (57.14%)		4 (7.14%)
Right-Hemispheric Lesion				
	Total Sample	Female		Male
Gender	69	34 (49.28%)		35 (50.72%)
	Mittelwert	Median	SD	Min – Max
Age	60.59	62.0	11.99	25 – 78
Barthel Index [a]	53.22	55	16.38	15 - 100
	High	Middle		Low
Education Level [b]	14(20.29%)	46 (66.67%)		9 (13.04%)

[a] The Barthel Index indicates the degree of independence of the patient. The scores range from 0 to 100, with 100 representing full independence and 0 representing complete dependence.

[b] The educational level represents the highest level of completed education of the participants. One value is missing.

Based on the cut-off values of the VATA test, the following results were found in the Left Brain-Damaged (LBD) group (n = 56):

- **VATA-NAT**: Five patients (8.9%) showed a mild form of anosognosia, three patients (5.4%) a moderate form, and no patient exhibited a severe form.
- **VATA-L**: Two patients (3.6%) were classified as borderline, and six patients (10.7%) were diagnosed with anosognosia.
- **VATA-M**: Ten patients (17.9%) showed a mild form of anosognosia, three patients (5.4%) a moderate form, and one patient (1.8%) a severe form.

In the Right Brain-Damaged (RBD) group for motor deficits (hemiplegia and hemiparesis), eleven patients (16.4%) were diagnosed with a mild form of anosognosia, and two patients (3.0%) with a moderate form.

Table 3 provides the descriptive statistics of discrepancy values used in the analysis. Based on the setup of the VLSM program, the groups were divided into overestimations and underestimations, and each was analyzed separately.

Table 3

Descriptive Statistics of Discrepancy Values, Separated by Overestimation and Underestimation

		Mean[a]	Median	SD	Min - Max
Overestimation					
LBD	L	82.89%	87.78%	20.59	12.22% – 100%
	NAT	88.94%	94.87%	15.03	46.15% – 100%
	M	88.59%	93.23%	14.29	32.29% - 100%
RBD	M	90.58%	93.75%	9.65	60.42 – 100%
Underestimation					
LBD	L	93.97%	95.56%	6.16	80 – 100%
	NAT	88.45%	91.67%	11.03	61.11 – 100%
	M	94.20%	96.88%	6.94	73.69 – 100%
RBD	M	96.77%	97.92%	4.15	84.38 – 100%

[a] All VATA test results were standardized to a score ranging from 0 to 100%. A discrepancy score of 0% thus represents the largest possible discrepancy between the two ratings, whereas a score of 100% indicates no discrepancy.

Note. In both groups, correct assessment—meaning a discrepancy of 0—is included and represents the best possible result (100%).

Voxel-Based-Lesion Analysis

The voxelwise statistical lesion-behavior mapping (VLSM) analysis showed significant regions only in patients with left-hemispheric lesions. For the right-hemispheric group, no matter the impaired cognitive domain, no voxels survived the thresholding process, including the additional calculations (deskewing the data and regressing for lesion volume). Robust results were found for impaired awareness of language deficits and impaired awareness of motor deficits, which remained significant even after additional calculations. For impaired awareness of apraxia, significant voxels were only observed after thresholding when lesion volume was regressed, but not when the data was deskewed. This implies that the skewed distribution affects the VLSM analysis, and the results should be taken with caution.

Impaired Awareness for Language Deficits and Associated Regions in the Left Hemisphere

In the analysis 39 participants were included. The general linear model included 242,345 voxels of those voxels analyzed 1,561 survived the threshold. The threshold z-value was -4.06 with a maximum z-value of -5.26. Table 4 provides a detailed description of the associated brain regions, their coordinates and the peak structure along with its corresponding z-value.

Table 4

Overview of Associated Significant Left hemispheric Regions for Impaired Insight into Language Deficits

Region of Peak Associaton	Z-Score of Peak	Peak MNI Coordinates (X, Y, Z)	Other Structures associated in Cluster	Cluster Volume (in Voxels)
Uncinate Fasciculus	-5.1	-22.7, 24.2, -4.7	Anterior Insula, Putamen, Corticospinal Tract, Inferior Occipitofrontal Fasciculus	919

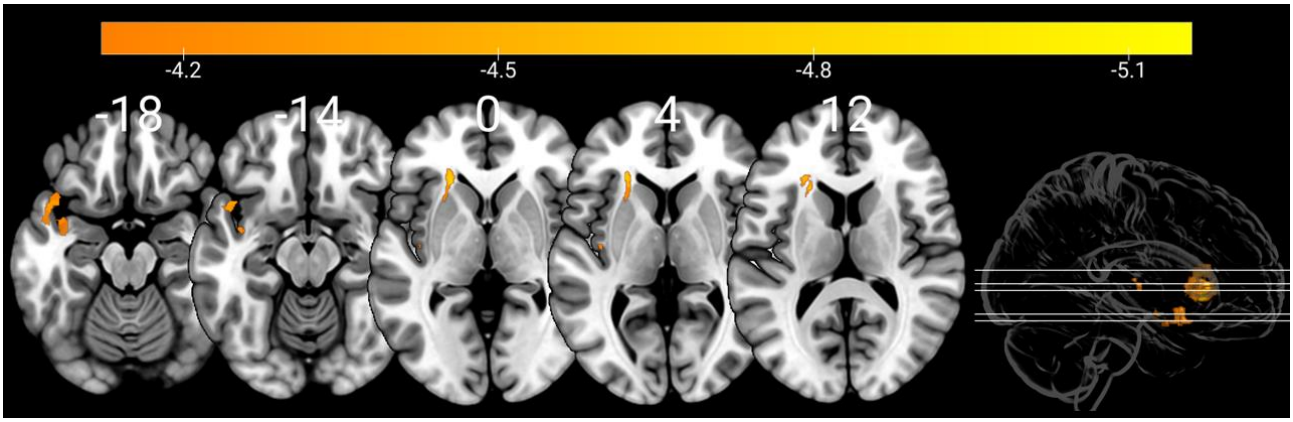
Middle Temporal Gyrus	-4.4	-50.0, 5.0, -18.7	Superior Temporal Gyrus, Middle Temporal Gyrus, Anterior Insula	430
Superior Temporal Pole	-5.0	-42.6, 2.8, -20.9	Middle Temporal Gyrus, Anterior Insula	93
Posterior Insula	-4.2	-38.2, 15.6, 6.4		43
Uncinate fasciculus	-4.2	-40.4, -3.8, -13.5	Superior Temporal Gyrus	34

Note. This table gives an overview of the significant associated structures. Note that the peak structure, does not imply that this structure had most associated voxels, but rather that the highest local z-value for that cluster was in that region.

Figure 1 shows the axial view of the significantly associated brain regions.

Figure 1

Axial View of Significant Brain Regions Associated with Impaired Insight for Language Deficits

