Mechanisms and Perspectives of Post-Stroke Depression: Neuroanatomical Substrates, Incentive Motivation, and Emotional Processing

Inauguraldissertation

zur Erlangung des Doktorgrades
der Humanwissenschaftlichen Fakultät
der Universität zu Köln
nach der Promotionsordnung vom 18.12.2018,
vorgelegt von:

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September 2023

Diese Dissertation wurde von der Humanwissenschaftlichen Fakultät der Universität zu Köln im März 2024 angenommen.

Acknowledgments

I would like to express my gratitude to everyone who shared a part of this journey with me. Without the practical, theoretical, technical, and emotional support of my colleagues, family, and friends, it would not have been possible for me to complete this dissertation. There are a few people I would like to give special thanks to:

First, I would like to thank my supervisor, PD Dr. Anne Rehme. She gave me the opportunity to work on this project, and I have learned a lot from her over the years. Her advice and support were invaluable, guiding me through the challenging moments and pointing me toward smoother paths. I also want to express my appreciation to my colleague and friend, Sebastian Krick. From the very beginning, we worked together on all these studies and spent countless hours bringing them to completion. Your support during our collaborative efforts and your consistent presence throughout the years have been genuinely invaluable. Furthermore, I would like to thank my second supervisor, Prof. Dr. Christian Grefkes, for providing essential advice and input throughout the project. Your guidance and supervision have made a significant impact on me.

I am also grateful to Prof. Dr. Gereon Fink for allowing me to conduct this project at the University Hospital Cologne, Department of Neurology. Additionally, I want to thank Prof. Dr. Jan Peters from the Department of Psychology for agreeing to supervise my dissertation.

Lastly, I want to express my special thanks to my partner, Selma Krasenbrink. Your emotional balance has been invaluable to me throughout these years, and I sincerely appreciate your help and understanding.

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Abstract

Post-stroke depression (PSD) is a prevalent affective condition after a stroke, which can impair functional and motor rehabilitation. While research on unipolar depression has been vast for decades, the characteristics of PSD regarding the neural, psychological, and neurobiological factors and influences remain fully unraveled. The present dissertation and the included studies aim to further our understanding of how different mechanisms after stroke affect the emergence and maintenance of depressive symptoms on different pathological levels. We identified brain networks corresponding to specific symptoms of PSD, examined the contribution of motor impairment and incentive motivation on PSD development, and observed specific associated emotional attention biases. For this, we executed three separate studies using several methodological applications, including different lesion-symptom mapping approaches, experimental task designs with different behavioral parameters, interviews, and test batteries.

Study 1 investigated the link between anatomical brain lesions and specific PSD symptoms. Rather than treating depression as a single global score, we aimed to identify lesion locations contributing to different PSD symptom domains. To achieve this, we created subscores that captured emotional, motivational, cognitive, somatic, and anxiety symptoms, enabling a more nuanced understanding of individual symptom profiles. We analyzed a large sample of early post-stroke patients using MRI scans, lesion masks, and a multivariate support-vector regression lesion-symptom mapping (SVR-LSM) approach. Through a comprehensive analysis of clinical-empirical and data-driven evidence, five sub-clusters of symptom domains were linked to specific lesion regions in the brain characterizing different functional brain networks. We found that more sensitive results emerged when examining individual symptom domains separately. Motivational deficits were associated with lesions in the orbitofrontal cortex, dorsolateral prefrontal cortex (dlPFC), pre- and postcentral gyrus, and basal ganglia. Emotional symptoms, like sadness, were linked to damage in the dorsal thalamus, anterior insula, and somatosensory cortex. Concentration deficits and cognitive symptoms of guilt and self-reproach were associated with dlPFC damage. Somatic symptoms, including loss of appetite and sleep disturbances, were connected to the insula, parietal operculum, and amygdala lesions. Overall depression severity, regardless of specific symptom domains, was primarily related to right-hemispheric lesions in the dlPFC and inferior frontal gyrus. Our results expand current understanding regarding the neural basis of depressive symptoms, highlighting that varying lesion patterns result in specific depressive symptoms during the early weeks following a stroke.

Study 2 researched the relationship between motor impairment and incentive motivation early after stroke and PSD symptoms, specifically motivational deficits. We were specifically interested in whether differences in motivation for physically demanding tasks could predict the development of PSD in patients with residual motor impairments. A monetary incentive grip force task was established to assess incentive motivation, with stroke patients and healthy controls holding their grip force for high and low rewards. Patients were reassessed >3 months later for depressive symptoms. We also examined the correlation between incentive motivation parameters and lesion volume in brain tracts related to motivational deficits and reward-based motor behavior. Both the stroke patients and the control group exhibited incentive motivation, with stronger grip force for high-reward trials and higher overall monetary gains in the task. Amongst stroke patients, those with more severe motor impairments displayed stronger incentive motivation, while early symptoms of PSD were linked to reduced incentive motivation. Additionally, larger lesions in corticostriatal tracts were associated with diminished incentive motivation. Importantly, long-term motivational deficits were predicted by initial reductions in incentive motivation and larger corticostriatal lesions shortly after the stroke. This suggests that more severe motor impairment drives reward-based motor engagement, whereas PSD symptoms and corticostriatal lesions may disrupt incentive motivation, increasing the risk of chronic PSD symptoms.

Study 3 examined emotion processing deficits after stroke and their relationship with PSD. Disrupted emotion processing abilities can deteriorate social relationships and promote and maintain depressive symptoms. Stroke patients and healthy controls performed an emotion processing task with shown videos of emotional faces (‘happy,’ ‘sad,’ ‘anger,’ ‘fear,’ and ‘neutral’) at different intensity levels (20%, 40%, 60%, 80%, 100%). Recognition accuracies and response times were measured, as well as scores of depressive symptoms. The primary goals of this study were to examine a potential selective negative attention bias towards negative facial expressions (e.g., sad, angry) in early and chronic PSD symptomatology and to explore lesion-symptom associations between depression and recognition accuracies of the separate facial emotional expressions, using the same approach as study 1. We observed that stroke patients performed worse in overall recognition accuracy compared to controls. Notably, more depressed stroke patients showed an attentional bias towards specific negative emotions, as they responded significantly faster to angry faces and recognized sad faces of low intensities significantly more accurately. These effects remained stable at follow-up. In the SVR-LSM, the recognition accuracy of different emotional categories was linked to brain lesions in emotion-

related processing circuits, including insula, basal ganglia, IFG, and MFG. PSD facilitates processing negative emotional stimuli, indicating a preference for mood-congruent emotions.

Concerning the findings of the three distinct studies incorporated in this dissertation, different mechanisms underlying the pathophysiology of PSD are discussed subsequently. Neural and psychological influences on PSD are compared, and potential treatment approaches and psychological concepts contributing to the development and maintenance of PSD are reviewed. Furthermore, the limitations of the applied methods and future study prospects are provided. Finally, our findings contribute to the further understanding of PSD and its underlying mechanisms. This should help to advance personalized therapeutic approaches and alleviate the burden of PSD characteristics for patients and caregivers.

Abbreviations

ACC	Anterior cingulate cortex
BDNF	Brain-derived neurotrophic factor
BOLD	Blood-oxygen-level dependent
CBT	Cognitive behavioral therapy
CSF	Cerebrospinal fluid
CT	Computer tomography
dlPFC	Dorsolateral prefrontal cortex
DWI	Diffusion-weighted images
FFA	Fusiform face area
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
GUI	Graphical user interface
HPA-axis	Hypothalamic-pituitary-adrenal axis
ICD-10	Internal Classification of Diseases, 10th revision
IFG	Inferior frontal gyrus
JTT	Jebsen Taylor Test of Hand Function
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major depressive disorder
MFG	Middle frontal gyrus
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
OFC	Orbitofrontal cortex
PFC	Prefrontal cortex
PSD	Post-stroke depression
RP	Radiofrequency pulse
rs-fMRI	Resting state – functional magnetic resonance imaging
rsFC	Resting state functional connectivity
SNRI	Selective noradrenaline reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
SVM	Support-vector machine

SVR	Support-vector regression
SVR-LSM	Support vector regression – lesion-symptom mapping
TCA	Tricyclic antidepressants
TMS	Transcranial magnetic stimulation
VLSM	Voxel-based lesion-symptom mapping
vmPFC	Ventromedial prefrontal cortex

1. Introduction

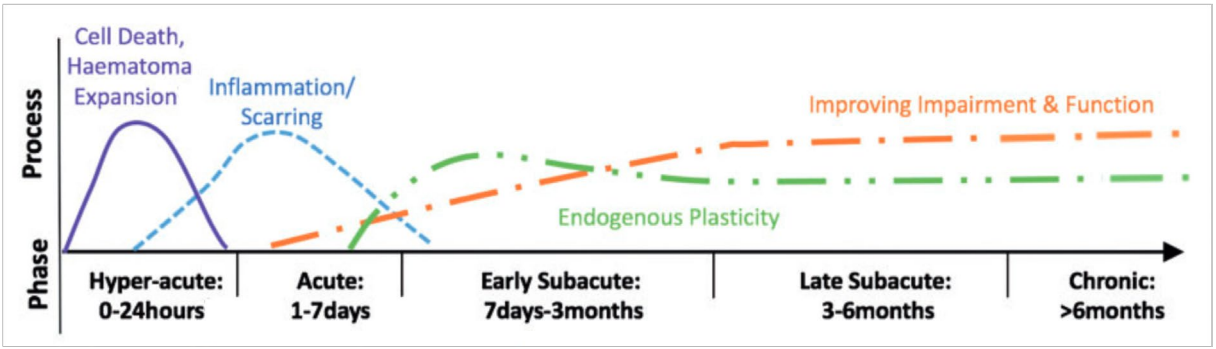
1.1 Stroke

Stroke is one of the most common neurological diseases in the world and a leading cause of mortality and permanent disability, with an annual prevalence of 13.7 million patients (Feigin et al., 2022; Nawata, 2020). According to estimates by the World Stroke Organization, this accounts for 6.5 million deaths worldwide (Feigin et al., 2022), whereas 75% of all strokes occur in persons aged 65 years or older (Yousufuddin & Young, 2019). Despite significant improvements in prevention and treatment approaches over the last decades, stroke cases could substantially increase in the upcoming years due to an aging population (Béjot et al., 2016; Strong et al., 2007; Truelsen et al., 2006), making it an enormous burden for patients, healthcare, economics, and society (Strilciuc et al., 2021; van Mastrigt et al., 2022).

Generally, a stroke can result from poor blood supply to the brain (ischemic) or intracranial bleeding (hemorrhagic). Most often (85%), stroke follows from ischemia, i.e., a disrupted blood flow due to a thrombus in cerebral arteries, stopping tissue from receiving oxygen and nutrients, thus leading to a brain lesion (Abdu et al., 2021). Figure 1 depicts a schematic illustration of the time course after stroke, including pathological events and recovery. Several biological, molecular, and cellular events occur within the first seconds to minutes to hours after stroke, causing cell death (Kolb & Whishaw, 2014). Next, brain tissue becomes inflamed and swollen, threatening the structural and functional integrity of cells that may be far from the stroke site, referred to as "diaschisis." Such sudden changes in input can lead to a temporary loss of neural function, both in areas adjacent to an injury and in regions that may be quite distant in the nervous system (Kolb & Whishaw, 2014). Generally, experiencing a stroke can lead to a range of symptoms and deficits, depending on size and location of lesions, involvement of structural and functional networks, as well as the timing of treatment and therapeutic efforts. Symptoms mainly include unilateral motor impairments of the upper and lower limbs or facial muscles, speech disturbances (aphasia), loss of balance and body coordination (ataxia), hemianopsia, dysfunction of motor execution independent of motor impairments (apraxia), and cognitive impairments (Lawrence et al., 2001). Besides acute stroke treatments (e.g., thrombolysis and thrombectomy), there are several rehabilitation programs, therapeutic treatments, and medication to prevent further strokes and regain the patient's functions (Langhorne et al., 2011). Rehabilitation aims to promote brain plasticity and reconnect functional neural networks to compensate for damaged brain regions and associated functional deficits. For example, physiotherapy promotes extremity activation and patient

mobility (Ernst, 1990). Also, speech training can be promising in aphasic patients, as well as occupational therapies, to strengthen the patient's abilities for daily activities such as eating, drinking, bathing, and dressing (Brady et al., 2016; Langhorne et al., 2011). Furthermore, transcranial magnetic stimulation (TMS) can stimulate healthy brain tissue bilateral to the lesioned hemisphere to promote functional restoration of motor function in combination with physical training (Grefkes & Fink, 2011; Lefaucheur et al., 2020). Depending on different factors, e.g., lesion location, stroke severity, functional impairment level, and social support, the patient learns to acquire and rely on compensation strategies (Cirstea & Levin, 2000). For example, patients adapt alternative patterns of movements and behavior instead of relying on pre-stroke physiological movements.

Figure 1: Biological and functional time cascade after stroke. Figure adapted and modified from Bernhardt et al., 2017



In addition to mere motor and bodily impairments after stroke, patients also reported experiencing a decrease in quality of life due to chronic disabilities and depressive symptoms, leading to an emotional burden for the patients and caregivers (Carod-Artal & Egido, 2009). It is well established that patients can also suffer from affective-depressive disorders after experiencing a stroke, commonly described as post-stroke depression (PSD) (Robinson & Jorge, 2016). Due to neurobiological changes post-stroke, functional deficits, and psychosocial factors, patients are at increased risk of developing a depressive episode (Towfighi et al., 2017).

1.2 Post-stroke depression

As introduced above, epidemiological studies revealed several psychopathological symptoms after stroke (Medeiros et al., 2020; Robinson & Jorge, 2016). Several studies and meta-analyses showed a prevalence between 18% and 38% for PSD (Espárrago Llorca et al., 2015; Hackett & Pickles, 2014; Liu et al., 2023; Mitchell et al., 2017; Robinson & Price, 1982).

Within the criteria of the International Classification of Diseases (ICD-10, 10th revision), in their clinical phenotype, stroke patients with PSD resemble patients with unipolar depression without stroke or with major depressive disorder (MDD) (ICD-10, F32.0 F32.2), and patients suffering from an adjustment disorder with depressed mood (ICD-10, F43.21). PSD describes a manifestation of depressive symptoms as a result of stroke, similar to those diagnosed with major depression (Medeiros et al., 2020; Robinson & Jorge, 2016). The term PSD was first introduced in the late 1970s to describe affective-depressive disturbances (Robins, 1976), whereas, in 1923, it was reported that brain lesions were also accompanied by psychopathological symptoms (Bleuler, 1923). The diagnosis of PSD can be classified as 'depressive (affective) disorder due to known organic or physiological condition' (F06.32) in the ICD-10. The mood changes must occur after the organic disorder and should not be misinterpreted as an emotional reaction to the disease or the consequence of chronic disabilities. Here, it becomes clear that the organic cause and, e.g., an emotional or motivational reaction may not always be distinguishable (Medeiros et al., 2020; Robinson & Jorge, 2016), which can result in debates about neural and psychological causes during PSD diagnosis. In general, the symptoms of an affective disorder with depressive features are primarily described through depressed mood, reduced drive, loss of joy, interest, and concentration, as well as disturbances in sleeping and eating behavior. Furthermore, impairment of self-esteem and self-confidence is portrayed, often accompanied by feelings of guilt and thoughts of worthlessness. The symptoms can be associated with somatic symptoms, such as psychomotor inhibition, agitation, weight loss, or libido loss. The number of symptoms usually defines the grade of depression severity.