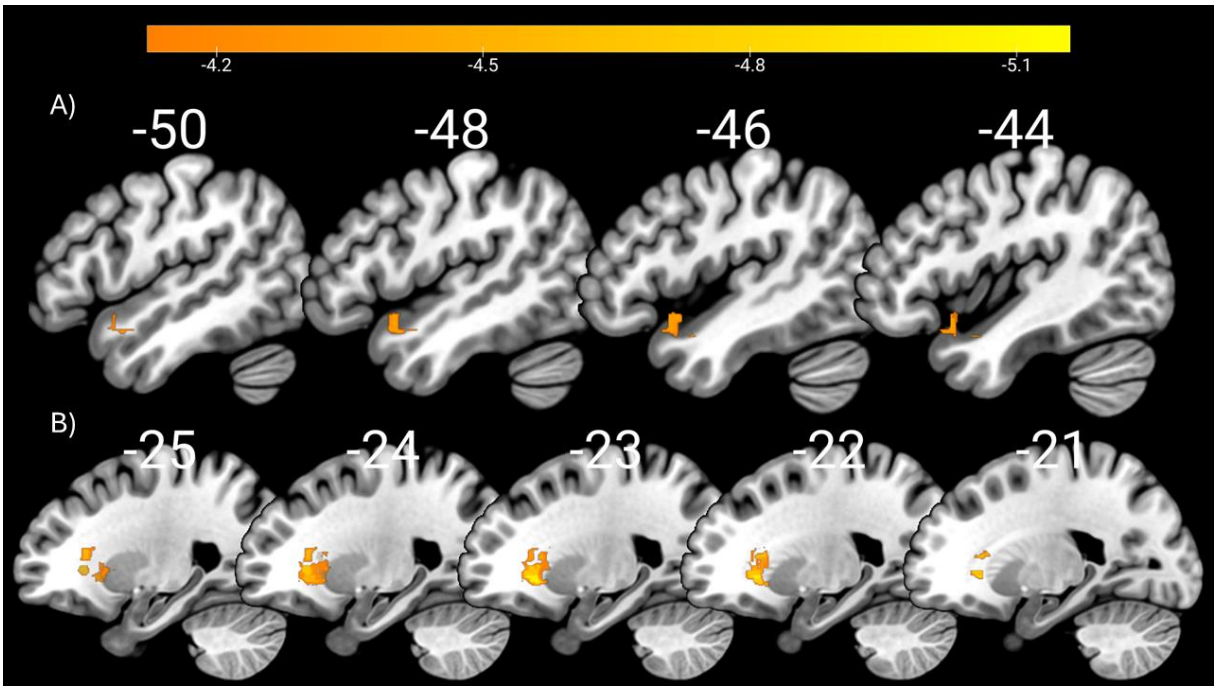


Note. Brighter colors indicate a higher z-score. The first two slices (-18, -14) mainly cover the superior temporal pole and the inferior longitudinal fasciculus. The other three slices (0, 4, 12) primarily cover the anterior insula, the putamen, the uncinate fasciculus, and the inferior occipitofrontal fasciculus.

Figure 2 shows the sagittal view of the significantly associated regions.

Figure 2

Sagittal Views of Significant Brain Regions Associated with Impaired Insight for Language Deficits



Note. Sagittal view of the two main associated clusters. The cluster shown in A), with 430 voxels, mainly covers the superior temporal pole. The cluster shown in B), with 919 voxels, includes the insula and the putamen, as well as white matter tracts.

There are two main significant regions, as measured by the number of significant voxels, associated with an impaired insight into language deficits. One of the regions (919 significant voxels) is a subcortical structure, which primarily consists of white matter tracts, mainly the corticospinal tract, the uncinate fasciculus, and the inferior fronto-occipital fasciculus, but also involves the putamen and the anterior part of the insula. The other large associated region (430 significant voxels) is located mainly in the superior temporal pole, peaking in the middle temporal region. Again, white matter tracts are also involved, namely the left inferior longitudinal fasciculus and the left uncinate fasciculus. This region is accompanied by a smaller cluster of significant voxels (43 voxels), located in the superior temporal pole, involving the left uncinate fasciculus as well. Another small area (43 significant voxels) consists of the insula.

Impaired Awareness for Motor Deficits and Associated Regions in the Left Hemisphere

In the analysis 42 participants were included. The general linear model included 278,081 voxels, of those voxels analyzed 5,279 survived the threshold. The threshold z-value was -3.80 with a maximum z-value of -5.01. Table 5 provides a

detailed description of the associated brain regions, their coordinates and the peak structure along with its corresponding z-value.

Table 5

Overview of Associated Significant Left hemispheric Regions for Impaired Insight into Motor Deficits

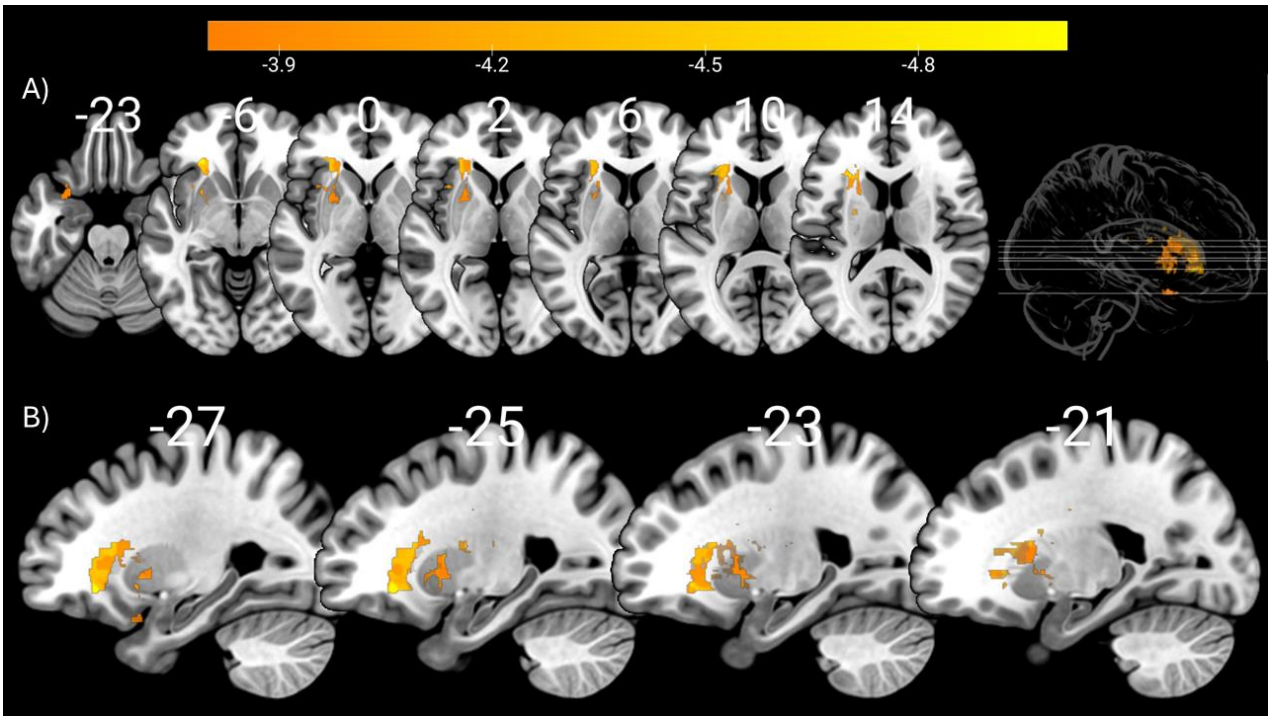
Region of Peak Associaton	Z-Score of Peak	Peak MNI Coordinates (X, Y, Z)	Other Structures associated in Cluster	Cluster Volume (in Voxels)
Inferior Frontal Gyrus, Orbital Part	-5.0	-27.8, 29.4, -8.3	Anterior Insula, Putamen, Pallidum, Inferior Frontal Gyrus – Triangular Part, Inferior occipitofrontal fasciculus, Uncinate fasciculus, internal capsule, Corticospinal tract	4,808
Superior Temporal Pole	-3.8	-27.1, 6.5, -23.8	Inferior Frontal Gyrus - Orbital Part	266
Capsula interna	-4.2	-21.9, -14.9, 14.5	Corticospinal tract	46
Anterior Insula	-4.0	-33.0, 12.4, -5.4		44

Note. This table provides an overview of significant associated structures. The peak structure does not imply that this structure had the most associated voxels but rather the highest local z-value for that cluster. All structures refer to the corresponding structure in the left hemisphere.

Figure 3 shows a visual representation of the significant voxels in an axial view and a sagittal view.

Figure 3

Axial and Sagittal View of Significant Brain Regions Associated with Impaired Insight for Motor Deficits



Note. The axial slices in A) show the large, differentiated cluster with 4,808 associated voxels. The slice at -23 shows a small association with the superior temporal pole. The sagittal view in B) highlights again the large associated cluster, primarily covering subcortical areas and white matter tracts.

One rather large area (4,808 significant voxels) was associated with impaired insight into motor deficits. This associated area covers brain regions consisting of cortical, subcortical, and white matter tracts. This includes cortical regions in the frontal inferior orbital gyrus, which is the peak region, the frontal inferior triangular gyrus and the anterior insula; subcortical regions in the lentiform nucleus, as part of the basal ganglia, namely the putamen and the pallidum; and white matter tracts involving the inferior occipito-frontal fasciculus, the uncinate fasciculus, the internal capsule, and the corticospinal tract. This diffuse area is by far the largest region that shows significant associations with impaired awareness and motor deficits. In addition to this area, there are other regions where significant voxels were found, including a region located in the anterior insula (44 significant voxels) and a region encompassing the superior temporal pole and the inferior frontal orbital gyrus (266 significant voxels), areas which were also involved in the larger cluster.