2. Theoretical background

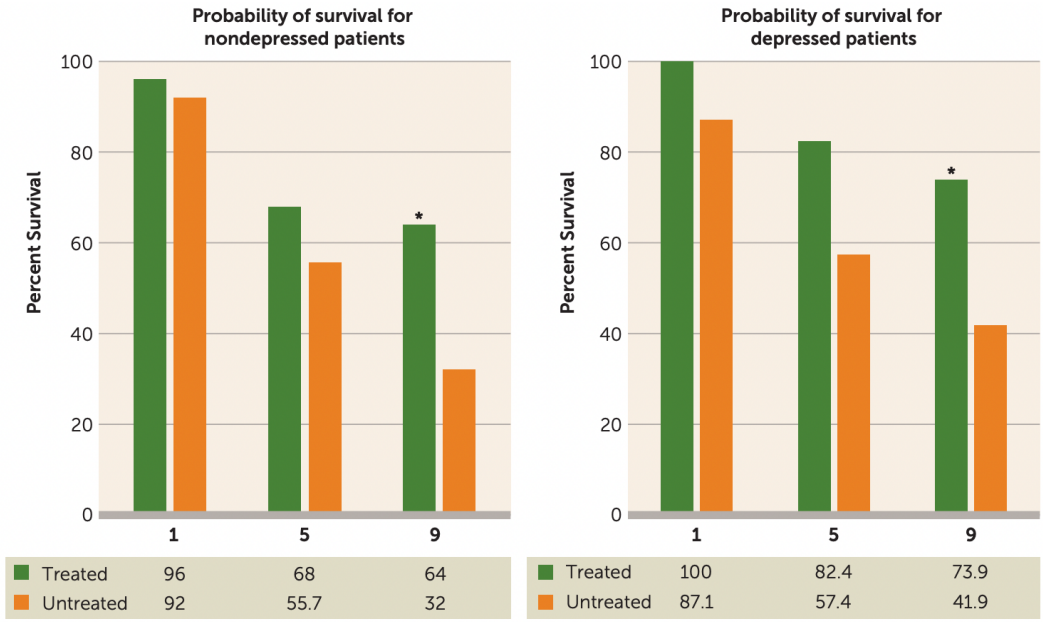
2.1 PSD and its influence on mortality, functional outcome, and rehabilitation

To date, PSD remains often neglected, although it hinders rehabilitation and functional outcomes after stroke (Medeiros et al., 2020; Robinson & Jorge, 2016). Studies found that only about 5% of stroke patients are diagnosed and treated for PSD (Herrmann et al., 2011; Swartz et al., 2016). Medeiros et al. (2020) reasoned about the difficulty of diagnosing depression after a stroke, as many symptoms can overlap with direct stroke consequences, e.g., cognitive deficits or somatic symptoms (sleep disturbances and appetite loss). Furthermore, clinicians may devalue PSD symptoms given the strokes' psychological impact on overall functioning (e.g.,

motor, speech, cognition). Especially in the early stage after stroke, i.e., days and weeks, it is hard to distinguish between an emotional reaction and PSD due to, e.g., functional impairments after stroke. The authors emphasize that depression is not a normal consequence of stroke, and many patients will not develop depressive symptoms despite major functional impairments. Furthermore, depressive symptoms can be treated even when functional deficits remain prevalent (Medeiros et al., 2020).

Several studies have investigated the association between depressive symptoms after stroke and functional recovery (Bilge et al., 2008; Paolucci et al., 2000; Parikh et al., 1990). Generally, findings suggest that PSD negatively affects motor and cognitive rehabilitation (Hackett & Anderson, 2005; Pohjasvaara et al., 2001) and increases the risk for recurrent strokes (Narushima & Robinson, 2002). Elevated mortality rates and increased suicidal tendencies are also reported within the context of PSD (Cai et al., 2019; Robinson & Jorge, 2016). Several studies showed that stroke patients who developed PSD had significantly higher mortality rates at any time point after stroke compared to non-depressed stroke patients (Ayerbe et al., 2014; Morris et al., 1993; Williams et al., 2004). Interestingly, findings suggest that treatment with antidepressants may positively impact long-term survival following PSD. In a 9-year follow-up study of patients treated with nortriptyline or fluoxetine for 12 weeks, those receiving active treatment showed an increased probability of survival compared to patients given a placebo (Figure 2) (Jorge et al., 2003). This beneficial effect on survival remained consistent regardless of whether the depression responded to treatment or whether the patient was depressed prior to treatment. Similarly, in another study involving veterans with stroke over seven years, antidepressant treatment was associated with improved long-term survival rates (Ried et al., 2011).

Figure 2: Relationship of survival rate and antidepressant treatment for 12 weeks after stroke in patients who were depressed and non-depressed followed over nine years. Patients were randomly assigned to treatment groups - nortriptyline (100 mg/day), fluoxetine (40 mg/day), or placebo group for 12 weeks. The probability of survival was significantly greater in patients receiving antidepressants, regardless of whether they were depressed prior to treatment. *$p=0.004$. Figure adapted from Robinson & Jorge, 2016.



Interestingly, treatments with antidepressants that primarily act on serotonergic and noradrenergic neurotransmitter systems caused improvements in motor deficits, too, in some cases independent of improvement in depressive symptoms (Chollet et al., 2011; Pariente et al., 2001; Wang et al., 2011). For instance, non-depressed patients with acute stroke who received the selective serotonin reuptake inhibitor (SSRI) fluoxetine or the tricyclic antidepressant (TCA) nortriptyline showed decreased disability at 12-month follow-up compared to those receiving placebo (Mikami et al., 2011). Moreover, in a functional magnetic resonance imaging (fMRI) study, it was demonstrated that a single administration of fluoxetine at 14 days poststroke led to an improvement in hand motor function and an increase in blood-oxygen-level-dependent (BOLD) activity in the damaged primary motor system (Pariente et al., 2001). Furthermore, a study showed that motor improvement after a single administration of the noradrenalin reuptake inhibitor reboxetine was associated with increased connectivity from premotor areas to the primary motor cortex in the damaged hemisphere (Wang et al., 2011). Together, these findings suggest a complex network underlying affective symptoms and motor

functions in stroke patients with neurological and functional mechanisms and psychological factors potentially interacting.

In general, it seems evident that there is a two-way relationship between functional impairment and PSD, with impairment affecting depression and depression affecting impairment (Robinson & Jorge, 2016). Notably, the development of PSD is influenced by various functional, neurological, psychological, biological, and social factors (Towfighi et al., 2017; Whyte & Mulsant, 2002). Notably, PSD is related to stroke severity and the extent of physical and cognitive impairment. However, it remains unclear whether the level of impairment plays a causal role in the development of PSD through reactive psychological mechanisms or if biological factors related to brain damage contribute to the bidirectional relationship between disability and depression (Robinson & Jorge, 2016). The following sections describe stroke severity in the sense of functional impairment and neurobiological approaches, which aim to shed light on the underlying mechanisms of PSD.

2.2 Origins and risk factors

PSD has been discussed as arising from a complex interplay of multi-dimensional biological, functional, and psychosocial aspects (Towfighi et al., 2017; Whyte & Mulsant, 2002). Until today, this issue remains a matter of debate. Specific neurophysiological mechanisms, effects, and interactions between neurological and psychological factors on PSD, as well as the impact of lesion location on a structural and network level, are described below. Also, PSD severity and potential risk factors may vary considerably depending on the time post-stroke (Robinson & Jorge, 2016; Towfighi et al., 2017). A meta-analysis indicated that PSD symptoms peak at >3 months post-stroke (Hackett & Pickles, 2014). Commonly reported risk factors for developing PSD include past depressive episodes, lack of social support, location of lesion, and the female gender (Malewska et al., 2016; Robinson & Jorge, 2016; Zhang et al., 2017). Presumably, there are interactions between the different predictors, and the direction of some predictors remains unclear (Williams, 2005). For instance, cognitive impairment as a consequence of stroke is frequently interpreted as a predictor of PSD, while, according to ICD-10, cognitive or concentration deficits can also be a consequence of depression. Besides, it is difficult to distinguish whether cognitive deficits result from the stroke itself and damaged brain regions or because of depressive symptoms (Williams, 2005).

Furthermore, some studies have revealed an association between PSD and functional deficits, indicating that PSD may be a partial psychological reaction to, e.g., cognitive

impairment, motor deficits (e.g., hemiplegia), and activities of daily living (Berg et al., 2003; Kauhanen et al., 1999; Ng et al., 1995; Nys et al., 2005; Singh et al., 2000). In contrast, an observed accumulation of depressive symptoms among stroke patients compared to patients with comparable deficits suggested that PSD goes beyond an adjustment disorder in response to stroke. For example, stroke patients have been reported to be at a three to four times higher risk for developing depression than orthopedic patients or traumatic brain injury patients with comparable impairments or lesion volumes (Folstein et al., 1977; Robinson & Szetela, 1981). Thus, pathophysiological characteristics of stroke may favor the development of depressive symptomatology, at least partly independent of stroke severity and functional impairment (Medeiros et al., 2020; Whyte & Mulsant, 2002). Likewise, Villa et al. (2018) postulated a two-way relationship, with depression increasing the risk for stroke, whereas depression or PSD is also a severe consequence after stroke. In the following sections, I will elaborate on how biological and pathophysiological mechanisms play a role in developing and maintaining depression and PSD.

2.3 Neurobiological mechanisms

Stroke patients with PSD exhibit clinical features similar to those observed in individuals with unipolar depression. Yet a difference remains in the presence of a brain lesion. Although the underlying factors responsible for PSD, whether psychological or neurological in nature, continue to be subjects of debate, it is hypothesized that the occurrence of a stroke may activate neurobiological processes that contribute to the development of depressive symptoms (Villa et al., 2018), similar to those shown in unipolar depressed patients (Maletic et al., 2007). Importantly, PSD's underlying processes must be understood more precisely to optimize pharmacological treatment. Various interconnected neurobiological mechanisms have been acknowledged, and important aspects of these models will be elucidated in the subsequent discussion.

2.3.1 Monoamine hypothesis

The Monoamine Hypothesis is a prominent explanatory model in the research of depression. Similarly, PSD has been linked to decreased availability of certain neurotransmitters in the brain, known as monoamines (dopamine, noradrenaline, and serotonin) (Loubinoux et al., 2012; Robinson & Jorge, 2016). Elevated levels of monoamine oxidase enzymes contribute to an accelerated breakdown of these monoamines in the synaptic clefts (Brigitta, 2022; Jesulola et al., 2018). As a result, there is a diminished supply of monoamines,

which are believed to be responsible for the manifestation of depressive symptoms (Hirschfeld, 2000). Heterogeneous depressive symptoms may arise from different variations of monoamine levels across individuals, leading to varying manifestations of depression (Athira et al., 2020).

Stroke-induced lesions are thought to induce a similar disruption in the monoaminergic system, leading to reduced levels of monoamines in the cerebrospinal fluid (CSF) (Loubinoux et al., 2012; Robinson & Jorge, 2016). The monoaminergic nuclei are located in the brainstem and send projections to various regions of the brain, including the cortex, limbic system, and basal ganglia, including the striatum. Ischemic lesions are believed to disrupt these corticostriatal projections from the nuclei, resulting in decreased levels of monoamines in cortical and subcortical circuits associated with the brain's reward system (such as the limbic system, basal ganglia, frontal cortices, ventral tegmental area, and nucleus accumbens). These regions are involved in the development of depressive symptoms in PSD, mood regulation, cognitive function, pleasure response, as well as the translation of motivation into behavior (Loubinoux et al., 2012; Mayberg, 1997; Medeiros et al., 2020; Robinson & Jorge, 2016). Also, lesions in these networks are associated with motivational deficits that negatively impact motor rehabilitation (Hama et al., 2007a; Rochat et al., 2013; Schmidt et al., 2008). It becomes clear that these networks and PSD symptoms constitute a quite heterogeneous clinical picture that remains fully unraveled. Of note, several studies have provided evidence suggesting that monoamine-based antidepressant medications positively alleviate PSD symptoms (Chollet et al., 2011; Villa et al., 2018). Moreover, stabilizing the monoaminergic system appears to have beneficial effects not only on depressive symptoms but also on other aspects of recovery, such as motor rehabilitation (Elzib et al., 2019; Nguyen et al., 2018).

2.3.2 BDNF hypothesis

Unipolar depression and PSD are associated with alterations in neurotrophic activity, particularly involving brain-derived neurotrophic factor (BDNF). Following a stroke, BDNF levels significantly increase as a compensatory response to neuronal tissue loss, promoting cell growth, maturation, and neuronal persistence (Loubinoux et al., 2012). BDNF plays a crucial role in adult neurogenesis and cell protection (Allen et al., 2013).

Interventions such as exercise, light stimulation, and antidepressant treatments have been shown to elevate BDNF levels (Bathina & Das, 2015). In the context of depressive disorders, reduced concentrations of BDNF have been observed, particularly in the hippocampus and dorsolateral prefrontal cortex (dlPFC) (Martinowich et al., 2007). Thus, neurotrophic activity, specifically in these brain regions, acts as a protective factor against

depression and correlates with improved depressive symptoms (Levy et al., 2018; Otte et al., 2016; Youssef et al., 2018). Studies in animals and humans have demonstrated the positive effects of maintaining BDNF levels. For instance, injecting neural progenitor cells to prevent decreased BDNF concentration reduced depression-like symptoms in rats after stroke (Moriyama et al., 2011). Similarly, meta-analyses have reported a higher risk of developing PSD associated with reduced BDNF concentration in humans (Xu et al., 2018). Moreover, individuals with fewer or abnormal functioning neurotrophins, including those with a genetic variant of the BDNF polymorphism Val66Met, are at risk for both MDD and PSD (Noonan et al., 2013; Verhagen et al., 2008; Youssef et al., 2018).

In stroke patients, the BDNF polymorphism Val66Met has also been linked to more severe disease progression and impaired motor rehabilitation (Di Lazzaro et al., 2015; Qin et al., 2014). Chang et al. (2014) demonstrated that the therapeutic success of repetitive TMS for motor recovery varied depending on the BDNF concentration. Generally, BDNF plays a critical role in both MDD and PSD, with its concentration influencing the risk of developing these conditions and the outcomes of motor rehabilitation interventions in stroke patients.

2.3.3 Glutamate hypothesis

As the primary excitatory neurotransmitter in the brain, glutamate plays a crucial role in facilitating communication between cells (Zhou & Danbolt, 2014). Studies have demonstrated pathological changes in the glutamatergic system among patients with MDD (Palucha & Pilc, 2005; Sanacora et al., 2012). Specifically, they show higher glutamate concentrations in the limbic and cortical areas (Sanacora et al., 2012). These elevated levels of glutamate can lead to detrimental effects such as dendritic remodeling synaptic and volumetric reductions, predominantly in the frontal cortex and hippocampal regions (Mitani et al., 2006; Sanacora et al., 2012).