Impaired Awareness for Apraxia and Associated Regions in the Left Hemisphere

In the analysis 34 participants were included. The general linear model included 186,726 voxels, of those voxels analyzed 3,616 survived the threshold. The

threshold z-value was -3.74 with a maximum z-value of -5.86 Notably, when the data were transformed to correct for skewness ('deskewed'), no significant voxels remained. This suggests that the initial significant findings may have been influenced by the skewed distribution of the data. Only the option "regress for lesion volume" was additionally applied for the General Linear Model and the FDR correction. Therefore, the results and associated regions must be interpreted with caution, as there is a skewed distribution present that could impact the univariate analysis and therefore the results. Table 6 provides a detailed description of the associated brain regions, their coordinates and the peak structure along with its corresponding z-value.

Table 6

Overview of Associated Significant Left Hemispheric Regions for Impaired Insight for tool use disorder (Apraxia)

Region of Peak Associaton	Z-Score of Peak	Peak MNI Coordinates (X, Y, Z)	Other Structures associated in Cluster	Cluster Volume (in Voxels)
Insula	-4.8	-35.9, 13.1, 1.2	Putamen, Inferior Frontal Gyrus – Opercular Part, Rolandic Operculum	1,516
Anterior Insula	-4.3	-24.1, 27.1, 9.4	Putamen, Pallidum, Uncinate Fasciculus, Inferior Occiptofrontal Fasciculus, Corticospinal Tract, Internal Capsule	1,261
Superior Temporal Gyrus	-4.1	-43.3, -9.7, -2.4	Posterior Insula, Heschl’s Gyrus	326
Corticospnal Tract	-4.7	-21.9, -17.1, 33.7	Internal Capsule, Corpus Callosum	182

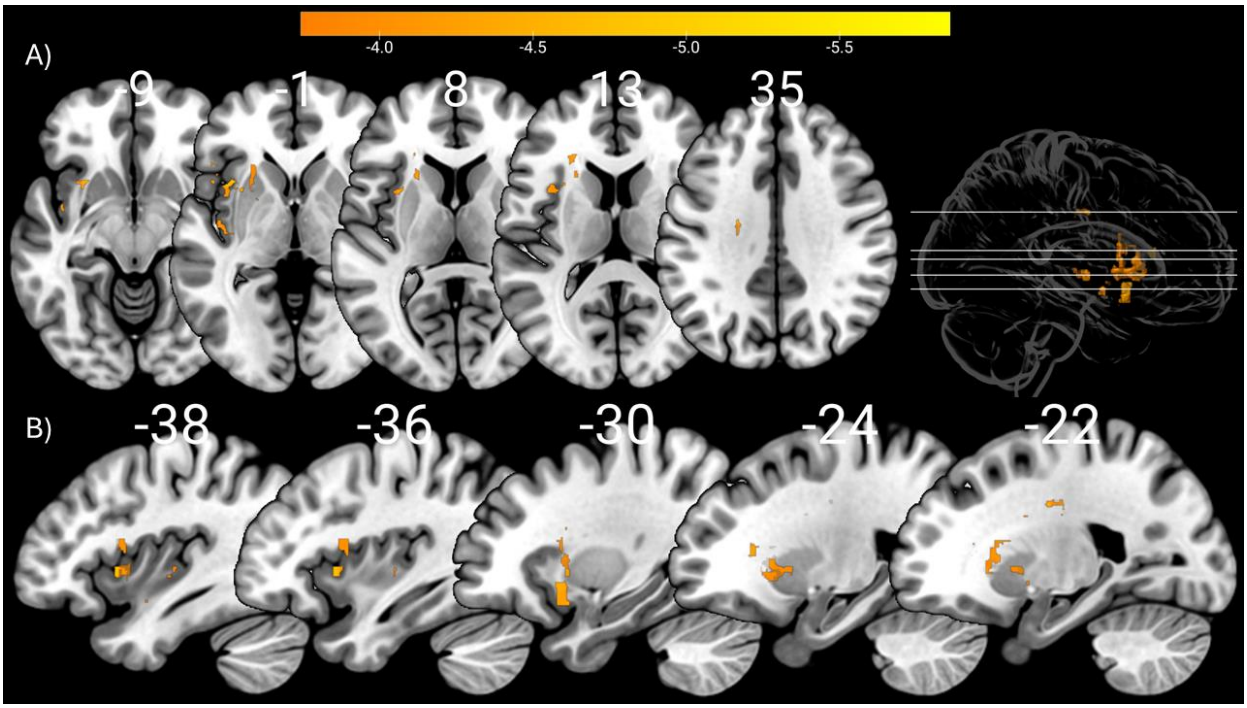
Superior Temporal Gyrus	-4.5	-40.4, -3.8, -11.3	Posterior Insula, Superior Temporal Pole	79
Inferior Frontal Gyrus – Opercular Part	-3.7	-23.4, 29.4, -9.1		42
Corticospinal Tract	-4.1	-23.4×0.6×29.3		40

Note. This table provides an overview of significant associated structures. The peak structure does not imply that this structure had the most associated voxels but rather the highest local z-value for that cluster. All structures refer to the corresponding structure in the left hemisphere.

Figure 4 shows a visual representation of the significant voxels in an axial view and a sagittal view.

Figure 4

Axial and Sagittal View of Significant Brain Regions Associated with Impaired Insight for goal-directed actions



Note. Both topographical views provide insight into the nuanced associated areas. The deeper structures (1,516 associated voxels) in the sagittal view (slices -30, -24, -

22) mainly cover the putamen, pallidum, insula, and the inferior occipitofrontal fasciculus; this area is also visible in the axial slices. The axial slice at 35 covers the corticospinal tract.

The significant areas are mainly clustered in the region of the anterior insula, where both of them have their peak, and regions surrounding the insula. Here, we have two larger clusters (1,261 and 1,516 significant voxels, respectively) that include subcortical structures, namely the pallidum and putamen (both part of the basal ganglia); cortical structures, such as the superior temporal pole, inferior frontal gyrus (triangular part), inferior frontal gyrus (opercular part), and Rolandic operculum; and white matter tracts, including the uncinate fasciculus, inferior fronto-occipital fasciculus, corticospinal tract, and left internal capsule. There are also smaller clusters of significant voxels, where again the insula and its surrounding cortical, subcortical and white matter tracts are involved.

Impaired Awareness for Motor Deficits and Associated Regions in the Right Hemisphere

The VLSM showed no significant voxels in relation to impaired awareness of motor deficits in the patient group with right hemispheric lesions. However, there is the possibility of generating a topographical representation of the voxel-based results included in the statistical analysis by manually setting Z-score thresholds. For this purpose, a minimum Z-score of -3.01 (corresponding to a p-value of 0.001) and a maximum Z-score of -4.27 (corresponding to a p-value of 0.00001) are used. It is important to note that this is merely a descriptive analysis, where no statistical tests were performed; thus, the results should be interpreted with caution. The associated regions are located in the parietal cortex and include the supramarginal, postcentral, and precentral gyri.

Table 7 provides a detailed description of the associated brain regions, their coordinates, and the peak structure along with its corresponding z-value.

Table 7

Overview of Associated Right Hemispheric Regions for Impaired Insight for Motor Deficits