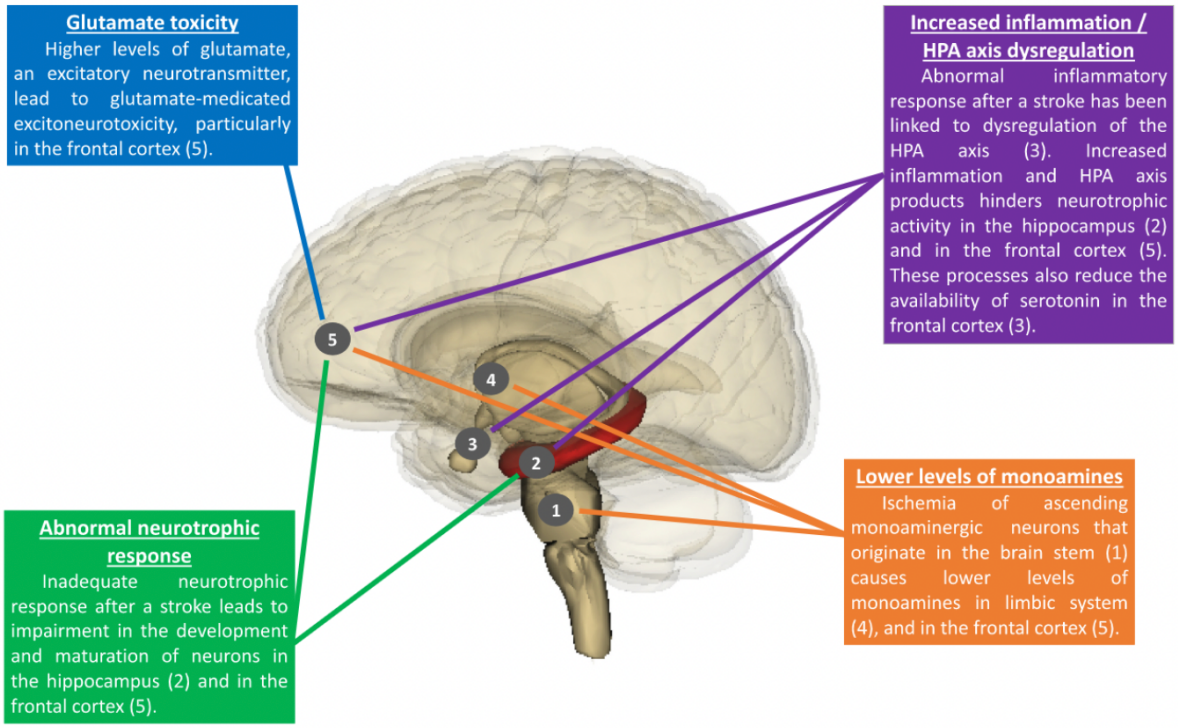
During a stroke, there is a significant increase in glutamate concentrations in the brain (Gruenbaum et al., 2020; Medeiros et al., 2020). Consequently, the excessive glutamate release causes neuronal damage beyond the infarcted tissue. Excessive glutamate stimulation of glutamate receptors results in cell swelling, apoptosis, and neuronal death, ultimately leading to poor neurological outcomes (Gruenbaum et al., 2020). Interestingly, in stroke patients, higher glutamate levels in the frontal lobe have been associated with depressive symptoms compared to non-depressed stroke patients and controls (Wang et al., 2012). Recent studies have shown successful treatments utilizing the glutamate antagonist ketamine, demonstrating antidepressant effects (Zhang et al., 2023) – also in stroke patients (Abdoulaye et al., 2021).

2.3.4 Inflammatory hypothesis

After a stroke, an acute inflammatory response occurs, leading to increased levels of pro-inflammatory cytokines and the release of glucocorticoids (Loubinoux et al., 2012; Robinson & Jorge, 2016). Chronic inflammation and higher glucocorticoid levels are associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which has been linked to both MDD and PSD (Cyranowski et al., 2007; Miller et al., 2009; Noonan et al., 2013; Otte et al., 2016; Suarez et al., 2004). Specifically, elevated cortisol levels and abnormal negative feedback control of cortisol secretion in the HPA axis are associated with the development of PSD (Åström et al., 1993; Robinson & Jorge, 2016). These processes decrease the transcription of neurotrophic factors, resulting in reduced neurogenesis and neuroplasticity, particularly in the hippocampus and frontal cortex. Impaired neurogenesis is considered a risk factor for depression, suggesting that inflammation and HPA dysregulation increase vulnerability to PSD, too (Medeiros et al., 2020).

To summarize, the association between PSD and neurobiological factors is based on empirical evidence suggesting alterations in ascending monoamine systems, HPA axis abnormalities, disruption of prefrontal-subcortical circuits, alterations in neuroplasticity and glutamate neurotransmission, and an excess of proinflammatory cytokines, among other possible neurobiological explanations. Figure 3 summarizes the most prominent pathophysiological mechanisms contributing to PSD. These pathophysiological processes should not be assumed to be distinct, but PSD symptoms are likely based on a combination of the processes (Medeiros et al., 2020).

Figure 3: Overview of the pathophysiological mechanisms contributing to developing and maintaining post-stroke depression. Decreased monoamine levels, altered BDNF levels, glutamate toxicity, and increased inflammation/ HPA axis dysregulation. *Hippocampus marked in red. Figure adapted from Medeiros et al., 2020



Different neurobiological mechanisms, such as lower levels of monoamines, abnormal neurotrophic responses, glutamate toxicity, and increased inflammation, should not be assumed to be distinct from each other. The pathophysiology of PSD is presumably based on a combination of the processes described above. Accordingly, Liu et al. (2020) showed that the administration of monoamine oxidase inhibitors is associated with a reduction in neuroinflammation post-stroke. The presence of inflammatory mediators, in turn, can lead to excessive activation of glutamate receptors, creating a harmful environment that can result in neurotoxicity (McNally et al., 2008; Miller, 2013). This suggests an interaction between the processes formulated within the hypotheses of the pathophysiological explanation of PSD.

Additionally, these mechanisms have been proposed to act bidirectionally. Interestingly, vaccinating salmonella bacteria has been shown to induce depressive mood in proportion to increased pro-inflammatory cytokines (Wright et al., 2005). In addition, psychological factors have a direct effect on neurodevelopment, causing a biological predisposition to depression. For instance, early life stress affects the HPA axis, making individuals more sensitive to future

stressors and increasing the risk of depression (Dean & Keshavan, 2017). A study indicated that early maltreatment alters brain structures, i.e., reduced structural integrity of the uncinate fasciculus connecting the amygdala and vmPFC, and is involved in affect regulation (Hanson et al., 2015).

Similarly, as described in the beginning, PSD is presumed to result from a complex relationship of multiple aspects. Amongst others, these include neural factors such as structural and functional brain network damage, neurobiological factors like the pathophysiological mechanisms mentioned above, functional disabilities, as well as psychosocial factors including, for instance, emotional and motivational aspects (Towfighi et al., 2017). A substantial body of scientific investigation regarding PSD has revealed notable similarities with research findings between MDD and PSD patients. Over the past few decades, there has been a notable expansion in research dedicated to PSD. In contrast, research on MDD has been conducted much earlier and has a temporally longer history (see, e.g., PubMed publications with keywords 'post-stroke depression' and 'major depressive disorder'). Numerous research inquiries on MDD have proven relevant for PSD investigations, as both conditions exhibit comparable affective clinical syndromes. By drawing parallels between these two conditions, research on PSD can potentially gain insights into common underlying mechanisms, symptomatology, and treatment approaches in terms of a lesion model.

Furthermore, by leveraging existing knowledge from unipolar depression research, researchers investigating PSD can benefit from established methodologies, theories, and assessment tools. This transfer of ideas and practices can accelerate progress in PSD research, saving time and resources that would otherwise be required to develop novel approaches from scratch. Additionally, exploring the distinct characteristics of PSD, such as the influence of brain lesions, can enhance our understanding of how structural and functional brain changes impact the development and progression of depression in general. A brain lesion presents an opportunity to explore the complex relationship between brain pathology and depressive symptoms. Understanding how these factors interact can inform the development of targeted interventions that address both the neurological and psychological aspects of depression.

In the subsequent sections, I will outline the theoretical concepts relevant to the studies in the present thesis, affecting similar yet different aspects and mechanisms of PSD. First, I provide an overview of the anatomical and functional network correlates of depression and introduce a heterogeneous perspective of depression. Then, I will describe the relationship between motivational deficits and depression and how motor impairment after stroke may

influence PSD. Finally, I will elucidate how the perception and processing of social cues in depression are altered, specifically the emotional face-processing abilities.

2.4. Structural and functional brain abnormalities in PSD and depression

In patients diagnosed with MDD, numerous studies utilizing structural and functional fMRI and machine learning approaches have identified significant alterations in specific brain regions. These regions include the frontal and prefrontal areas such as the orbitofrontal cortex (OFC), dlPFC, and anterior cingulate cortex (ACC), as well as subcortical structures like the insula, putamen, caudate nucleus, thalamus, amygdala, and hippocampus (Drevets et al., 2008; Kempton et al., 2011; Lorenzetti et al., 2009; Schmaal et al., 2016; Schwartz et al., 2019; Wang et al., 2012). These findings provide evidence for a "depression network" within the human brain, which contributes to the severity of depression and determines specific symptom domains.

In contrast to the extensive research on the neural mechanisms underlying unipolar depression, fewer studies were performed in stroke and PSD patients. Nevertheless, in the last decade, several studies investigated whether specific lesion locations and damaged brain networks are associated with PSD. Different methodological approaches were utilized, including lesion subtraction, mass-univariate voxel-based lesion-symptom mapping (VLSM), multivariate VLSM, including support-vector regression lesion-symptom mapping (SVR-LSM), as well as functional activity analyses (i.e., resting-state fMRI), and connectome analyses. These studies across PSD have partially produced inconsistent findings (Nickel & Thomalla, 2017; Pan, et al., 2022a), which may arise from differences in sample characteristics, depression assessment methods, and the time elapsed since the stroke occurred. Moreover, methodological aspects of neuroimaging analyses, such as low spatial resolution of lesion maps, false-positive results due to multiple testing and flawed corrections, and the neglect of voxelwise dependencies in structural and functional brain networks can contribute to discrepant findings (Douven et al., 2017; Robinson & Jorge, 2016; Towfighi et al., 2017). I will dive into more detail regarding specifically voxel-based LSM approaches in the corresponding passage in the *Methods* section. In short, VLSM relates specific brain lesions to behavioral deficits by examining the statistical association between the location of brain lesions and the presence or severity of symptoms at the voxel level, allowing the identification of brain-behavior relationships. Multivariate VLSM approaches enable the examination of multiple voxels simultaneously and dependently, which has statistical and practical advantages over mass-

univariate VLSM approaches, which assess each voxel independently. At this point, I will predominantly introduce the clinical perspective of structural and functional irregularities in PSD and report some of the major findings in recent years.

Using a multivariate VLSM approach, (Grajny et al., 2016) observed that lesions in the dlPFC were associated with higher levels of depression in chronic stroke patients. Similarly, in chronic patients with focal brain lesions, Trapp et al. (2022) found an association between bilateral insula and dlPFC lesions and depression. On the other hand, (Weaver, Lim, et al., 2021) identified the right amygdala and right ventral pallidum as regions structurally linked to PSD within one year of the stroke. (Sutoko et al., 2020) investigated acute ischemic stroke patients and found that lesions in the right rolandic operculum were linked to apathy, anxiety, perceived stress, and depression post-stroke. A study including patients with several lesion etiologies showed that instead of the lesion location itself, functional connectivity of lesions with left dlPFC was significantly related to depression (Padmanabhan et al., 2019). The paper suggested a depression connection hub centered in the left dlPFC. Of note, the dlPFC is one of the most discussed and predominant brain regions involved in depression (Koenigs & Grafman, 2009).

Likewise, by using resting-state fMRI (rs-fMRI), a study revealed higher fluctuations of BOLD signal in individuals with PSD at three months post-stroke compared to non-PSD patients in left dlPFC and right precentral gyrus (Egorova et al., 2017). Furthermore, a significant association was found between higher severity of PSD symptoms and increased resting-state fluctuations in the left insula. In another study using rs-fMRI, a significant association was observed between the severity of PSD and BOLD fluctuations in regions including the frontostriatal, temporal, thalamic, and cerebellar areas (Goodin et al., 2019). Generally, rs-fMRI is a technique that measures spontaneous brain activity in the absence of explicit tasks or stimuli. It can measure the amplitude of fluctuation in this brain activity, represented by correlations of the BOLD signal. The BOLD signal in fMRI represents the relative changes in blood oxygenation levels in the magnetic field (Logothetis, 2002). An increased need for blood oxygen in specific brain areas indicates an increased correlation with neural activity.

In contrast to task-based fMRI, rs-fMRI is particularly advantageous for investigating stroke populations due to the absence of performing potentially challenging tasks in the scanner as well as for investigating structural, vascular, and perfusion changes in regions distant to lesion sites (Veldsman et al., 2015). Functional connectivity is derived from rs-fMRI, too, by measuring the temporal correlation of spontaneous fluctuations between different brain regions,

indicating their synchronized activity and communication. Overall, rs-fMRI provides valuable insights into the brain's intrinsic functional organization and has been used to investigate various neurological and psychiatric conditions and explore the functional connectivity between brain regions during rest.

Similarly, studies examined neural PSD correlates by performing functional connectivity analyses. One study focusing on frontal stroke patients revealed that individuals with PSD exhibited decreased resting-state functional connectivity (rsFC) between ACC and the prefrontal cortex (PFC), cingulate cortex, and motor cortex but increased rsFC with the hippocampus, parahippocampal gyrus, insula, and amygdala (Shi et al., 2017). Another study involving temporal stroke patients found that PSD patients had increased rsFC between the left amygdala and the bilateral precuneus and right orbital frontal lobe but decreased rsFC with the right putamen (Zhang et al., 2019). In contrast, the right amygdala exhibited increased rsFC with the right temporal pole, right rectus gyrus, and left orbital frontal lobe but decreased rsFC with the right primary sensory area.

Generally speaking, and concerning the neural pathophysiology of PSD, there is a solid basis to propose that PSD could be a multi-faceted disconnection syndrome arising from the disruption of interrelated networks among brain regions (Gong & He, 2015). Besides somewhat discrepant findings in neural substrates, several studies have regularly implicated the PFC as a critical structure in the development of PSD. Despite differences in etiology and symptom profiles (Albert, 2018; Da Rocha E Silva et al., 2013), PSD and MDD may share a common neural basis. Clinical trials have also demonstrated that repetitive TMS targeted at the left dlPFC can effectively alleviate symptoms in PSD and MDD (George et al., 2000; Lefaucheur et al., 2020; Pascual-Leone et al., 1996; Sackeim et al., 2020). While the neural substrates of PSD and their clinical applications still require more investigation, findings in PSD research may apply to depressive disorders in neurologically healthy populations (Fox, 2018; Pan, et al., 2022a; Vaidya et al., 2019). It is important to note that depression does not result from a single brain region or neurotransmitter system dysfunction but should be seen as a multi-dimensional disorder affecting distinct but functionally joint networks (Mayberg, 2003). Moreover, depression is not simply the result of dysfunction in one or more of these elements but also involves failure of the remaining system to maintain homeostatic emotional control during increased cognitive and somatic stress (Mayberg, 2003).