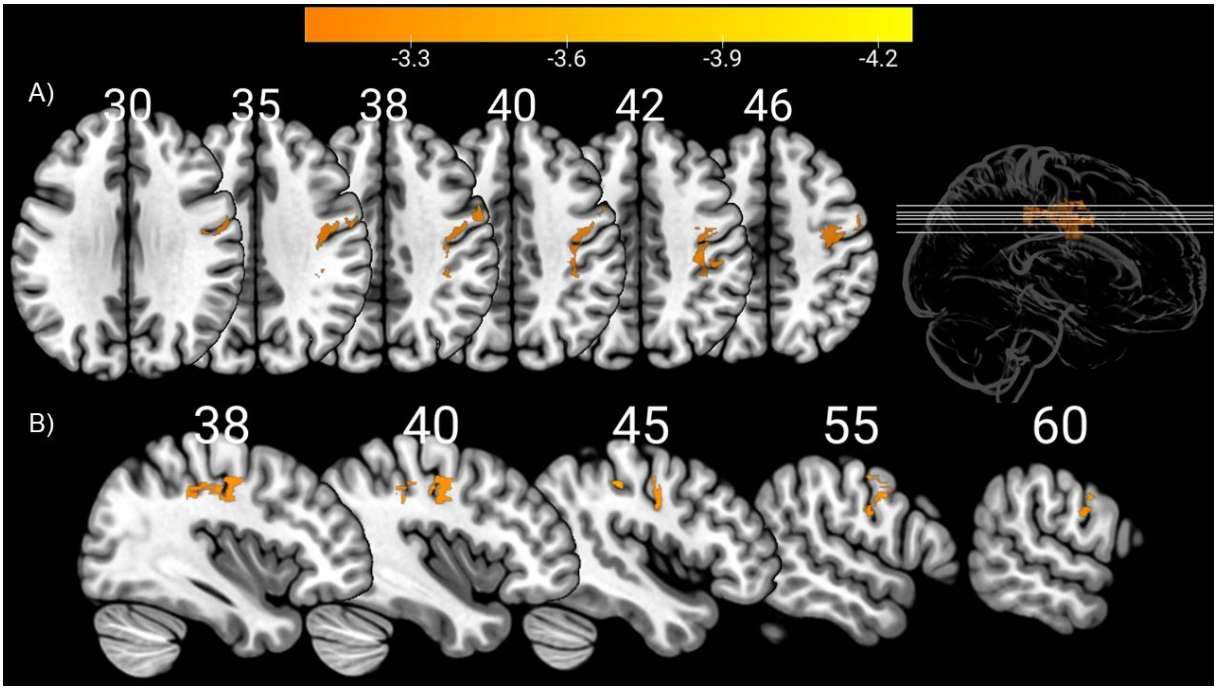
Region of Peak Associaton	Z-Score of Peak	Peak MNI Coordinates (X, Y, Z)	Other Structures associated in Cluster	Cluster Volume (in Voxels)
Supramarginal Gyrus	-3.6	43.7, 33.3, 44.8	Precentral Gyrus, Postcentral Gyrus, Supramarginal Gyrus	2,262
Precentral Gyrus	-3.4	54.0, 6.8, 47.7		103

Note. This table provides an overview of significant associated structures. The peak structure does not imply that this structure had the most associated voxels but rather the highest local z-value for that cluster. All structures refer to the corresponding structure in the right hemisphere.

A topographical map of the associated areas in a axial and sagittal view is shown in Figure 5.

Figure 5

Axial and Sagittal View of Brain Regions Associated with Impaired Insight for Motor Deficits



Note. The axial view in A) and the sagittal view in B) both provide a visual insight into the associated areas. These structures cover the posterior frontal and anterior parietal cortex and include the supramarginal, postcentral, and precentral gyri.

The main associated area (2,262 voxels) covers parts of the supramarginal gyrus, the postcentral gyrus, and the precentral gyrus. The other smaller associated area (103 voxels) also covers parts of the precentral gyrus. The associated regions are, therefore, all part of cortical regions, spanning from the posterior part of the frontal lobe (precentral gyrus) to the anterior part of the parietal lobe (postcentral gyrus) and the inferior lateral part of the parietal lobe (supramarginal gyrus).

Comparison of Associated Brain Areas in Over- and Underestimation of Specific Abilities

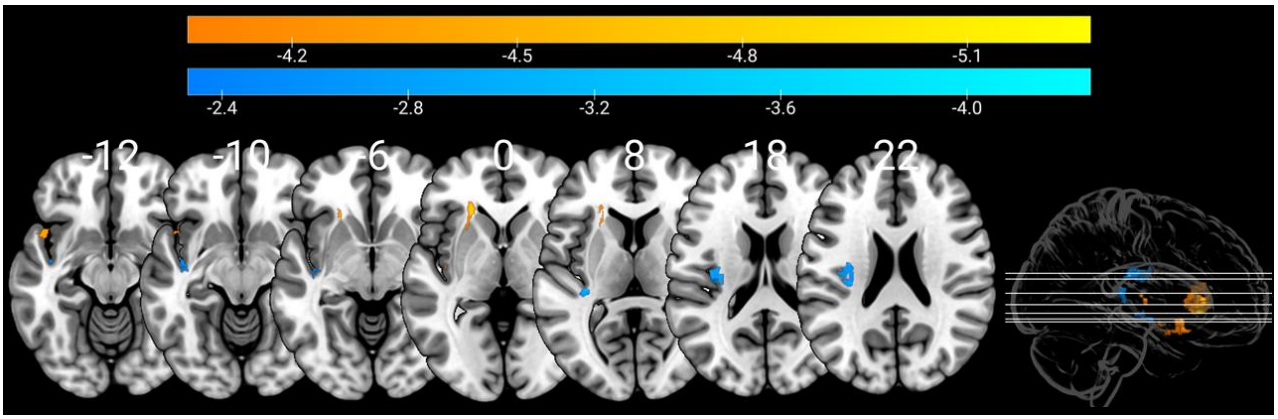
The following compares the previously described brain regions associated with impaired awareness of illness, and thus an overestimation of one's abilities, with the brain areas associated with an underestimation of one's abilities. This additional analysis was included to examine whether the associated areas differ between overestimation and underestimation of one’s abilities or whether there are overlaps. It should be noted that this is purely a descriptive analysis, with no statistical or computational calculations performed, as the VLSM yielded no significant results, likely due to the small sample size of patients who underestimated their abilities (see Table 1). Consequently, these results should be interpreted with caution. In the population of patients who underestimated their abilities, no significant voxels survived the VLSM. Therefore, the topographical representation of the voxel-based results is here used with manual z-scores.

Comparison of Associated Brain Areas in Over- and Underestimation of Language Deficits in the Left Hemisphere

For descriptive purposes, we manually set z-value thresholds to visualize the associated left hemispheric brain areas of patients who overestimated their language deficits. The minimum for included voxels is a z-value of -2.33, corresponding to a p-value of 0.01, and the maximum is a z-value of -4.27, corresponding to a p-value of 0.00 001. Figure 6 shows the visual topography of regions associated with both overestimation and underestimation of abilities in the context of language deficits.

Figure 6

Comparison of Regions Associated with Over- or Underestimation of Language Deficits



Note. Axial topography of the over- and underestimation of language deficits. The overestimation of deficits is represented by cooler colors, while underestimation is represented by warmer colors. Overestimation is mainly associated with regions in the posterior insula. The use of different z-values is due to the fact that the VLSM yielded no significant results for the patient group that underestimated their abilities. In this case, manual z-values were applied. For the group that overestimated their abilities, the z-cutoff values provided by the VLSM were utilized. Since these values offer a more robust and significant overview of the correlated areas, they were used for the comparison instead of the same manual z-values.

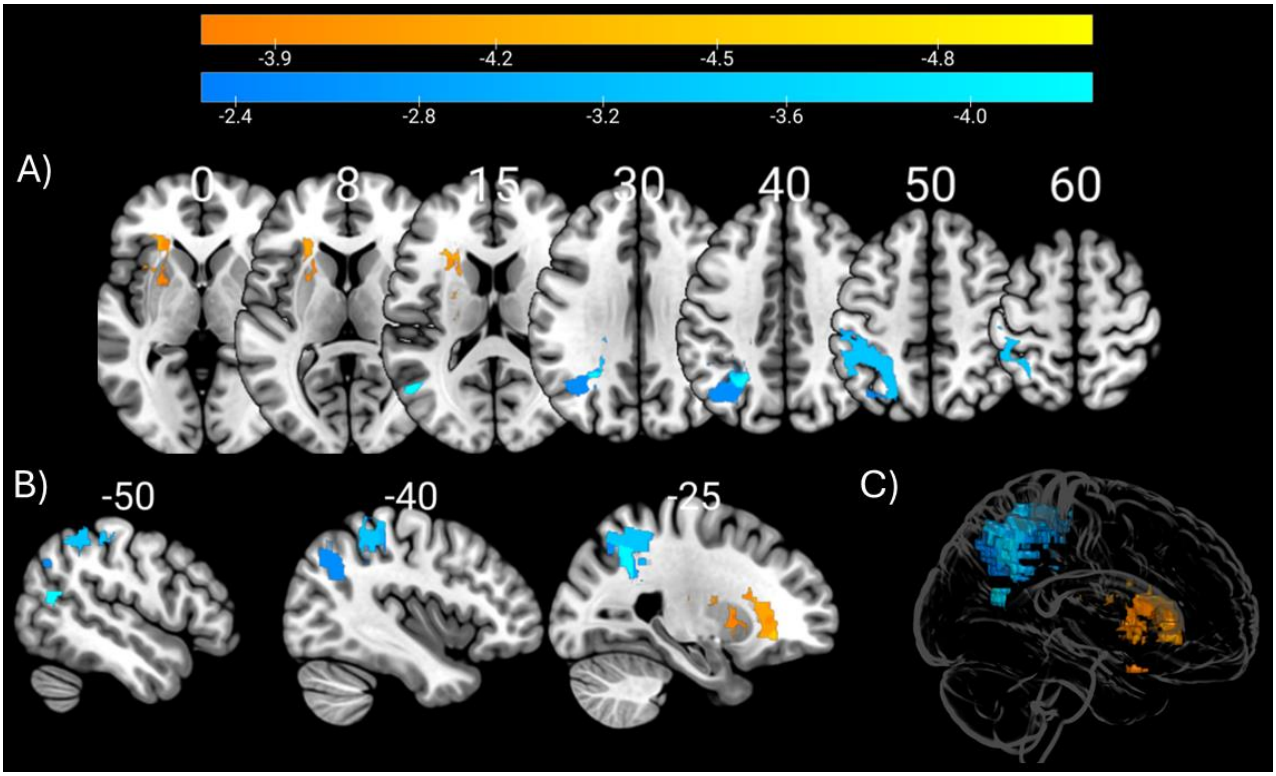
The associated left hemispheric brain areas for impaired insights of language deficits have already been described earlier in the results section. The associated brain areas for underestimation consist of three regions, with one of them comprising the largest part (904 voxels). This region, like two clusters in the group of patients who overestimated their abilities, is partly located in the insula, but in the posterior rather than the anterior area. Therefore, no common brain areas were found between the two groups.