2.4.1 Depression as a multi-dimensional syndrome

An interesting development in recent years is the growing recognition that different depressive symptoms may have different biopsychosocial risk factors (Fried et al., 2014; Moriarity et al., 2022). Regarding PSD, most studies are based on a dichotomized PSD diagnosis or a depression scale sum score (Pan et al., 2022a). Recent suggestions propose that the neural substrates of PSD may be uncovered by examining individual symptom levels rather than aiming to identify mechanisms of the whole syndrome (Padmanabhan et al., 2019; Pan et al., 2022a; Robinson & Jorge, 2016). One critical reason for the relatively divergent results in lesion-symptom mapping studies of PSD may be the heterogeneity of symptoms that constitute the diagnosis of depression (Davidson et al., 2002; Mayberg, 1997). Therefore, patients with PSD with similar overall depression scores may significantly differ in their clinical phenotype and underlying lesion-symptom associations. For instance, patients with somatic depression may have different lesion locations than those with predominantly motivational or cognitive symptoms.

Consequently, analyzing the relationships between brain structure and function using only global depression scores would inevitably blend different symptom categories. Notably, such analyses are only feasible with sample sizes that account for the heterogeneity of symptoms encountered in PSD. To the best of my knowledge, a recent study by Pan et al. (2023) was the first one performing VLSM in a large-scale acute stroke patient sample to investigate the neuroanatomical substrates of individual PSD symptoms. Thirteen symptoms were included in the analyses, extracted from depression items of the Hamilton Depression Rating Scale. ‘Depressed mood’, ‘psychiatric anxiety’, and ‘loss of interest’ were identified as central symptoms related to lesions in basal ganglia and capsular regions (Pan et al., 2023). Other symptoms, such as insomnia, retardation, or agitation, showed no significant lesion-symptom associations in the analyses. However, specifying thirteen items underlying depression might have induced excessive sensitivity, further reducing the statistical power of each symptom score and, thus, VLSM analysis. Therefore, striving for a balance between precision and statistical power is important to accurately investigate lesion-symptom associations.

By seeing PSD as a multi-dimensional syndrome in a more complex network, one can extend the topic of neural substrates of PSD by increasing the focus on specific symptom clusters and mechanisms. Thus, the differentiated understanding of a symptom-specific PSD, in the sense of biological, neurological, and psychological aspects, targeted interventions, and personalized therapeutic treatments, can alleviate the patient’s burden.

2.5 Motivational deficits in PSD and depression

In the last century, multiple theories and definitions of motivation have emerged (Hull, 1952; Pardee, 1990). While there are some variations, these theories generally agree that motivation is a process wherein individuals strive to satisfy their prevailing needs through their actions (Maslow, 1954; Pardee, 1990). The environment provides various incentives that can contribute to the fulfillment of these needs (Heckhausen & Heckhausen, 2005). However, achieving these incentives requires effort from the individual, which is evaluated through cost-benefit considerations due to limited resources (Heckhausen & Gollwitzer, 1987; Pessiglione et al., 2007).

The concept of "incentive motivation" can be understood as a driving force in this process (Bindra, 1968; Toates, 1995, 1986). It essentially refers to the degree to which a reward and its associated stimuli become objects of desire (Bindra, 1968; Locke, 1968). In the Bolles-Bindra-Toates formulation (Bindra, 1968), the reward is deconstructed into three aspects: "liking" (hedonic value of a reward), "learning" (acquisition of knowledge to predict future rewards), and "wanting" (striving for a reward based on its existing incentive salience). Incentive motivation is primarily associated with the "wanting" aspect and refers to the functional process of translating expected rewards into physical or cognitive effort (Berridge, 2004, 2007).

The diagnosis of a depressive episode can also be based solely on motivational symptoms such as loss of interest, apathy, disturbances in drive, psychomotor retardation, and fatigue (Hama, et al., 2007b). Apathy is commonly observed after stroke and is defined by reduced motivation and lack of emotion, interest, or concern (Starkstein et al., 1993). Notably, apathic patients may not be motivated to engage in rehabilitation programs, resulting in delayed physical and affective recovery (Hama, et al., 2007b). Motivational deficits are often associated with disruptions in the mesolimbic and mesocortical dopamine systems, involving the PFC, ventral tegmentum, and ventral striatum, and are therefore linked to lesions within the cortico-striatal-limbic loops, following the model of the monoamine hypothesis (Eshel & Roiser, 2010; Robinson et al., 1975). Studies have shown that such upward or downward regulations of the dopaminergic concentrations in this ‘reward circuit’ lead to corresponding changes in individual effort within reward paradigms (Apitz & Bunzeck, 2014; Michely et al., 2020; Pessiglione et al., 2006). The translation of motivation into action can be investigated in paradigms in which the level of physical effort is modulated by the magnitude of an anticipated reward serving as an “incentive” (Pessiglione et al., 2007). This task, for instance, represents a variation of the classical monetary incentive delay task (Knutson et al., 2008). Healthy

participants exhibited a reward-dependent increase in BOLD activity in the ventral striatum upon presentation of the incentive, which predicted physical effort during the subsequent motor execution phase (Pessiglione et al., 2007; Schmidt et al., 2012). Effective connectivity analyses further revealed that ventral striatum activation led to increased activity in the supplementary motor area and dorsal striatum (putamen) during the execution phase (Plichta et al., 2013; Schmidt et al., 2012).

In various mental and physical illnesses, incentive motivation appears to be diminished. Studies including unipolar depressed patients showed impaired reward-learning processes and reduced monetary outcomes (Admon & Pizzagalli, 2015; Cléry-Melin et al., 2019), especially when task-dependent effort was required (Cléry-Melin et al., 2011; Treadway et al., 2012). Furthermore, depressed individuals exhibit reduced reactivity to reward-related stimuli (Henriques & Davidson, 2010; Knutson et al., 2008). On the neural level, reduced reward responsiveness seems to disrupt the functionality of the reward circuit in the brain, particularly in frontal areas, nucleus accumbens, and caudate (Henriques & Davidson, 2010; Pizzagalli et al., 2009). Similarly, reduced incentive motivation correlates with reduced BOLD activity in the dlPFC and ventral striatum in depressed patients (Knutson et al., 2008; Robinson et al., 2012).

Behavioral studies showed that patients with basal ganglia damage are capable of processing rewards in terms of physical exertion (grip force) and reaction time and even show physiological arousal as measured by skin conductance (Rochat et al., 2013; Schmidt et al., 2008). However, these patients lack a reward-dependent performance modulation, indicating impaired incentive motivation. Neuroimaging evidence showed that corticostriatal networks subserve reward-related motor behavior, and corresponding lesions correlate with motivational deficits (Hama et al., 2007a; Rochat et al., 2013; Schmidt et al., 2008). Furthermore, lesions in these networks may worsen motor rehabilitation after a stroke (Hama et al., 2007a). Additionally, a more recent fMRI study found reduced striatal activation in stroke survivors in response to rewarding motor performance feedback, which suggests an impaired consolidation of motor skill learning after stroke (Widmer et al., 2019).

2.6 Emotional processing in PSD and depression

Recognizing facial expressions is essential for social functioning, allowing individuals to understand the emotional state of others and respond accordingly (Fusar-Poli et al., 2009). Facial perception involves both perceptual processing (identifying geometric features) and

understanding the emotional meaning of stimuli by integrating visual sensory input with retrievable memory (Adolphs, 2002; Fusar-Poli et al., 2009).

As described in the preceding sections, stroke patients with depressive symptoms and unipolar depressed patients exhibit several clinical, behavioral, and neurological similarities. Furthermore, the role of emotional stimulus processing has been investigated in empirical studies involving depressed patients (Stuhrmann et al., 2011). However, understanding how emotion processing abilities in stroke patients may contribute to PSD development and maintenance remains limited. Consequently, this theoretical background section will highlight important findings about emotion processing in unipolar depression and stroke patients with and without PSD.

Generally, the 'right-hemisphere hypothesis' proposes that emotional processing involves strategies and functions primarily associated with the neuroanatomical design and neurophysiological organization of the brain's right hemisphere (Gainotti, 1972, 2012). These include non-verbal, synthetic, integrative, and holistic processing. Facial perception, an aspect of emotional processing, has been extensively studied using functional neuroimaging, revealing the presence of the 'fusiform face area' (FFA). The FFA, located in the middle part of the fusiform gyrus, exhibits activation primarily in the right hemisphere (Haxby et al., 1999). The FFA shows strong activation during face perception and identification, with significantly greater response to faces compared to non-face stimuli like objects and the back of animals or human heads (Tong et al., 2010). Additionally, the 'valence hypothesis' suggests that the right hemisphere is responsible for processing more negative or unpleasant emotions, while the left hemisphere is involved in processing rather positive and pleasant emotions (Adolphs et al., 2001; Ahern & Schwartz, 1985; Wedding & Stalans, 2009). Some studies indicate simultaneous involvement of both hypotheses (Gainotti, 2019; Killgore & Yurgelun-Todd, 2007). Until today, the dominance of one hypothesis remains a topic of debate, and both are supported by extensive research data. There may be a missing aspect that provides a more accurate description of how emotions are processed in the brain (Ross, 2021).

In the clinical research of emotional processing, numerous behavioral and neural studies have focused on the interactive role of depression disorders. Cognitive models of depression propose that mood-congruent processing and selective attentional bias towards negative stimuli play important roles in the development, maintenance, and recurrence of depressive episodes (Beck, 1964; Lewinsohn, 1974). This bias is manifested towards negative emotional faces (e.g., sad faces) and reduced attention towards positive emotional faces (e.g., happy faces) (Leppänen, 2006; Surguladze et al., 2004; Suslow et al., 2019). Depressed patients also exhibit

enhanced memory for negative emotional cues (Leppänen, 2006) and demonstrate a negative response bias towards sadness in general, as well as increased vigilance towards sad facial expressions and reduced accuracy in recognizing sad and happy expressions (Bourke et al., 2010). Furthermore, findings suggest that depressive patients exhibit a greater attentional bias towards angry faces regarding reaction time and eye-tracking indices (Leyman et al., 2007; Woody et al., 2016). Interestingly, a study by Domes et al. (2016) revealed that the administration of oxytocin, an enhancing hormone of social bonding, reduced attention allocation toward angry faces and increased attention toward happy faces in chronically depressed patients. Sad and angry facial stimuli are considered relevant to depressed individuals, with sad emotions signaling a mood-congruent emotional state of another person indirectly relevant to the observer, while angry faces express personal rejection and failure, which may be particularly salient to the cognitive processing of depressed patients (Gilboa-Schechtman et al., 2004; Leyman et al., 2007). Overall, processing emotional cues appears to be a core challenge in major depression. Lewinsohn's social reinforcement theory suggests that depression arises from a lack of sufficient reinforcement associated with behaviors, leading to a reduced recognition of positive stimuli (Lewinsohn, 1974). Thus, attentional bias towards negative emotional cues and away from positive cues may result from learned behavior in depression.

In addition to behavioral studies, brain imaging techniques have been employed to investigate emotion processing in unipolar depression. A meta-analysis of fMRI studies has demonstrated increased baseline activity in the amygdala, insula, and dorsal anterior cingulate cortex in depressed patients compared to healthy individuals when exposed to negative emotional stimuli (Hamilton et al., 2012). Conversely, reduced activity has been observed in the dorsal striatum, dlPFC, and ventromedial prefrontal cortex (vmPFC). These findings have further supported the establishment of the ‘limbic-cortical dysregulation model’ in depression, which proposes that depression is associated with altered reactivity of the limbic system (Mayberg, 1997) and facilitates attention toward negative information (Poulsen et al., 2009). The limbic system comprises interconnected cortical and subcortical structures that link visceral states, emotions, cognition, and behavior (Catani et al., 2013).

Furthermore, decreased activity in the dlPFC and vmPFC has been associated with a lack of cognitive regulation of negative emotions in depression (Davidson et al., 2002; Mayberg, 1997). Supporting the limbic-cortical dysregulation model, an fMRI study revealed increased activation in cortical and limbic regions and reduced interaction between the amygdala, dlPFC, and ACC when depressed patients viewed negative and neutral emotional

stimuli (Anand et al., 2005). Moreover, Carballedo et al. (2011) could show, in a face-matching fMRI task, that there is a functional disconnection between limbic and frontal brain regions in depressed patients while matching either sad or angry facial expressions with a target facial expression. In addition, a lateralized disconnection between the right amygdala and ACC, as well as between ACC and PFC, may explain a more important role for the right hemisphere in emotion processing (Carballedo et al., 2011).

Extensive research has been conducted on emotional processing following stroke in recent decades. To investigate how emotions are processed after stroke, researchers have utilized behavioral paradigms (e.g., dichotic listening and tachistoscopic viewing), expression tasks (facial asymmetry, vocal, verbal, gestural/postural), brain lesion methods, and functional neuroimaging techniques (Borod & Madigan, 2000; Yuvaraj et al., 2013). Consistent findings support the view of an overall deficit in emotion processing in stroke patients in terms of recognition accuracy, perception, empathy and behavioral regulation, especially in patients with right-hemispheric lesions (Blonder et al., 2012; Braun et al., 2005; Luo et al., 2022; Nijsse et al., 2019b; O'Connell et al., 2022; Tippett et al., 2018; van den Berg et al., 2021). Based on these findings, a right hemisphere specialization in processing emotional stimuli is proposed in stroke patients (Yuvaraj et al., 2013).

A neural network involving various cortical and subcortical regions is believed to be responsible for the cognition and processing of emotions. These regions include the occipital-temporal cortices, including the FFA, which play a role in forming perceptual representations of facial signals, as well as the amygdala, hippocampus, orbitofrontal cortex, basal ganglia, insula, cingulum, striatum, and somatosensory cortex, which are involved in representing the emotional value of facial expressions (Craig, 2009; Damasio, 2003; Gasquoine, 2014; Leppänen, 2006; Palomero-Gallagher & Amunts, 2022; Pessoa & Adolphs, 2010; Phan et al., 2002). The amygdala plays an important role in early-stage processing of facial expressions by responding fast to emotionally intense stimuli and assigning significance to social and environmental cues (Breiter et al., 1996; Morris et al., 1993). The amygdala then provides social communicative information for further processing by cortical areas (LeDoux, 1996). Neuroimaging studies in depressed patients have demonstrated both structural and functional brain changes as well as altered neural responses to emotional faces within these networks (Davidson et al., 2002; Fu et al., 2008; Lee et al., 2008; Peluso et al., 2009; Phillips, 2003; Surguladze et al., 2005). For stroke patients, in a structural MRI study, Tippett et al. (2018) reported that acute lesions in the right amygdala or right anterior insula exhibited significantly worse accuracy in recognizing happy and angry faces than patients with lesions in other

locations. A recent voxel-based lesion-symptom mapping study investigated for the first time which specific emotion recognition deficits are related to which lesion site in stroke patients (van den Berg et al., 2021). The authors found significant lesion-symptom associations in right-hemispheric regions including the insula, putamen, and rolandic operculum, as well as the middle and superior frontal gyrus (anger), caudate nucleus (disgust), middle frontal gyrus (MFG) (happiness), and inferior frontal gyrus (IFG) (sadness). Together, the findings of healthy individuals, unipolar depression, and stroke patients support the view of a complex neural network for perceiving and processing emotionally valenced stimuli.

Generally, it should be noted that evidence regarding emotional processing in stroke patients sometimes yields inconsistent findings due to various factors, such as differences in patient characteristics (e.g., disease stage, cognitive impairment, medication, illness severity, behavioral symptoms) and variations in emotional task structures (e.g., stimulus modalities, task types, and types of emotions) (Yuvaraj et al., 2013). Consequently, it remains uncertain whether stroke patients perform poorly in emotion processing tasks due to an inability to recognize emotions or because of, e.g., limitations in executive functions or decision-making skills. Nevertheless, studies have demonstrated that emotion processing abilities in stroke patients are related to interpersonal difficulties, e.g., frustration in social relations, discomfort, and social isolation (Aben et al., 2020; Blonder et al., 2012; Cooper et al., 2013; Dombovy et al., 1986; Langer et al., 1998; Yeates et al., 2016; Yuvaraj et al., 2013). Thus, the association between depressive symptomatology after stroke and emotion processing abilities remains an important issue to be dissolved, as studies specifically investigating this aspect are relatively scarce.

As one of the limited number of studies in this field, Montagne et al. (2007) conducted an emotion recognition task using dynamic face stimuli with varying intensity levels and found that stroke patients with depression demonstrated lower accuracy in recognizing emotions such as anger, disgust, happiness, and sadness compared to stroke patients without depressive symptoms. Furthermore, stroke patients with depressive symptoms required stronger emotional expressions to correctly identify angry, sad, and happy faces compared to patients without depressive symptoms. The authors suggest that these findings were not attributable to general deficits in face- or emotion processing or stroke severity but rather to depressive symptoms. Similarly, de Souza et al. (2021) observed a significant correlation between better recognition of sad faces and increasing levels of depression in stroke patients. To conclude this section, emotion processing deficits are common after stroke and are also known to go along with

depressive symptoms. Few is known about the influence of symptoms of PSD and specific brain lesions on altered emotion processing abilities.

3. Study objectives

The purpose of the present thesis is to obtain a more comprehensive understanding of the structural and functional brain networks corresponding to specific PSD sub-symptoms and how these are related to motor impairments, as well as motivational and emotional manifestations. We investigated the corresponding pathophysiology in three different studies. Study 1 was a large-scale study with a cross-sectional design to identify lesions involved in distinct depressive symptom domains and global depression in acute stroke patients using a multivariate SVR-LSM. Studies 2 and 3 consisted of two behavioral experimental designs, examining 1) motor incentive motivation of motor-impaired stroke patients and 2) emotion processing abilities in the acute and chronic stages.

Understanding the pathophysiology of post-stroke depression can potentially lead to more effective treatments in the future. Furthermore, it remains to be disentangled whether PSD is a rather "reactive" psychological adjustment or a more brain-organic caused disorder. By investigating the complex relationship between neural networks, motor dysfunction, and emotional processing in PSD, this project aims to advance therapeutic approaches and enhance the well-being of individuals affected by PSD. This knowledge can provide personalized interventions that address specific neural dysfunctions contributing to the condition.

1. Are distinct lesion locations associated with specific symptoms of PSD?

Study 1: Neuroanatomy of symptom-specific correlates in post-stroke depression: the association between symptom clusters and lesion location.

Accepted in *Brain Communications* (01.09.2023)

Study 1 aimed to investigate whether specific anatomical lesion patterns are associated with distinct symptoms of PSD. Acknowledging the heterogeneity of depression, our goal was to disentangle PSD symptoms in the neuropsychological assessment of stroke patients in hospital settings. Rather than treating depression as a single global score, we aimed to identify lesion locations contributing to different PSD symptoms. To achieve this, we created subscores that captured emotional, motivational, cognitive, behavioral, and somatic symptoms, enabling a more nuanced understanding of individual symptom profiles. This cross-sectional study utilized MRI scans and depressive symptom subscores from a large sample of early stroke patients, employing a multivariate SVR-LSM approach. Previous lesion-symptom mapping studies have yielded inconsistent results regarding the relationship between infarct locations and depression

(Nickel & Thomalla, 2017; Towfighi et al., 2017), potentially due to depression sum scores that mix different symptom dimensions. This study can potentially observe lesion locations and lesion lateralizations responsible for specific PSD symptoms. Since stroke and PSD are life-changing events that substantially impact the patient's health, this may reveal specific therapeutic targets for future interventions individually fitted to specific symptoms in post-stroke patients, promoting optimal rehabilitative outcomes.

2. How do motor impairment and incentive motivation after stroke influence motivational capabilities?

Study 2: To engage or not engage: Early incentive motivation prevents symptoms of chronic post-stroke depression – A longitudinal study. (2023). *NeuroImage: Clinical, 37, https://doi.org/10.1016/j.nicl.2023.103360*

This study investigated the relationship between motor impairment and incentive motivation early after stroke and PSD symptoms, specifically motivational deficits. These associations are poorly understood despite the known impact on motor rehabilitation. We were particularly interested in whether individual differences in the motivation to engage in physically demanding tasks could indicate the development of PSD in patients with motor impairments. A monetary incentive grip force task was used to assess monetary incentive motivation, where participants held their grip force for high and low rewards to maximize their monetary outcome. We assessed 20 early-stage stroke patients with mild-to-moderate hand motor impairment and 24 age-matched healthy participants as a control group. Patients were reassessed >3 months later in the chronic stage post-stroke on their depressive symptomatology. Furthermore, incentive motivation parameters were correlated with lesion volume in corticostriatal tracts, which are known to subserve reward-related motor behavior, and corresponding lesions correlated with motivational deficits, which may worsen motor rehabilitation (Hama et al., 2007a; Rochat et al., 2013; Schmidt et al., 2008). Regarding stroke rehabilitation, our task evaluates whether motor impairment decreases or increases incentive motivation and whether early-stage incentive behavior may prevent the development of PSD symptoms at the chronic stage. By this, we aim to identify key targets for early interventions to improve rehabilitation outcomes and life quality in patients and caregivers.

3. How does PSD affect emotional processing abilities, and how are these reflected in lesioned brain regions?

Study 3: Lesion-symptom mapping and negative attentional bias of facial emotion processing in post-stroke depression. *In preparation, final draft prior to submission*

Emotion processing deficits are common after stroke and are also known to accompany depressive symptoms. Furthermore, research in MDD patients suggests a biased emotion processing towards negative facial expressions (e.g., angry, sad faces), reduced processing of positive stimuli (e.g., happy faces), as well as a tendency to attribute more negative meaning to neutral stimuli (Bourke et al., 2010; Leppänen, 2006; Peckham et al., 2010). Yet, little is known about the influence of symptoms of PSD on emotion processing abilities, including recognition accuracy, recognition time, and perception characteristics. Disrupted emotion processing abilities deteriorate social relationships and can promote and maintain depressive symptoms. In this study, we use an emotion-recognition task to investigate how symptoms of PSD affect emotion processing abilities. This task was developed to measure the processing of dynamic facial expression videos of persons with four basic emotions (anger, fear, happiness, and sadness) at different intensity levels. We examined patients in the acute stage and the chronic stage post-stroke, as well as a control group of healthy participants. This study aimed to investigate emotion processing abilities (e.g., recognition accuracy, recognition time) in stroke patients and to assess how PSD symptoms influence the bias of attending toward negative emotions early after stroke and in the chronic stage. We assumed that increased PSD symptomatology would lead to an increased selective attentional bias toward processing negative emotions. Furthermore, SVR-LSM analyses allowed us to detect specific lesioned brain sites associated with recognition accuracy deficits of specific emotion categories (van den Berg et al., 2021).

4. Methods

In the following, I will give an overview of the technical and practical methods we used in the studies. Importantly, for each of the three studies, we used images of MRI scans from the patient's medical records to obtain brain lesion maps for lesion-symptom association analyses. For this, we used the diffusion-weighted images (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences of stroke patients. Of note, each patient experiencing a stroke received an MRI or Computer Tomography (CT) after admission to the hospital. At the end of this chapter, I will describe the neuropsychological and motor tests and the depression scales and interviews used to assess the participant's behavioral characteristics.

4.1 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a radiology technique that creates detailed images of the body's anatomy and physiological processes. MRI scanners utilize powerful magnetic fields, magnetic field gradients, and radio waves to generate high-resolution images of the body's organs. The so-called B0 field, the static magnetic field, aligns the body's hydrogen nuclei (protons) (Hylton & Crooks, 1991). Then, a short radiofrequency pulse (RF) is applied to the head using a coil. This pulse is tuned to the Larmor frequency, corresponding to the magnetic field's strength. It causes the aligned protons to flip and align briefly with a transverse magnetic field. After the radiofrequency pulse ends, the protons return to their original alignment, emitting energy detected by receiver coils. These signals are converted into electrical signals and processed to create an image (Hylton & Crooks, 1991).

Several scanning sequences can be applied in research or clinical settings using MRI scanners. In the following, I will briefly describe common sequences and which ones we used for our research purposes. T1-weighted images provide anatomical details with good contrast between different tissues and can highlight fat-containing structures (Leiva-Salinas & Wintermark, 2010). Also, T1-weighted images effectively depict CSF-filled structures after the death of brain cells and, thus, are important in the subacute to the chronic phase after a stroke. T2-weighted images can show differences in water content between tissues and are sensitive to fluid-related abnormalities. It is useful for detecting pathology, such as acute stroke, edema, inflammation, and tumors (Zimny et al., 2015). FMRI sequences capture changes in BOLD signal in the brain, allowing researchers to study brain activity and connectivity associated with various tasks or conditions (Logothetis, 2002).

Two scanning sequences were of particular interest for our lesion-symptom association research: DWI and FLAIR images. They provide valuable information about different tissue properties. Firstly, DWI measures the random motion of water molecules in body tissues. It provides information about the microstructural integrity of tissues (Le Bihan et al., 1986; Zimny et al., 2015). In this sequence, a pair of RF pulses called diffusion gradients is applied before and after the RF excitation pulse. The differences in signal intensity caused by the motion of water molecules are used to generate DWI images. Importantly, DWI is highly sensitive to the restricted diffusion of water molecules, which occurs in areas of acute ischemic stroke. Thus, DWI can identify the location and extent of the ischemic lesion very early, often within minutes of symptom onset. For our research purposes and subsequent lesion masking, the bright signal on DWI indicates areas of restricted diffusion, representing the core infarcted tissue (Van Everdingen et al., 1998). Secondly, FLAIR imaging suppresses fluid signals, particularly CSF, to highlight pathological abnormalities (Bakshi et al., 2001). It is achieved by using a selective inversion pulse to null the signal from fluids before the RF excitation pulse. By suppressing the bright CSF signal, FLAIR images enhance the visibility of lesions or abnormalities in the brain. Importantly, FLAIR images help to differentiate acute stroke lesions from chronic or old lesions. Old lesions appear as hyperintense on FLAIR due to gliosis or tissue scarring, whereas acute stroke lesions appear hypointense (Meshksar et al., 2014).

In summary, DWI and FLAIR imaging are valuable tools in stroke diagnosis and detecting brain lesions. DWI's sensitivity to restricted diffusion helps identify acute ischemic strokes, while FLAIR provides information on lesion chronicity. Besides valuable research utilization, both sequences aid in detecting various brain lesions, contributing to accurate diagnosis and treatment planning. In the subsequent sections, I will describe how structural lesion-symptom mapping techniques evolved in the last years and how we used the MR images of DWI and FLAIR sequences for our research questions on lesion-symptom associations.

4.2 Introduction of voxel-based lesion-symptom mapping (VLSM)

Lesion-behavior research has advanced with noninvasive imaging techniques such as CT and MRI, allowing for studying lesion-behavior relationships in vivo. Using these techniques to map behavioral deficits in stroke patients has been a research focus for several decades. Methods became easier to handle and increased in validity over the years to identify a brain lesion significantly associated with a behavioral deficit through statistical group analyses,

as a single patient's brain is simply not representative to make an association with a specific deficit at a particular location (Rorden & Karnath, 2004).

A traditional approach for studying the relationship between lesions and behavior is known as lesion subtraction analysis. This method is primarily descriptive rather than statistical. It involves forming two groups: one with the behavioral deficit in interest and one without. The lesion overlap map of the group without the deficit is subtracted from the group with the deficit, resulting in a subtraction map specific to the behavioral deficit. By examining regions where lesions are more common in patients with the deficit compared to those without, this approach allows for identifying relevant brain areas associated with the deficit (Karnath et al., 2020).

In order to establish more robust conclusions regarding the relationship between the brain and behavior, VLSM was introduced. This approach examines each voxel in a brain scan individually, utilizing a two-sample t-test with the behavior of interest. Voxel-level differences that demonstrate statistically significant associations with behavior are inferred to be related to specific cognitive functions or behavioral symptoms. Because each voxel is observed individually, this analysis is called mass-univariate due to its voxel-by-voxel comparison (Sperber et al., 2019). However, this approach has certain limitations. Conducting thousands of t-tests increases the likelihood of false positives, necessitating strict corrections for multiple comparisons (Groppe et al., 2011). Additionally, assuming independence between voxels is inaccurate in the brain, as regions are organized in structural and network patterns. Furthermore, the probability of neighboring voxels being lesioned is not random. Instead, they are more likely to be lesioned as well. Therefore, a mass-univariate analysis fails to identify coherent brain networks solely based on voxel-level comparisons (Sperber et al., 2019). Of note, during a stroke, there is always damage to the vascular system in the brain. A lesion is not randomly distributed across the brain (Price et al., 2017). If the blood flow of a specific blood vessel is interrupted, regions supplied by this blood vessel are typically the regions that are being damaged (Karnath et al., 2020). Thus, the mass-univariate approach is prone to an anatomical bias by considering only single voxels and not surrounding voxels.

To overcome these challenges, Zhang et al. (2014) proposed a novel approach to lesion-symptom mapping called support vector regression-lesion symptom mapping (SVR-LSM). Unlike mass-univariate methods, SVR-LSM is a multivariate approach that compares multiple voxels simultaneously. It utilizes support vector regression (SVR), implemented in a support vector machine (SVM). An SVM is a machine learning algorithm for classification problems (e.g., a disease either present or absent). First, the data is used as input to train the machine. Then, the trained classifier is used to categorically predict unobserved data (Cortes & Vapnik,

1995). The downside of a classical SVM is that it can only predict categorical binary variables. In lesion-symptom mapping, voxels represent the independent variable, and the behavior is the dependent variable. The advantage of SVR-LSM, as introduced by Zhang et al. (2014), over classical SVMs is its ability to classify continuous variables, which is crucial for lesion-symptom mapping. The precision of SVR-LSM was evaluated using real data from patients with post-stroke aphasia and synthetic lesion-behavior data. The results demonstrated that SVR-LSM exhibits higher specificity and sensitivity than univariate VLSM when using synthetic data, and it also outperformed univariate VLSM in detecting lesion-symptom associations with real data (Zhang et al., 2014). Multivariate SVR-LSM has been extensively used in lesion-symptom studies involving stroke patients with various functional impairments, such as aphasia, cognitive impairment, and visuospatial neglect. These studies have successfully identified specific regions in the frontal, temporal, and parietal cortices associated with respective clinical symptoms (Lacey et al., 2017; Wiesen et al., 2019; Zhao et al., 2018). As a result, the multivariate SVR-LSM approach has gained widespread use in lesion-symptom mapping studies.