Comparison of Associated Brain Areas in Over- and Underestimation of motor deficits in the left hemisphere

Manual z-values were used for the associated left-hemispheric brain areas of patients who overestimated their motor deficits. The minimum for included voxels is a z-value of -2.33, corresponding to a p-value of 0.01, and the maximum is a z-value of -4.27, corresponding to a p-value of 0.00001. Figure 7 shows the visual topography of regions associated with over- or underestimation of abilities in the context of motor deficits.

Figure 7

Comparison of Regions Associated with Over- or Underestimation of Motor Deficits



Note. Axial and sagittal topography of the over- and underestimation of motor deficits. Overestimation of deficits is represented by cooler colors, while underestimation is represented by warmer colors. Underestimation is associated with more subcortical and white matter structures, whereas overestimation covers areas in the posterior parietal and anterior occipital lobes. There is no overlap between the two groups. The use of different z-values is due to the fact that the VLSM yielded no significant results for the patient group that underestimated their abilities. In this case, manual z-values were applied. For the group that overestimated their abilities, the z-cutoff values provided by the VLSM were utilized. Since these values offer a more robust and significant overview of the correlated areas, they were used for the comparison instead of the same manual z-values.

The associated left-hemispheric brain areas for impaired insight into motor deficits have already been described earlier in the results section. The associated brain areas for underestimation consist of one large associated cluster (13,759 voxels), covering brain areas in the parietal lobe (inferior parietal lobe, superior parietal lobe, postcentral gyrus) and regions in the occipital lobe (middle occipital gyrus). The figure shows that for the patient group that overestimated their motor

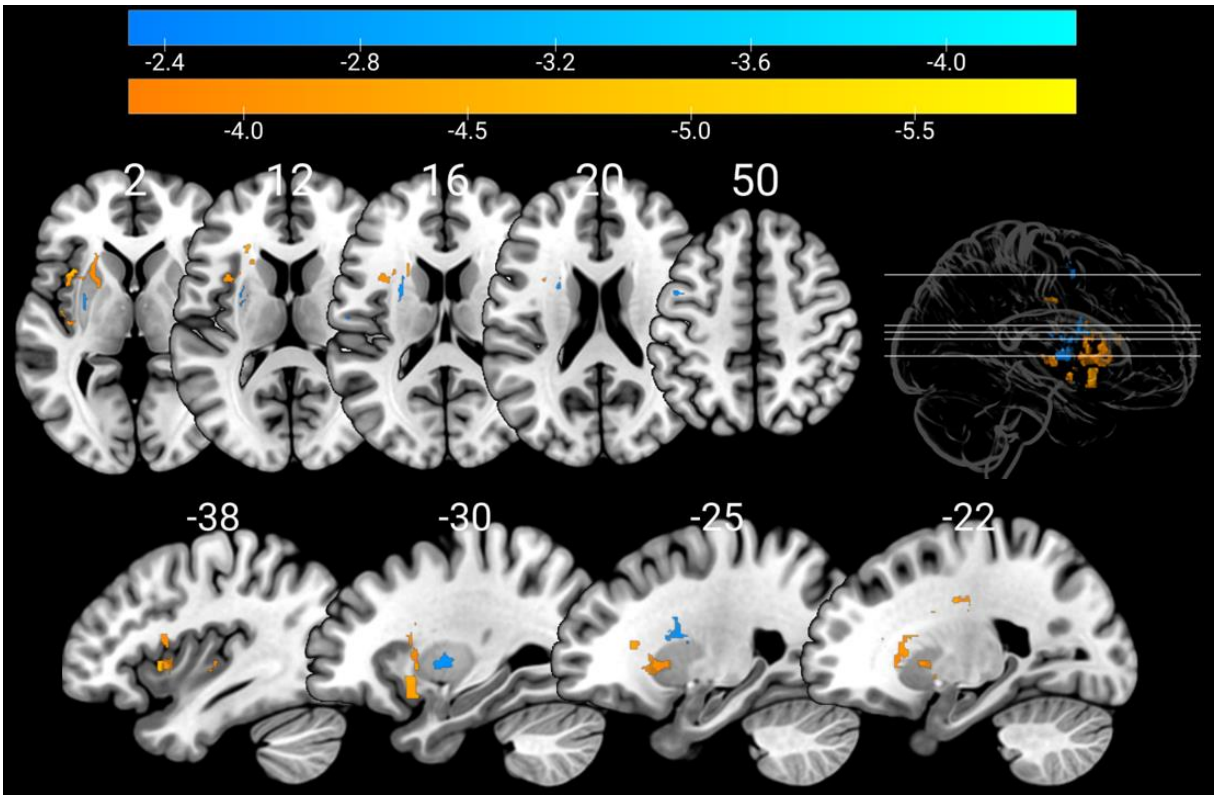
deficits, the associated regions are more in the outer layers of the parietal and occipital cortex, whereas the patient group that underestimated their motor deficits shows deeper associated structures, including subcortical areas and white matter tracts. Therefore, no common brain areas were found between the two groups.

Comparison of Associated Brain Areas in Over- and Underestimation of Apraxia in the Left Hemisphere

Manual z-values were used for the associated left-hemispheric brain areas of patients who overestimated their apraxia-related deficits. The minimum for included voxels is a z-value of -2.33, corresponding to a p-value of 0.01, and the maximum is a z-value of -4.27 corresponding to a p-value of 0.00001. The associated left-hemispheric brain areas for impaired insight into apraxia have already been described earlier in the results section. Figure 8 shows the visual topography of regions associated with over- or underestimation of abilities in the context of apraxia related deficits.

Figure 8

Comparison of Regions Associated with the Over- or Underestimation of Apraxic Deficits



Note. Axial and sagittal views of the over- and underestimation of apraxia-related

deficits. Overestimation of deficits is represented by cooler colors, while underestimation is represented by warmer colors. Although both groups are associated with a diffuse cluster of regions, no overlap was found. In the sagittal slice at -30, there is a relatively large associated area covering the medial part of the putamen. The use of different z-values is due to the fact that the VLSM yielded no significant results for the patient group that underestimated their abilities. In this case, manual z-values were applied. For the group that overestimated their abilities, the z-cutoff values provided by the VLSM were utilized. Since these values offer a more robust and significant overview of the correlated areas, they were used for the comparison instead of the same manual z-values.

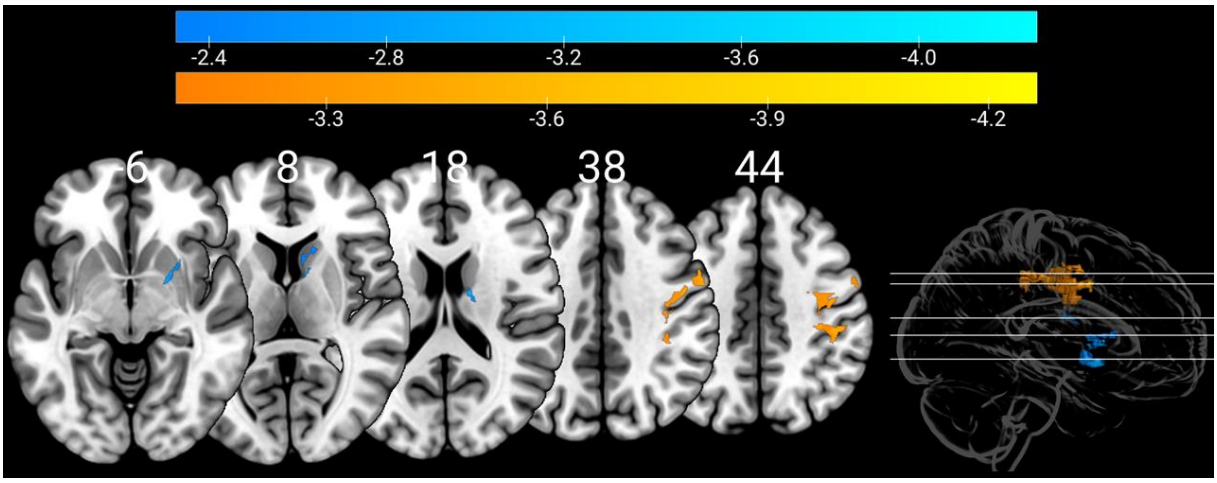
The underestimation of one's abilities was associated with lesions in the putamen and in the precentral gyrus (precentral gyrus). Overestimation also showed associated lesions in the putamen, but in the anterior ventral part of the putamen, while the underestimation was located in the medial region of the putamen. No overlap between the associated brain areas of these two groups could be found.

Comparison of Associated Brain Areas in Over- and Underestimation of Motor Deficits in the Right Hemisphere

Manual z-values were used for the associated right-hemispheric brain areas of patients who overestimated their motor deficits. The minimum for included voxels is a z-value of -3.10, corresponding to a p-value of 0.001, and the maximum is a z-value of -4.27, corresponding to a p-value of 0.00001. The associated right-hemispheric brain areas for impaired insight into motor deficits have already been described earlier in the results section. Figure 9 shows the visual topography of regions associated with over- or underestimation of abilities in the context of motor deficits.

Figure 9

Comparison of Regions Associated with Over- or Underestimation of Motor Deficits



Note. Axial view of the over- and underestimation of motor deficits. Overestimation of deficits is represented by cooler colors, while underestimation is represented by warmer colors. Overestimation is associated with more subcortical and white matter structures, whereas underestimation covers areas in the anterior parietal and posterior frontal lobes. There is no overlap between the two groups. Interestingly, compared to the left hemisphere lesion group, the associated areas appear somewhat reversed in this comparison. The use of different z-values is due to the fact that the VLSM yielded no significant results for the patient group that underestimated their abilities. In this case, manual z-values were applied. For the group that overestimated their abilities, the z-cutoff values provided by the VLSM were utilized. Since these values offer a more robust and significant overview of the correlated areas, they were used for the comparison instead of the same manual z-values.

The associated areas of overestimation of motor deficits have already been described and primarily cover areas in the posterior frontal lobe and anterior parietal lobe, whereas the associated regions for underestimation are located in the basal ganglia (namely the caudate nucleus, the putamen, and the globus pallidus) and also involve white matter tracts (namely the fornix, the uncinate fasciculus, and the anterior commissure). Therefore, no common brain areas were found between the two groups.

Discussion

Building upon the hypotheses, the expectation was for a correlation between impaired insight (anosognosia) specifically related to language deficits (aphasia),

motor deficits (hemiplegia, hemiparesis), and deficits for goal-directed actions (apraxia), and brain regions in the fronto-parietal cortex, the insula (particularly the anterior part), the supplementary motor area (SMA), and the anterior cingulate cortex (ACC). For patients with right-hemispheric lesions, these hypotheses focused only on associations between impaired disease-related insight for motor deficits, given that aphasia and apraxia typically do not occur with right-hemispheric damage. An exploratory approach was also employed to investigate whether other brain areas or white matter tracts are associated with reduced illness insight.

In the patient group with left-hemispheric lesions, results indicated that all examined domains, including language deficits, deficits for common tool-use disorder, and motor deficits, are associated with significant, statistically robust brain regions. For the group with right-hemispheric lesions, no significant correlation between specific brain areas and reduced illness insight in motor deficits was observed. These results suggest that anosognosia can occur following left-hemispheric brain lesions and can manifest not only in motor deficits but also in language deficits (aphasia) and impairments of common tool-use disorder (apraxia). This finding challenges the hypothesis that anosognosia is predominantly caused by right-hemispheric damage, an assumption mainly based on studies involving both populations with right- and left-brain damage, experiments using the WADA test to temporarily anesthetize one hemisphere, and theoretical models (Orfei et al., 2007). It is possible that the prevalence of impaired insight (anosognosia) after left-hemispheric lesions is underestimated due to these theoretical assumptions, and because the often highly verbal diagnostic tools significantly complicate or even prevent the application of these criteria for diagnosing anosognosia, as confirmed by Della Sala et al. (2009).

For the patient group with right-hemispheric lesions, no significant results were found using voxel-based lesion-symptom mapping (VLSM). This outcome was expected for language deficits (aphasia) and impairments in goal-directed movements, as these are strongly associated with left-hemispheric lesions. However, the lack of significant findings regarding reduced insight into motor deficits is noteworthy, particularly given that the majority of studies on neural correlates are based on discoveries in the right hemisphere with deficits for hemiplegia or hemiparesis.

One of the main hypotheses was that lesions in the insula, particularly in the anterior part, would be associated with reduced illness insight. This hypothesis was confirmed for all specific disorders except for motor deficits in right-hemispheric lesions. In cases of language deficits, reduced illness insight was associated with regions in the left anterior and posterior insula; for motor deficits, it was linked to areas in the left anterior insula; and in apraxia, with regions in both the anterior and posterior insula. These results support the hypotheses that the insula plays a crucial role in integrating various sensory signals related to self-perception (Preuschoff et al., 2008; Seymour et al., 2004), aligning with numerous studies that have demonstrated a similar association between the insula and reduced illness insight (Berti et al., 2005; Fotopoulou et al., 2010; Karnath et al., 2005; Kletenik et al., 2023; Klingbeil et al., 2020; Orfei et al., 2007; Pacella et al., 2019; Starkstein et al., 2010; Vocat et al., 2010).

Furthermore, the insula is not only associated with reduced illness insight in motor deficits but also in language deficits (aphasia) and deficits in the goal-directed execution of movements. The current results provide novel scientific knowledge in this area, as studies on anosognosia in apraxia and aphasia are scarce or virtually non-existent.

Besides the already mentioned sensory processing and subjective representation of proprioception, sensations, and movements (Craig, 2009; Critchley et al., 2004; Farrer et al., 2003; Farrer & Frith, 2002; Tsakiris et al., 2007) the insular cortex also plays a role in auditory processing and speech (Augustine, 1996; Uddin et al., 2017), although its exact function remains unclear. One possible explanation is that damage to the insular cortex may prevent the appropriate interpretation of the discrepancy between intended verbal communication (e.g., expressing a need) and its faulty execution (e.g., due to word-finding difficulties or paraphasia). Consequently, the insula can no longer fulfill its role as an integrator, and the affected person cannot adequately recognize this discrepancy. This results in unawareness of their language impairments, leading to reduced or absent illness insight. This assumption is consistent with the areas assessed by the VATA-L (Cocchini, Gregg, et al., 2010), which evaluates a wide range of language comprehension and production abilities. Lesions to the insula have also shown an association with increased impairment in tool use, known as apraxia. One possible explanation is that the insula plays a more general role in recognizing self-generated errors. Errors occur more

often depending on the functional deficit following brain damage. Thus, lesions may impair the ability to detect errors in motor actions, leading individuals to be unaware of their own apraxic deficits (Canzano et al., 2014). Additionally, since the insula integrates bodily states with subjective awareness, damage to this area may disrupt the internal representation of motor commands, resulting in diminished awareness of impairments like apraxia (Karnath et al., 2005). Another hypothesis suggests that because the insula is critical for coordinating sensorimotor information, lesions may prevent the alignment of intended and actual movements. This misalignment could contribute to anosognosia for apraxia by obstructing the feedback needed for self-assessment (Besharati et al., 2014). In summary, lesions to the insula may disrupt awareness of apraxia by impairing error detection, sensorimotor integration, emotional processing, and the internal representation of bodily actions.