Consequently, in 2018, DeMarco & Turkeltaub (2018) developed a graphical user interface (GUI) for SVR-LSM based on the original code by Zhang et al. (2014) (available at https://github.com/atdemarco/svrlsmgui). This GUI, implemented in MATLAB, offers several advantages over the original implementation. One notable advantage is the inclusion of an option to control for lesion size by regressing lesion volume from the behavioral score and lesion maps. Overall, SVR-LSM represents a superior lesion-symptom mapping approach, allowing the exploration of coherent brain networks and yielding accurate lesion-behavior associations.

4.2.1 Support vector regression - lesion-symptom mapping (SVR-LSM) toolbox

The SVR-LSM toolbox (DeMarco & Turkeltaub, 2018) was employed to identify brain lesions strongly associated with behavioral variables in stroke patients. This MATLAB-based toolbox allows specifying a minimum lesion overlap threshold to ensure that a sufficient number of patients show a lesion at a specific voxel to allow robust lesion-symptom associations. This threshold is set depending on sample size, sample, i.e., lesion heterogeneity, and targeted statistical specificity. Voxels damaged in less than 5–10% of the sample are typically excluded (Karnath et al., 2020). Furthermore, controlling for lesion volume is crucial in lesion-symptom mapping, as larger lesions may lead to more severe deficits. Moreover, patients with lesions occupying a particular voxel are likely to have larger strokes than those

without lesions at that voxel, leading to a bias in identifying lesion-behavior associations even in regions unrelated to the behavior under investigation. One method to address this issue is to regress lesion volume out of behavioral scores, transforming the scores to remove their association with lesion volume before conducting lesion-symptom mapping analysis (Karnath et al., 2004; Schwartz et al., 2012). As recommended for dealing with the problem of lesion volume as a confound for lesion-behavior mapping (DeMarco & Turkeltaub, 2018), the option "regression out of both" regresses lesion volume out of both, the lesion maps, and the behavioral variables to remove the relationship with the lesion volume.

Further toolbox settings were applied according to our study and hypothesis purposes. The directionality of the hypothesis was set to "High scores are bad" since higher scores on the MADRS interview indicate more severe depressive symptoms. K-fold cross-validation with five folds was used to create the SVR-ß maps. This application splits the available data into training and test data. It trains the machine multiple times with 1/K of the data left out for testing purposes to assess the predictive performance of a model (Bengio & Grandvalet, 2003). By this, the model's ability to make accurate predictions on unseen data is evaluated, providing insights into its generalizability. In this case, 4/5 of the data was used for training the model 10 times. During training, the voxel values of the lesion map are coded as either 1 (lesioned tissue) or 0 (healthy tissue), and the behavioral score is the object to be trained with (DeMarco, 2018). Of note, it was not the purpose of our study analyses to aim for a model with the highest prediction accuracy possible. Rather, we were interested in the lesion-symptom associations of the model only. Then, the SVR-ß map is generated from the model when the data is projected back into a normalized brain. Random permutation testing with 10,000 permutations was performed to create a probability map from the SVR-ß map. The behavioral data is randomly shuffled with the lesion data when permuting results. The null hypothesis would be true if the randomly shuffled data were identical to the real data.

The analysis utilized the total MADRS score as input for the behavioral variable, and additional analyses were conducted using individual MADRS items grouped into five symptom categories. MATLAB 2019a and the toolbox SVR-LSM GUI were used for the analyses. The results after permutation testing were thresholded at a voxel-wise p-value of $p < .05$, and clusters with significant voxels were identified using the Anatomy Toolbox implemented in Statistical Parametric Mapping (SPM 12) (Eickhoff et al., 2005).

Clusters were further filtered by size, excluding those smaller than 100 voxels for interpretation purposes. The analysis aimed to uncover brain regions associated with depressive symptoms in stroke patients using advanced MRI techniques and statistical analyses.

4.2.2 Lesion masking and preprocessing

Images showing the lesions were extracted from the internal patient database of the University Hospital Cologne, Department of Neurology (DWI and FLAIR). Depending on the scanner type, sequence settings, and patient head size, different numbers of horizontal slices (z-slices) were obtained from the scans. To create lesion masks, which depict the infarct location of the patient, lesions were manually drawn and segmented on the horizontal slices of DWI images using MRICRON (Rorden et al., 2007) and underwent quality control by a second reviewer. In order to prepare the data for subsequent analyses, DWI, FLAIR, and lesion masks underwent several preprocessing steps. First, during coregistration, images are linearly aligned to correct for differences in contrast and spatial resolution between the patient's scans. It uses mutual information, a measure of statistical dependence between voxels in different images, to determine the optimal alignment. The process involves iterative steps, estimating an initial alignment, calculating mutual information, and adjusting transformation parameters until convergence is achieved (Ashby, 2011). Coregistration ensures that functional and structural images have the same spatial resolution and are registered to a common coordinate system, enabling effective patient comparison and analysis. Next, spatial normalization aligns images from different subjects to a common reference space, such as the Montreal Neurological Institute (MNI) space, which is based on the average of a large number of healthy individuals (Fonov et al., 2009). Nonlinear registration methods adjust for interindividual anatomical variability by warping and stretching the images to match the reference space. This step enables group-level analyses and facilitates meaningful comparisons across subjects. Spatial normalization increases statistical power, allows the identification of common anatomical structures, and aids in detecting patterns and differences in brain structure. Lastly, spatial smoothing involves the application of a Gaussian kernel to each voxel. This process replaces the value of a voxel (e.g., 0 = no lesion; 1 = lesioned voxel) with a weighted average of its neighboring voxels based on the size of the Gaussian kernel. The primary purpose of smoothing is to "blur" the data, reducing high-frequency fluctuations and improving the signal-to-noise ratio. This blurring effect enhances the ability to detect changes at a larger spatial scale, encompassing multiple neighboring voxels. By reducing noise and increasing the coherence of the data, smoothing facilitates the identification of meaningful patterns and effects.

Additionally, smoothing has the effect of altering the distribution of the data toward normality. This is advantageous for subsequent statistical analyses that often assume a normal distribution. Smoothing helps to approximate a normal distribution, ensuring the validity of various statistical tests and enhancing the reliability of the results. For these preprocessing steps

of images, we used the SPM 12 software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) as implemented in MATLAB 2019a (MathWorks Inc, Natick MA). Final preprocessing results were manually checked for correct registration and normalization of lesions. The results are normalized binary lesion maps for each patient. Together with the behavioral score (e.g., MADRS score, experimental variable), these lesion masks can now be used as input for the SVR-LSM analyses.

4.3 Behavioral assessments

4.3.1 Montgomery Åsberg Depression Rating Scale

The Montgomery Åsberg Depression Rating Scale (MADRS) is an observer-rated semi-structured interview that assesses depressive symptoms (Montgomery & Åsberg, 1979). It consists of ten items, each scored on a scale from zero to six, evaluated by several detailed interview questions. It measures the severity of depressive symptoms based on the patient's condition over the past week, with higher scores indicating more severe depression (ranging from 0 to 60). The ten items include (i) apparent sadness, (ii) reported sadness, (iii) inner tension, (iv) reduced sleep, (v) reduced appetite, (vi) concentration difficulties, (vii) lassitude, (viii) inability to feel, (ix) pessimistic thoughts, and (x) suicidal thoughts. The experimenter asked provided key questions, such as inquiring about feelings of sadness during the past week and the intensity of these emotions. The cut-off scores for depression severity are (Herrmann et al., 1998): 0 to 6: no depression, 7 to 19: mild depression, 20 to 34: moderate depression, >34: severe depression (major depression).

As introduced earlier, depression constitutes a heterogeneous syndrome including e.g., emotional, cognitive, motivational, or somatic symptoms. For our study purposes, we were interested in specific symptoms of depression. Therefore, we calculated subscores for the MADRS interview to pinpoint specific domains of depression symptoms. These subscores were determined based on the sum of single items that align with particular behavioral domains outlined in ICD-10. This selection was informed by an extensive review of existing literature on the MADRS cluster structure (e.g., Quilty et al., 2013), as well as the expertise of six clinical psychologists, resulting in high agreement of Fleiss' Kappa = 0.847 (Landis & Koch, 1977). Of note, single MADRS items do not reflect separate entities but overlap between different domains (Williams & Kobak, 2008). Thus, MADRS items were categorized into specific symptom domains that best represented their characteristic. These domains of depressive symptoms were: Motivational Symptoms: This domain included items such as "lassitude" (lack of energy) and "inability to feel." Questions were designed to assess difficulties initiating and maintaining everyday activities, apathy, reduced interest in pleasurable surroundings or activities, and impaired adequate emotional processing. Emotional Symptoms: Items within this domain were "apparent sadness" and "reported sadness." Through interview questions, the intensity, duration, and extent of sadness, depressed mood, low spirit, helplessness, apparent despondency, gloom, despair, and emotional expression were evaluated.

Cognitive Symptoms: This domain encompassed "concentration difficulties," "pessimistic thoughts," and "suicidal thoughts." Questions focused on deficits in concentration and thoughts

of guilt, inferiority, remorse, ruin, and suicidal thoughts and attempts. Somatic Symptoms: This domain consisted of "reduced sleep" and "reduced appetite." The assessment involved questions about reduced sleep duration or depth and loss of appetite. Anxiety: This domain included the item "inner tension." Questions aimed to capture sensations of ill-defined discomfort, edginess, inner turmoil, and mental tension accompanied by panic, dread, or anguish.

4.3.2 National Institutes of Health Stroke Scale

The National Institutes of Health Stroke Scale (NIHSS) provides an observer-rated global score to quantify neurological impairments resulting from stroke (Brott et al., 1989). We utilized this score in our studies to evaluate the stroke severity of the patients and how these impairments may affect other behavior parameters, such as PSD and experimental variables. The scale consists of 11 items, including the level of consciousness (e.g., responsiveness, orientation), eye movement (following finger), visual field test, facial paresis (symmetry of facial expression), motor arm (lift and holding arm), motor leg (lift and holding leg), limb ataxia (coordination of arm and leg), sensory testing (feeling pricks at arms and legs), aphasia (e.g., word-finding deficits, loss of fluency), dysarthria (lack of motor skills to produce speech), extinction (spatial neglect of one side of space). The symptomatology was evaluated on an ordinal scale ranging from 0 (normal) to 2, 3, or 4, depending on the item (maximally impaired).

4.3.3 Jebsen Taylor Test of Hand Function

The Jebsen-Taylor Hand Function Test (JTT) was used to assess motor impairments in stroke patients (Jebsen et al., 1969). This test measures the time it takes to perform various upper-limb motor activities. It consists of seven tasks that simulate everyday activities: i) writing a 24-letter sentence (not performed in our study due to difficulties with non-dominant handwriting), ii) simulated newspaper browsing by turning over four 7.6×12.7 cm cards, iii) picking up small, common items (such as pennies, paper clips, and bottle caps) and putting them in a container, iv) stacking checkers to evaluate eye-hand coordination, v) using a spoon to simulate feeding by putting up beans, vi) moving large empty cans, vii) moving large weighted cans (0.45 kg).

Each task must be completed as quickly as possible using each hand separately within a 120-second time limit, starting with the unaffected hand. If a task cannot be performed, a score of 120 seconds is assigned (Duncan et al., 1998). The average time required for all tasks is reported as a test score for each hand, with a higher score indicating a more pronounced deficit. To obtain a single test score representing the hand performance deficits of the affected

hand relative to the unaffected hand, a JTT index score is calculated (JTT index = unaffected hand / affected hand). A lower index (<100%) indicates a higher motor deficit.

5. Empirical section

Study 1

†Krick, S., †Koob, J. L., Latarnik, S., Fink, G. R., Grefkes, C., Rehme, A. K. (2023). Neuroanatomy of symptom-specific correlates in post-stroke depression. Accepted in *Brain Communications* (01.09.2023); no DOI or volume yet

† Shared first-authorship: these authors contributed equally to this work

Study 2

Koob, J. L., Viswanathan, S., Mustin, M., Mallick, I., Krick, S., Fink, G. R., Grefkes, C., Rehme, A. K. (2023). To engage or not engage: Early incentive motivation prevents symptoms of chronic post-stroke depression–A longitudinal study. *NeuroImage: Clinical, 37*. https://doi.org/10.1016/j.nicl.2023.103360

Study 3

Koob, J. L., Gorski, M., Krick, S., Mustin, M., Fink, G. R., Grefkes, C., Rehme, A. K. Lesion-symptom mapping and negative attentional bias of facial emotion processing in post-stroke depression. *In preparation, final draft prior to submission (September 11, 2023)*

5.1 Neuroanatomy of symptom-specific correlates in post-stroke depression.

†Krick, S., †Koob, J. L., Latarnik, S., Fink, G. R., Grefkes, C., Rehme, A. K.

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Accepted in *Brain Communications* (01.09.2023); no DOI or volume yet

Neuroanatomy of post-stroke depression: the association between symptom clusters and lesion location

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Abstract

Post-stroke depression (PSD) affects about 30% of stroke patients and often hampers functional recovery. The diagnosis of depression encompasses heterogeneous symptoms at emotional, motivational, cognitive, behavioral, or somatic levels. Evidence indicates that depression is caused by disruption of bio-aminergic fiber tracts between prefrontal and limbic or striatal brain regions comprising different functional networks. Voxel-based lesion-symptom mapping studies reported discrepant findings regarding the association between infarct locations and depression. Inconsistencies may be due to the usage of sum scores, thereby mixing different symptoms of depression.

In this cross-sectional study, we used multivariate support vector regression for lesion-symptom mapping to identify regions significantly involved in distinct depressive symptom domains and global depression. MRI lesion data were included from 200 patients with acute first-ever ischemic stroke (mean 0.9±1.5 days post-stroke). The Montgomery-Åsberg-Depression-Rating interview assessed depression severity in five symptom domains encompassing motivational, emotional, and cognitive symptoms deficits, anxiety, and somatic symptoms and was examined 8.4 days post-stroke (±4.3).

We found that global depression severity, irrespective of individual symptom domains, was primarily linked to right-hemispheric lesions in the dorsolateral prefrontal cortex (dlPFC) and inferior frontal gyrus (IFG). In contrast, when considering distinct symptom domains individually, the analyses yielded much more sensitive results in regions where the correlations with the global depression score yielded no effects. Accordingly, motivational deficits were associated with lesions in orbitofrontal cortex, dlPFC, pre- and postcentral gyrus, and basal ganglia, including putamen and pallidum. Lesions affecting the dorsal thalamus, anterior

insula, and somatosensory cortex were significantly associated with emotional symptoms such as sadness. Damage to dlPFC was associated with concentration deficits, cognitive symptoms of guilt, and self-reproach. Furthermore, somatic symptoms, including loss of appetite and sleep disturbances, were linked to the insula, parietal operculum, and amygdala lesions. Likewise, anxiety was associated with lesions impacting the central operculum, insula, and IFG. Interestingly, symptoms of anxiety were exclusively left-hemispheric, whereas the lesion-symptom associations of the other domains were lateralized to the right hemisphere.