Another hypothesis was that reduced awareness of illness is associated with lesions in the fronto-temporo-parietal cortex, an anatomically large area with many different structures and associated functions. In this context, a specific brain region, namely the superior part of the temporal pole, showed a significant association with reduced awareness of illness in all three groups with left hemispheric lesions. The temporal pole is the most rostral part of the temporal lobe and is divided into superior, middle, and inferior regions in the AAL atlas (Rolls et al., 2020). The superior part is anatomically located directly adjacent to the inferior anterior region of the insula; therefore, a significant cluster was partially observed that included both regions.

The temporal pole is considered a hub where various higher-order functions are integrated; among other things, multimodal sensory integration takes place here (Roland et al., 1990; Sergent et al., 1992; Vandenberghe et al., 1995). The temporal pole itself can be further subdivided into various subregions with markedly different connectivity profiles (Pascual et al., 2015). In their review of the temporal pole, Herlin et al. (2021) conclude that it acts as a hub by integrating different higher-order information and processing numerous high-level cognitive tasks across various modalities, which explains its diverse and complex functions.

Both the insula and the temporal pole function as hubs in the brain, with the insula primarily processing body-related sensory stimuli in a bottom-up manner, while the temporal pole integrates cortically derived information in a top-down fashion. Given their proximity, it is plausible to hypothesize that this adjacency facilitates a

more comprehensive integration of top-down and bottom-up processing. Lesions in this area could disrupt adequate encoding, causing an individual's self-assessment to deviate significantly from the judgments of others. This assumption aligns with a study by Reniers et al. (2014), which showed that the temporal pole responds more strongly to signals related to Theory of Mind than to empathically associated stimuli. Similarly, Zheng et al. (2017) demonstrated that a higher "trait modesty score" is associated with a larger gray matter volume in the left temporal pole. The authors link the trait of modesty with self-assessment, self-regulation, and social cognition, all characteristics that are also impaired in anosognosia. These findings are consistent with those of Nachtergaele et al. (2020), who showed in their anatomical study that the temporal cortex (including the temporal pole) and the insula are directly connected via white matter fibers. They propose the term “temporoinsular projection system” for this complex. Additionally, there is functional connectivity between temporal areas and the insula, suggesting coordinated activity for sensory integration and emotion regulation (Cauda et al., 2011). A review by Olson et al. (2007) concluded that the temporal pole receives projections from the insular cortex and forms part of a network involved in multimodal sensory integration and emotional processing. All these results support the assumption that a lesion in the temporal pole, similar to a lesion in the insula, interferes with the adequate integration of various sensory stimuli. This would explain why these regions are associated not only with impaired insight into motor deficits but also with language and apraxia-related deficits. Although these impairments of insight pertain to seemingly different clinical phenomena, the successful integration of sensory information remains a key factor for accurate self-assessment, regardless of the specific clinical anomaly.

There were also other temporal structures significantly associated with an impaired insight, such as the middle temporal gyrus and the superior temporal gyrus. The middle temporal gyrus (MTG) was associated with an impaired insight for language deficits. This MTG interacts with other regions in the default mode network, which are involved in self-reflection and metacognition. Damage here could impair the broader network responsible for insight into one’s language abilities, resulting in anosognosia for aphasia (Antoine et al., 2019). It is also known that the MTG plays a role in auditory comprehension, which is critical for self-monitoring in language. Lesions in these regions could hinder the integration of auditory feedback needed to recognize language deficits, contributing to anosognosia (Lwi et al., 2021). The

superior temporal gyrus (STG) has been significantly associated with impaired insight into apraxia-related deficits. This association may be due to the STG's role in integrating auditory feedback, action monitoring, and spatial awareness. Lesions in the STG can impair the detection of errors in spatial and gestural actions, affecting patients' awareness of errors in limb or facial movements (Scandola et al., 2021). Furthermore, the STG is part of a larger network responsible for spatial and visuomotor integration. Damage in this area could disrupt spatial processing essential for motor tasks, potentially leading to unawareness of motor deficits in apraxic patients (Rousseaux et al., 2015). It has also been shown that the STG is essential for processing sensory feedback related to actions. Lesions here may disrupt the feedback needed to monitor and adjust movements, causing patients to remain unaware of their own apraxic errors (Canzano et al., 2014). These findings suggest that temporal structures like the MTG and the STG may play a role in the development of impaired insight into language and apraxia-related deficits.

For the non-significant group analyzing impaired insight into motor deficits, custom z-scores still indicated associated areas of impaired insight. Although these should be analyzed with caution, there was a large cluster involving the precentral, postcentral and supramarginal gyrus. Despite the precentral gyrus being involved in motor functions (Hanakawa et al., 2005; Yousry et al., 1997), which makes this region as an associated region for impaired insight into motor deficits difficult to comprehend, since motor deficits are usually related to a region involved in motor actions, there could be the potential for a interplay between these regions, since they are anatomically and functionally interconnected.

Subcortical structures that showed significant associations across different measured domains of impaired insight were the putamen and the globus pallidus (also known as the pallidum). The putamen was significantly associated with impaired insight in language impairment, motor impairment, and impairments in goal-directed actions. The globus pallidus showed significant associations with impaired insight into motor impairments and impairments in goal-directed actions. Both of these structures are part of the lentiform nucleus (also known as the lenticular nucleus), which itself is part of the basal ganglia (Utter & Basso, 2008). The basal ganglia have been linked to anosognosia in previous literature (Fotopoulou et al., 2010; Moro et al., 2011; Pia et al., 2004; Romano et al., 2014). Vuilleumier (2004) hypothesized that damage to subcortical circuits, such as the basal ganglia, which

are involved in motivation and error detection, might lead to an inability to engage self-monitoring processes. Both the putamen and the globus pallidus serve as major hubs within the basal ganglia. The globus pallidus functions as a key output station, as most outputs from the basal ganglia exit here, while most inputs are received mainly from the cerebral cortex through the putamen, among other areas (Watson et al., 2010). These structures have been linked to Parkinson's disease (Chenery et al., 2008) and Huntington's disease (Bohanna et al., 2008; Paulsen, 2009). A meta-analysis by Arsalidou et al. (2013) concluded that motor processes occupy central basal ganglia structures, namely the putamen and globus pallidus, and that somatosensory processing, particularly pain, shows preferential activation in the dorsal putamen. The authors also found that body movements have the highest likelihood of activating the left putamen, and that working memory processes (maintaining and manipulating information) recruit large areas of the basal ganglia, primarily centered over the anterior putamen. Additionally, the globus pallidus plays a central role in processing both motor and non-motor information in the brain (Dong et al., 2021). These findings align with previous associations of these structures with impaired insight. The globus pallidus and the putamen appear to serve as important integrative centers, receiving and sending crucial self-referential information to subcortical and cortical structures. This pair of structures is significantly associated with impaired insight for different types of deficits, serving as central integrators that converge various kinds of information.

Since the atlas from the NatBrainLab (de Schotten et al., 2011) was included in the study, it was possible to observe significant associated voxels within large white matter tracts. A white matter tract that was significantly impaired in all of the left hemisphere anosognosia groups was the uncinate fasciculus. This tract is a white matter association tract, meaning it connects cortical areas within the same cerebral hemisphere (Konstantopoulos & Giakoumettis, 2023). The uncinate fasciculus originates in the area surrounding the anterior part of the temporal lobe, including the temporal pole. It then curves around the insular cortex and enters into a ventro-lateral branch, terminating in the lateral orbitofrontal cortex (de Schotten et al., 2012). A review by Von Der Heide et al. (2013) evaluated the role of the uncinate fasciculus in various psychiatric disorders and in episodic memory, language, and socio-emotional processing. The authors proposed that it is possible some types of learning, such as devaluation, could be disrupted by damage to the uncinate fasciculus. This

hypothesis might also apply to a failure to learn new bodily and functional states in patients with neuropsychological and neurological disorders. Furthermore, the uncinate fasciculus is a dense white matter tract that encompasses previously mentioned associated brain regions, such as the insular cortex and the temporal pole. Damage to this tract would result in limited or dysfunctional connections between regions important for self-referential processes. Several other white matter tracts were also involved, such as the corticospinal tract (significantly associated with all three left hemispheric insight deficits), the inferior fronto-occipital fasciculus (significantly associated with left hemispheric impaired insight into language and motor deficits), the internal capsule (associated with left hemispheric impaired insight into motor deficits and apraxia-related symptoms), and the inferior occipitofrontal fasciculus (also associated with left hemispheric impaired insight into motor deficits and apraxia-related symptoms). For an overview of these white matter tracts, see Catani and de Schotten (2012). A detailed analysis of these fiber tracts exceeds the scope of this work. However, it can generally be stated that these tracts represent highly central structures connecting various cortical, subcortical, and peripheral nervous systems, including the significantly associated areas presented in this study. This seems logical, as theoretical considerations of impaired insight as a deviant systemic, interconnected structure support these findings. Not only can lesions in specific individual areas cause a faulty perception of one's own abilities, but so can damage to axonal connection structures that enable the integration of the various responsible evaluation, stimulus processing, and memory structures.