In conclusion, this large-scale study shows that in acute stroke patients, differential PSD symptom domains are associated with specific structural correlates. Our findings extend existing concepts on the neural underpinnings of depressive symptoms, indicating that differential lesion patterns lead to distinct depressive symptoms in the first weeks post-stroke. These findings may facilitate the development of personalized treatments to improve post-stroke rehabilitation.

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Running title

Neuroanatomy of PSD symptoms

Keywords

large-scale; MADRS; SVR-LSM, multivariate, neural substrates

Introduction

Stroke patients are at an increased risk of developing depressive symptoms, usually described as post-stroke depression (PSD) symptom complex.[1,2] PSD is the most common neuropsychiatric consequence following stroke, with a prevalence of ~30% of all patients.[3,4] Notably, PSD symptoms hinder rehabilitation and functional outcome.[1,2] Therefore, a better understanding of the neural mechanisms underlying PSD is critical for its prevention and the development of personalized treatment approaches.

According to the International Classification of Diseases, 10th revision (ICD-10), depression is based on heterogeneous symptomatology, affecting several domains of behavior, including emotion, motivation, cognition, anxiety, or somatic symptoms, e.g., sleep and appetite (World Health Organization, 1992). Based on the monoamine hypothesis,[5,6] the heterogeneity of depressive symptoms is linked to a dysfunction of ascending and descending bio-aminergic fiber tracts. In patients with major depression (MD), various studies using structural and functional MRI with different methodological approaches found significant alterations in frontal and prefrontal regions, including orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), and subcortical structures, e.g., insula, putamen, caudate nucleus, thalamus, amygdala, and hippocampus.[7–12] These findings provide evidence for a 'depression network' within the human brain that contributes to depression severity and determines characteristic symptom domains.

In stroke patients, several studies aimed to determine whether specific lesion locations are associated with PSD. Many studies used univariate approaches such as voxel-based lesion-symptom mapping (VLSM) to investigate associations between infarct location and PSD.[13–15] However, meta-analyses and reviews reported discrepant evidence, questioning a robust association between lesion sites or affected hemispheres and depressive symptoms.[2,16–20] The reported inconsistencies across PSD studies may result from differences in samples, depression ratings, and time since stroke onset. Moreover, methodological aspects of neuroimaging analyses may cause discrepant findings such as low spatial resolutions of lesion maps, false-positive results after multiple testing, and neglecting voxelwise dependencies in univariate VLSM.[2,16,21]

Machine learning approaches address some of these limitations. Especially multivariate support-vector regression lesion-symptom mapping (SVR-LSM) allows us to compare all lesioned voxels simultaneously to predict continuous behavior.[22] SVR-LSM has been proven

more sensitive and specific than classical mass-univariate analyses in detecting lesion-symptom relationships.[23] Particularly, the probability of lesions in neighboring voxels is not random, as brain regions are organized in networks at both the structural and functional levels favoring multivariate approaches.[22,24–26] Multivariate SVR-LSM has been used extensively in lesion-symptom studies investigating stroke patients with different functional impairments, including aphasia,[27] cognitive impairment,[28] or visuospatial neglect,[29] and identified specific regions in the frontal, temporal and parietal cortices to be associated with the respective clinical symptoms. In unipolar MD patients, multivariate machine learning analyses of structural and functional MRI data revealed altered anatomical cortico-limbic networks associated with depressive symptoms.[30–32]

In contrast to the rich literature on the neural mechanisms underlying MD, few studies have thus far investigated putative structural correlates of PSD using multivariate lesion-symptom mapping methods, often with discrepant findings.[33–36] Grajny *et al.*[33] found lesions in dlPFC to be associated with higher levels of depression in chronic stroke patients, whereas Weaver *et al.*[34] identified the right amygdala and right ventral pallidum as regions structurally linked to PSD in ischemic stroke patients (<1-year post-stroke). Likewise, in chronic patients with focal brain lesions, Trapp *et al.*[35] found a bilateral insula and dlPFC association with depression. Conversely, Sutoko *et al.*[36] assessed acute ischemic stroke patients and found lesions in the right rolandic operculum linked to apathy, anxiety, perceived stress, and depression post-stroke.

A critical reason for diverging results in PSD lesion-symptom mapping studies may lie in the heterogeneity of symptoms that constitute the diagnosis of depression.[6,37] Thus, patients with PSD presenting similar global depression sum scores may considerably differ in clinical phenotype and underlying lesion-symptom associations. It was recently suggested that neural substrates of PSD might be uncovered at the individual symptom level instead of using a sum score.[38,39] For example, patients with somatic depression may suffer from different lesion locations than depressive patients with predominantly motivational or cognitive symptoms. Consequently, analyzing structure-function relationships using only global depression scores will inevitably mix different symptom categories and hence contribute to the inconsistency of lesion-symptom associations in depression. Notably, such analyses are only feasible with sample sizes that allow accounting for the heterogeneity of symptoms encountered in PSD.

Therefore, we investigated a large sample (n = 200) of acute stroke patients to link different functional domains of PSD symptomatology to lesion location using multivariate

SVR-LSM.[22,24] To identify lesion networks that contribute to different domains of depression, we built symptom domains of the Montgomery-Åsberg Depression Rating Scale (MADRS) interview,[40] based on a conceptual-empirical approach according to ICD-10 criteria and internal psychological expertise. The resulting symptom domains consisted of motivational deficits, emotional symptoms, cognitive deficits, somatic symptoms, and anxiety. To substantiate our results, we further computed five factors based on the MADRS items using principal component analysis (PCA) and performed identical SVR-LSM analyses based on this data-driven approach.

Following previous multivariate SVR-LSM findings, we hypothesized that stroke lesions in the left dlPFC and ventral basal ganglia are associated with more severe depression.[33,34] Furthermore, an essential aim of the present study was to identify lesion locations linked to different behavioral domains of PSD for the first time. Based on the literature on neural structures in MD patients, we expected lesions in prefrontal regions, limbic or striatal systems, and insula to be specifically associated with distinct symptom domains, such as cognitive deficits, emotional dysregulation, motivational deficits, including apathy, and somatic symptoms, e.g., sleep disturbances and loss of appetite.[41–45]

Materials and methods

Study sample

Patients included in this study were retrospectively chosen from records of inpatients admitted to the early rehabilitation program of the University Hospital of Cologne between 2015 and 2021. This program encompasses medical care and specialized early therapeutic interventions within the first four weeks post-stroke. According to the German DRG (diagnosis-related groups) system, admission to this program requires a certain degree of impairment based on the Early Rehabilitation Barthel Index,[46] i.e., a score of 25 or less, indicating severe dependence on support for activities of daily living.

All patient data were extracted from the hospital patient database. Inclusion criteria were: first-ever ischemic stroke, MRI scan, National Institutes of Health Stroke Scale (NIHSS)[47] score, and sufficient cognitive and verbal abilities to undergo a MADRS interview. Patients with hemorrhagic stroke, spinal ischemia, drug abuse, antidepressant medication, or previous neurological or psychiatric disorders based on past diagnoses and current medical records were excluded from the study. A total of 1496 patients were admitted to the early rehabilitation program between 2015 and 2021. Two-hundred twenty-eight patients met our inclusion criteria. For 28 patients, only global MADRS sum scores were available from the medical records, whereas individual item symptom scores were available for 200 patients included in this study. In terms of modeling voxel-wise lesion location in SVR-LSM, Sperber *et al.*[48] suggested a sample size larger than 140 subjects to be optimal. Patient data collection and study protocol were approved by the local ethics committee of the University Hospital of Cologne under the guidelines of the Declaration of Helsinki (revised in 2008).

Lesion mapping and preprocessing

MRI scans were assessed on the patient's admission to the hospital on average 0.9 days (±1.5) after the stroke. Diffusion-weighted images (DWI) and fluid-attenuated inversion recovery (FLAIR) images were used to map the individual lesions. Three different clinical MRI scanners with similar voxel sizes were used. Exact MRI protocols and scan parameters are reported in the Supplementary material. Lesions were manually segmented using the patient's DWI scans by qualified neurologists, psychologists, and neuroscientists using MRIcron.[49] Lesion drawings underwent quality control by a second reviewer. DWI, FLAIR, and lesion masks were spatially

normalized to a standard Montreal Neurological Institute (MNI) template (1x1x1mm) using the unified segmentation approach[50] with masked lesions in SPM12 (https://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB R2020a (The MathWorks Inc, Natick, MA, USA) and FMRIB Software Library (FSL). Note that unlike many other lesion-symptom mapping studies in stroke research, lesions were not systematically flipped to a particular hemisphere, i.e., information on inter-hemispheric differences in lesion location was preserved. Final preprocessing results were manually checked to ensure accurate co-registration and normalization of lesions.

Lesion-symptom mapping

A MATLAB-based toolbox was used for multivariate lesion-symptom mapping,[24] which is based on the SVR-LSM implementation introduced by Zhang *et al.*[22] Support vector regression (SVR) is a special case of support vector machines, which are employed to solve binary classification problems, e.g., whether a disease is either present or absent.[51,52] In contrast, SVR allows the prediction of continuous variables based on the lesion status of multiple voxels. The toolbox used for this study consists of an epsilon-SVR with a nonlinear Gaussian radial basis function kernel. All analyses were conducted using MATLAB R2020a on a high-throughput computing (HTC) cluster of the Forschungszentrum Jülich (https://www.fz-juelich.de/inm/inm-7).

Controlling for lesion volume is essential in lesion-symptom mapping because patients with larger lesions tend to show more significant deficits.[24] Thus, after correcting both the behavioral scores and the lesioned voxels for lesion volume, the interpretation of SVR-LSM results allows answering questions about whether the behavior of interest is more strongly related to lesions in a particular brain area relative to all other brain regions rather than a mere correlative interpretation of whether lesions are associated with the behavior of interest.[24] Therefore, lesion volume was regressed from both the lesion maps and the behavioral variables for all SVR-LSM analyses. Stroke severity, as assessed by the NIHSS, age, and sex were used as confound regressors. Of note, mild cognitive deficits as a symptom of both, stroke or depression, were difficult to disentangle and may still represent a potential confounder. A minimum lesion threshold of five lesions per voxel was used to ensure sufficient lesion overlap. The analysis design is one-tailed. Thus, the analyses were set to be negatively tailed based on the assumption that lesion presence was associated with higher MADRS scores indicating more severe depressive symptoms.

For model estimation, five-fold cross-validation was used. Statistical significance was determined by a non-parametric approach using 10,000 permutations. A voxel was considered significant when passing a threshold of $p < 0.005$. Final permutation-based voxel-wise thresholded *p*-maps were smoothed using a 2mm isotropic Gaussian smoothing kernel in SPM 12 to reduce cluster independence of neighboring lesion voxels. Classification of significant anatomical structures was performed using the Harvard-Oxford Cortical and Subcortical structural atlases as implemented in FSL.

Assessment of depressive symptoms

The MADRS interview is an observer-rated semi-structured depression scale consisting of ten items, each scored on a scale from zero to six, evaluated by several detailed interview questions.[40] It measures the severity of depressive symptoms based on the patient's condition over the past week, with higher scores indicating more severe depression. The following items are part of the MADRS: (i) apparent sadness, (ii) reported sadness, (iii) inner tension, (iv) reduced sleep, (v) reduced appetite, (vi) concentration difficulties, (vii) lassitude, (viii) inability to feel, (ix) pessimistic thoughts, and (x) suicidal thoughts. Importantly, each item was rated using detailed questions from a clinical rater based on published clinical guidelines.[53] All patients received a standardized neuropsychological assessment as part of the early rehabilitation program. In our sample, the MADRS interview was assessed on average 8.4 days (±4.3) post-stroke.

Categorization of depressive symptoms

Conceptual-empirical approach

To test whether individual symptoms of depression were differentially linked to brain lesion locations, we used depressive symptom domains based on detailed clinical questions for each item of the MADRS interview. In a conceptual-empirical approach, five symptom domains were formed, covering distinct aspects of depression. These were based on the sum of single items, which were content-related to a specific behavioral domain as described in ICD-10 and based on the expertise of six clinical psychologists, resulting in a high agreement of Fleiss' Kappa = 0.847.[54] Additionally, extensive previous literature search was done to assess symptom cluster structures of the MADRS and other depression scales to form content-related specific symptom domains in our study.[55] Generally, there are high cross-correlations between

specific depressive symptoms (Supplementary Table 1), therefore, single MADRS items do not reflect separate entities but overlap between different domains.[53] MADRS items were assigned to a symptom domain, which most likely represents the specific item. The depressive symptom domains were: *'Motivational symptoms'*, including the items 'lassitude' and 'inability to feel' with questions such as difficulties in getting started or slowness in initiating and maintaining everyday activities, apathy, reduced interest in surroundings or activities that usually give pleasure, and reduced adequate emotional processing. *'Emotional symptoms'*, including the items 'apparent sadness' and 'reported sadness', assessed by interview questions on sadness, depressed mood, low spirit, helplessness, according to intensity, duration, and extent, as well as apparent despondency, gloom, and despair, reflected in speech, facial expression, and posture. *'Cognitive symptoms'* consisted of the items: 'concentration difficulties', 'pessimistic thoughts', and 'suicidal thoughts', including questions about concentration deficits, thoughts of guilt, inferiority, remorse, and ruin as well as suicidal thoughts and attempts. *'Somatic symptoms'*, including the items 'reduced sleep' and 'reduced appetite', based on questions about reduced duration or depth of sleep and loss of appetite. *'Anxiety'* included the item 'inner tension', defined by questions on ill-defined discomfort, edginess, inner turmoil, mental tension with panic, dread, or anguish. The scores of the conceptual-empirical categorization are summarized in Table 1.

Data-driven corroboration

In a data-driven approach, we aimed to further substantiate the conceptual-empirical categorization of five depression domains by computing a factor analysis in SPSS 28 (IBM Corp, Armonk, NY, USA) using the ten MADRS item scores of the patient sample. Therefore, a principal component analysis (PCA) was performed with an oblique rotation procedure to obtain a realistic representation of the correlative structure underlying depression factors.[56,57] We entered a fixed number of five factors for factor extraction derived from the five conceptual-empirical symptom domains, applying the total variance explained extraction criterion. This criterion suggests extracting factors until a specific threshold of explained cumulative variance is reached, which is usually set between 70% and 90%.[58,59] Extracting five factors resulted to a cumulative explained variance of 72%, which corresponds to an Eigenvalue threshold of 0.8 in our data (Supplementary Table 2 and 3, Supplementary Fig. 3). Factor-score coefficients were estimated and used as behavioral input variables in SVR-LSM. All SVR-LSM analyses were carried out identically to the analyses of the conceptual-empirical

domains. The clinical designation of the factors, factor loadings, eigenvalues, explained variance, as well as the corresponding SVR-LSM analyses and significant voxels of cluster regions, are reported in the Supplementary material.