Limitations

Several limitations should be considered in this study. Due to the relatively small sample size, the discrepancy scores from the VATA tests were used instead of the cut-off scores that classify the severity of anosognosia. Consequently, all deviant discrepancy values were included in the analysis, including those considered clinically insignificant. Realistic self-assessment is challenging even for individuals without clinical impairments, and moderate deviations between self-assessment and psychometrically measured ability levels are often observed in cognitive domains (Freund & Kasten, 2012). However, the VATA items describe very concrete, everyday tasks that are significantly clearer and more realistic to assess. Using all discrepancy

values may have led to overestimation or underestimation of certain areas in the analysis.

Another aspect related to test theory is the skewed distribution of discrepancy values. As previously described, most neuropsychological test procedures exhibit a skewed distribution: participants tend to show either no impairment in the tested domain or a strong impairment, violating the assumption of a normal distribution. While the NiiStat program offers a function to deskew the data (NiiStat, 2020), it does not fully meet this basic prerequisite, as minimizing skewness did not result in a normal distribution. Additionally, patients with large lesions can distort the results in VLSM analyses (de Haan & Karnath, 2018). Large lesion areas often result in affected individuals displaying deficits across multiple domains (Kimberg et al., 2007; Mirman et al., 2018), making precise identification of associated areas difficult. This issue was addressed in NiiStat by using the "Regress for Lesion Volume" option, which should minimize its impact on interpretation.

The timing of the testing should also be considered a limitation. Most study participants were in the post-acute phase following their stroke (classified as up to six months). However, the imaging was conducted relatively soon after the onset of the stroke, resulting in a temporal discrepancy between the behavioral data and the lesion images. A prospective study by Vocat et al. (2010) demonstrated that anosognosia for right brain damage is most prevalent during the hyperacute (within 3 days) and subacute (around 1 week) phases following a stroke, but it rarely persists 6 months post-stroke. This finding suggests that in the post-acute phase, many individuals undergo significant neuronal reorganization at both cortical and subcortical levels, potentially restoring self-awareness of their impairments. Notably, because the study primarily involved patients in the post-acute phase, affected structures predominantly included central integrative regions and white matter tracts rather than primarily cortical areas. This observation raises a hypothesis requiring further investigation: lesions in cortical regions, which are strongly linked to impaired self-awareness (as indicated by a meta-analysis by Pia et al., 2004), may undergo faster reorganization than deeper, integrative regions that are less easily compensated. This phenomenon could apply at both the neuronal and psychological levels, underscoring the need for additional research to fully understand the differential patterns of recovery across brain regions. However, these observations and results apply exclusively to anosognosia caused by right-hemispheric lesions. To

date, no data are available on the temporal course of anosognosia following left-hemispheric lesions. This difference could result in distinct temporal patterns between left- and right-hemispheric lesions. In this study, where the mean time after stroke was 68 days (median = 43), corresponding to the subacute stage, only the left-hemispheric lesions yielded significant results. This finding possibly points to different processing mechanisms in the hemispheres, leading to distinct temporal variations. According to Gainotti (2021), one possible explanation for the higher prevalence of anosognosia for hemiplegia in the right hemisphere could be the dominance of the right hemisphere in emotional representations. A lesion in this region might create a maladaptive reaction, resulting in impaired acknowledgment of the deficit. This would align the phenomenon more with a psychological motivational cause. Hemispheric differences might be a key factor in the variations of anosognosia between left- and right-hemispheric lesions and represent a compelling avenue for future research.

Another noteworthy aspect is the limited sample size for the patient group that tended to underestimate their abilities. The discrepancy values indicating underestimation showed only slight deviations in most patients; however, there were isolated cases with more significant differences. This led to comparatively low statistical power within this group, which may explain why analyses of underestimations did not yield significant results. This limitation significantly affects the analysis and complicates the understanding of neural correlates, as well as the differentiation between overestimation and underestimation at the neuronal level.

Despite these limitations, this research question offers potential for further insights. A more detailed investigation could contribute to a deeper understanding of aspects such as self-evaluation and self-perception, providing new insights into the phenomenon of anosognosia. A clinically relevant level of ability assessment, where individuals significantly underestimate their own abilities, can also have substantial effects on the affected person, their social environment, prognosis, and rehabilitation.

Future Implications

The results of this study support the increasingly accepted assumption in recent years (Berlingeri et al., 2015; Ham et al., 2014; Kletenik et al., 2023; Klingbeil et al., 2020; Monai et al., 2020; Mondragón et al., 2019; Pacella et al., 2019) that anosognosia is a connectivity disorder. This suggests that it is not a single specific

brain area responsible for the inaccurate assessment of one's own abilities, but rather complex, dynamic interactions between multiple hubs, known as large-scale brain networks (Betzel & Bassett, 2017), that function as relay stations integrating diverse information and are disrupted.

This perspective aligns with the discovery of various networks such as the Default Mode Network (Raichle, 2015), the fronto-parietal network (Zanto & Gazzaley, 2013) and the Salience Network (Uddin, 2016). Interestingly, in a study by Menon & Uddin (2010), the anterior insula is considered an integral hub of the Salience Network, which is involved in externally oriented attention and internally oriented or self-related cognition.

This theory can be applied to the findings of this study, in which the insula, particularly its anterior part, was associated with all significant results. Anosognosia, or the failure to metacognitively evaluate one's own abilities, could therefore be viewed as resulting from faulty integration of external and internal information, leading to this neuropsychological phenomenon. Furthermore, other associated regions, namely the putamen, globus pallidus, and temporal pole, also serve as hubs that integrate bottom-up and top-down information for a coherent self-analysis of one's functions and abilities.

In the future, applying such integrative network analyses more intensively to the phenomenon of anosognosia could be beneficial. This approach might not only help those affected in the best possible way but also provide fascinating theoretical insights into the complexity of self-assessment.

Furthermore, the use of discrepancy scores (such as VATA tests), which can also be determined nonverbally, enables the inclusion of populations (e.g., patients with left-hemispheric lesions and aphasia) that were previously often excluded. This allows for a more differentiated analysis, particularly with regard to hemispheric differences, as well as neural correlates and temporal aspects of the processing and analysis of self-referential information.

Conclusion

This study demonstrates that impaired self-awareness in motor deficits (hemiparesis/hemiplegia), language impairments (aphasia), and common tool-use impairments (apraxia) following a left hemispheric stroke involves a broad network of

brain areas, including the left insula, left temporal pole, and left basal ganglia. Additionally, lesions were identified in regions traversed by major white matter tracts, underscoring anosognosia as a connectivity disorder. The globus pallidus, specifically, showed a significant association with impaired insight in motor and common tool-use. Together, these areas likely serve as hubs that integrate multimodal sensory and self-referential information from cortical, subcortical, and bodily sources. Damage to these hubs and their connecting white matter tracts may disrupt the necessary integration for realistic self-assessment, resulting in misinterpretation of self-referential information.

The current findings highlight the complexity of self-referential processing and suggest that accurate self-assessment relies on the dynamic interplay between brain regions and white matter connectivity, encompassing interpersonal, bodily, and memory-related factors. When any of these domains or the converging signals are compromised, the result is the multifaceted and variable phenomenon of anosognosia.

Notably, this study is among the first to investigate the neural correlates of anosognosia in patients with aphasia and apraxia. The results indicate that similar neural structures are affected in these conditions as in motor deficits such as hemiparesis and hemiplegia. These findings suggest that processes of self-reflection and self-assessment may share common neural mechanisms across different domains and are not limited to motor deficits or lesions in the right hemisphere.

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