Statistical analysis

Spearman correlations for ordinal-scaled variables were used to assess sample associations between the MADRS scores (sum score and symptom domains of the conceptual-empirical approach) and NIHSS, age, and lesion volume in SPSS 28. To assess differences in depressive symptoms between sexes, we performed a one-way ANOVA. False-discovery rate (FDR) correction for multiple testing was applied for all analyses.[60] Importantly, to investigate the potential influence of functional impairment on depression most accurately, we applied the individual NIHSS which was assessed closest to the MADRS interview for the statistical analyses and SVR-LSM. The MADRS interview (8.4 days (±4.3) post-stroke) was assessed always after potential interventions like thrombectomy, thrombolysis, or tissue plasminogen activator medication. The NIHSS scores were assessed 3.40 days (±2.01, range: 0-14) post-stroke. Thus, NIHSS scores are only indirectly related to the initial level of impairment assessed upon admission and whether a patient received immediate treatment.

A total of eleven multivariate SVR-LSM analyses were carried out, including the global MADRS score, the conceptual-empirical scores, and the data-driven factor coefficients for five symptom domains as behavioral variables.

The Dice coefficient (DC) was calculated to quantify the similarity of spatial lesion-overlap of *p*-maps of the conceptual-empirical approach and the corresponding data-driven approach.[61] We used the 'fslstats' and 'fslmaths' commands implemented in FSL to compute overlapping voxels between each of the five symptom domains and clinically corresponding factors (see Supplementary material) by multiplying both maps with each other. To calculate the DC, we used the formula $DC(X,Y) = (2|X \cap Y|) / (|X|+|Y|)$, where $|X|$ is the total number of significant voxels in lesion map X and $|Y|$ the total number of significant voxels in lesion map Y. $|X \cap Y|$ indicates the number of overlapping voxels of both lesion maps. DC was computed for each of the five pairs of symptom domains and corresponding factors. The coefficient ranges from 0 to 1, with 0 indicating no overlap and 1 indicating perfect overlap (low: 0 to 0.19, low-moderate: 0.20 to 0.39, moderate: 0.40 to 0.59, moderate-high: 0.60 to 0.79, high: 0.80 to 1.00).[62]

Data availability

Derived anonymized data supporting the findings of this study, and resulting signature region of interest masks, are available upon reasonable request.

Results

Clinical and demographic data are shown in Table 1. MADRS scores were distributed in the sample as follows: 89 patients (44.5%) showed no depressive symptoms, 95 patients (47.5%) were mildly depressed, 15 patients (7.5%) were moderately depressed, and one patient (0.5%) showed severe depressive symptoms.[63] Note that due to the admission criteria for entering early rehabilitation treatment, patients had a more significant neurological impairment than the general stroke population,[64] which is also evident from the relatively high mean NIHSS score of 12.85 (±4.56) (Table 1).

Correlational analyses between the depression sum score, depressive domains, and the one-way ANOVA comparing depression scores between sexes revealed no associations with age, lesion volume, sex, or stroke severity (NIHSS), respectively (all $p > 0.384$; FDR-corrected). This suggests that symptoms of depression were not solely explained by the amount of stroke-induced functional impairments.

SVR-LSM results

The average lesion volume was 33.58 cm^3 (±50.91 cm^3, range: 0.01 cm^3 - 268.11 cm^3). Fig. 1 shows the lesion coverage for the entire patient sample ($n = 200$). The region with the highest overlap was at the right putamen ($n = 41$, 20.5%). High lesion coverage of the left and right hemispheres was observed, except regions surrounding frontal and occipital poles, cingulate gyrus, and precuneus. Eighty-one patients had lesions in the left hemisphere, 104 patients had right hemispheric lesions, and 15 had bilateral damage. A lesion overlap map of n ≥ 5 patients included in the SVR-LSM is displayed in the Supplementary Fig. 1. Please note that the MADRS interview was not assessed in patients who were unable to comprehend and adequately respond to an interview. Thus, as aphasia mostly results from left-sided lesions, patients with severe aphasia were not included in our sample. Therefore, the imbalance of right and left hemispheric lesions may be caused by the inability to assess severely aphasic stroke patients in a formal interview. Similarly, patients with severe cognitive impairment were excluded from MADRS interviews. Of note, cognitive dysfunction might display a potential confounder in the analysis of depression symptoms in the acute stage post-stroke. Although patients with severe cognitive dysfunctions were not included in our sample, it is still possible that mild cognitive decline has an impact on our findings.

SVR-LSM results revealed that the MADRS sum score was specifically related to lesions in dlPFC and inferior frontal gyrus (IFG). Thus, patients with lesions in these locations indicated higher depression scores. Results are displayed in Fig. 2 and Fig. 3A.

We analyzed lesion-symptom relationships for the five different domains of depression defined by the conceptual-empirical criteria (Fig. 3B, Fig. 4, Table 2). Motivational deficits showed lesion associations with the OFC, dlPFC, pre- and postcentral gyrus, and basal ganglia, including putamen and pallidum. Emotional symptoms were significantly related to lesions in the dorsal thalamus, anterior insula, and somatosensory cortex. Cognitive symptoms were primarily associated with damage to dlPFC. Additionally, somatic symptoms were linked to insula, parietal operculum, and amygdala lesions, whereas symptoms of anxiety were associated with lesions in the central operculum, insula, and IFG (see Supplementary Fig. 2 for individual maps). In summary, SVR-LSM results of the depressive symptom domains revealed a differential and precise picture with lesion-symptom associations not detected in the SVR-LSM analysis of the MADRS sum score.

SVR-LSM results of the data-driven symptom classification yielded highly similar results and are reported in the Supplementary material (Supplementary Fig. 4, Supplementary Table 4). As a measure of similarity, the Dice coefficient yielded moderate-high overlap (0.64 ±0.08), averaged across all analyses.[62] For the respective symptom domains, the coefficients ranged between moderate and moderate-high similarities: motivational symptoms/Factor 5 DC = 0.52; emotional symptoms/Factor 3 DC = 0.64; cognitive symptoms/Factor 4 DC = 0.73; somatic symptoms/Factor 2 DC = 0.63; anxiety/Factor 1 DC = 0.69. See Supplementary material for further contextual information on the comparison between the conceptual-empirical and data-driven SVR-LSM results.

Discussion

We used large-scale multivariate lesion-symptom mapping to identify lesion patterns associated with distinct behavioral domains of depression in the acute stage post-stroke. We obtained a much more differential picture of the structural correlates underlying distinct depressive symptoms, than the usage of a sum score for depression. Importantly, by controlling for various covariates (neurological and psychiatric history, lesion volume, stroke severity, age, sex), SVR-LSM findings from our study are specifically related to the acute depressive symptomatology post-stroke, thereby providing further evidence that depressive symptoms may derive from lesions to specific brain areas than representing a mere adjustment disorder. Likewise, lesion-symptom associations were primarily independent of the categorization approach of standard MADRS depression interview scores using either conceptual-empirical or data-driven classification.

Depression as a multi-dimensional syndrome

The finding that specific brain structures contribute to distinct domains of depression, including emotional, motivational, and cognitive deficits as well as somatic symptoms and anxiety, enables a new taxonomy to further our understanding of depression in general. Additionally, by using a multivariate SVR-LSM approach with continuous behavioral scores, the sensitivity and robustness of lesion-symptom associations are increased compared to classical mass univariate LSM analyses.[22] Furthermore, we observed symptom-specific hemispheric lateralization of brain-behavior associations: Despite fewer left hemispheric lesions (Fig. 1, Table 1), we found that symptoms of anxiety were predominantly associated with left-lateralized lesions in both classification approaches. All other four symptom domains (emotional, somatic, motivational, and cognitive) were associated with right hemispheric lesions. The role of lesion lateralization in PSD remains a topic of scientific debate. Several meta-analyses and reviews reported no significant influence,[16,18,20] whereas some found left-hemispheric lateralization,[17] and others found right-hemispheric lateralization but only in the subacute stage post-stroke.[19] The present findings provide first evidence that lesion lateralization in PSD might be symptom-specific. This discovery suggests that lateralization may only be revealed by considering PSD as a multi-dimensional disorder. This heterogeneous classification of depressive symptoms and associated neural substrates furthers our understanding of the mechanisms underlying the brain-behavior relationship in PSD.

The results of the global depression score revealed no other lesion-symptom associations beyond the lesions in brain areas that were specifically related to different symptom domains of depression. The findings for the global depression score partially corroborate evidence based on previous multivariate lesion-symptom mapping studies in subacute and chronic stroke.[33–35] In line with our results, structural lesions in dlPFC, amygdala, and ventral pallidum were linked to more severe depression. In the following, neural correlates of individual depressive symptom domains will be discussed.

Motivational symptoms

Motivational deficits were based on item questions such as difficulties in getting started or slowness in initiating and maintaining everyday activities, apathy, reduced interest, and reduced adequate emotional processing.[40,53,63] We found that pronounced motivational deficits were primarily related to damage in OFC, dlPFC, pre- and postcentral gyrus, and basal ganglia, including putamen and pallidum. These regions constitute the human cortico-striatal reward network, which subserves incentive motivational behavior by transforming motivations and cognitions into actions.[6,65–67] This motivational system may be differentiated into ventral and dorsal cortico-striatal networks, organized by reciprocal loops in a topographic manner to translate motivations into actions, regulate emotions and mediate goal-directed behavior.[65,68] Functional MRI activity in dlPFC and striatum has been reported to correlate with reduced incentive motivation in MD patients.[69,70] Besides, reduced incentive motivation in stroke patients is affected by apathy post-stroke, resulting from damage to bilateral basal ganglia, including the ventral striatum.[71,72] Our analyses revealed lesion-symptom associations in OFC and basal ganglia, which play a crucial role in the human cortico-striatal reward system.[6,67]

Emotional symptoms

More significant emotional symptoms of perceived and observed sadness, depressed mood, low spirit, helplessness, gloom, and despair were linked to lesions in the anterior-ventral part of the insula, dorsal part of the thalamus, and postcentral gyrus. In a large-scale meta-analysis, the anterior-ventral insula was found to be relevant for emotion and empathy.[73] The broad literature supports the finding that the insula, specifically the anterior part, is an essential correlate for socio-emotional stimulus processing.[74–79] Furthermore, a structural MRI study by Tippett *et al.*[80] observed that acute stroke patients with lesions in the right amygdala and right

anterior insula performed significantly worse in facial emotion recognition tasks than patients with other lesion locations.

Further correlations were observed between emotional symptoms and lesions of the dorsal thalamus. The thalamus is seen as the gatekeeper to the cerebral cortex due to interconnections to various brain areas, including the insula, amygdala, or frontal cortex, which contribute to attention, memory, consciousness, sleep, arousal, and emotion.[81,82] The thalamus may therefore not be primarily involved in the emotional symptoms of PSD, but lesions may influence its modulating role on connected areas.

Furthermore, emotional symptoms correlated with lesions in the postcentral gyrus and parietal operculum, i.e., the primary somatosensory cortex (S-I) and secondary somatosensory cortex (S-II). One study found structural and functional S-I and S-II changes in patients with mental disorders including depression, anxiety, and panic disorder.[83] There is further evidence that the somatosensory cortex is involved in regulating emotions evoked by somatosensory stimuli by using strategies of attention direction in the context of social adequacy.[83] Likewise, somatosensory representation in recognizing emotional states in facial expressions has previously been associated with damage to the right S-I, S-II, and insula, even with the absence of lesions in primary visual brain areas.[84]

Cognitive symptoms

The cognitive symptom domain included concentration deficits and different items referring to ‘mindsets’ consisting of thoughts of guilt, inferiority, remorse, and ruin, as well as suicidal thoughts. It was primarily correlated with more pronounced lesions in large parts of the middle frontal gyrus (MFG), including dlPFC. The dlPFC is mainly involved in executive functions, including attentional processing and working memory for goal-directed actions.[85] Therefore, dysfunction of dlPFC may severely affect cognitive and executive functions such as attentional processing and divided attention,[86] which also results in concentration deficits in MD patients.[87,88]

Previous literature already showed that a reduction of gray matter tissue in dlPFC contributes to depressive symptoms in late-life depression.[89] In line with the monoamine hypothesis of cortico-limbic dysregulation, reduced functional connectivity of dlPFC, amygdala, and ACC is associated with impaired regulation of negative emotion processing based on enhanced processing of negative stimuli.[6,37,90–92] Lesion-symptom mapping studies on PSD reported strong correlations between dlPFC lesions and global depression.[33] Moreover,

repetitive transcranial magnetic stimulation (rTMS) to dlPFC is an established approach for treating depression.[93–95] Of note, a recent study including patients with several lesion etiologies in five different data sets showed that instead of the lesion location itself, functional connectivity of lesions with left dlPFC was significantly related to depression.[14] The authors concluded that dlPFC represents a connection hub for depressive symptoms and a target for interventions.

Our results at the acute stage post-stroke, together with previous literature, support the hypothesis that the dlPFC holds a critical role in depression,[14,17,20,33,96,97] and further extend these findings by specifying cognitive symptoms of depression, specifically concentration deficits, to be a dominant symptom in stroke patients with dlPFC damage.

Somatic symptoms

We found somatic depressive symptoms like sleep disorders and loss of appetite were primarily associated with damage to the insula, parietal operculum, amygdala, and parietal lobe. The posterior insula has been shown to play a role in integrating primary interoceptive signals with stronger emotionally salient information gradually represented by anterior insula which was significantly associated with somatic symptoms in our SVR-LSM analysis.[98] The amygdala is involved in encoding emotional valence from emotionally salient stimuli.[99] Furthermore, the parietal operculum, i.e., S-II, and insula mediate gustatory and olfactory processing.[73,100] There is broad evidence that interoceptive sensations like fatigue, hunger, pain, or sexual drive but also heartbeat are disturbed in MD patients.[101–105] These effects are mediated by reduced insula activation, probably via inter-connections with primary and secondary somatosensory areas in the parietal cortex.[106,107]

Interestingly, a recent review found low-frequency rTMS over the right dlPFC or posterior parietal cortex to reduce sleep problems in patients with primary insomnia.[108] Thus, depression may lead to misinterpretation of bodily signals to achieve homeostasis of somatic needs.[98,102,103] The misinterpretation of bodily sensations may affect other behavioral dysfunctions in depression, including motivational deficits, emotional dysregulation, or even alexithymia.[101,105,109]

Anxiety

More significant anxiety, in particular inner tension such as discomfort, edginess, inner turmoil, panic, dread, anguish, and loss of interest, was linked to lesions in the insula, IFG, central

operculum, and parietal, temporal, and occipital cortices. A recent study on ischemic stroke patients suggested that post-stroke apathy, anxiety, and depression were associated with damage to the central operculum.[36] Previous studies in healthy subjects identified the insula as an essential neural correlate in mediating anxious traits.[101,110,111] Specifically, the insula plays a crucial role in detecting differences between an expected and observed body state followed by increased anxious feelings, which leads to increased anxiety in anticipation of a future aversive body state.[101] Likewise, a study examining stroke patients with frontal brain lesions found that structural abnormalities in the insula are closely related to elevated sensitivity to anxiety.[112] Thus, the existing literature suggests a predominant role of the insular cortex in states of stress and anxiety associated with uncertain situations, overestimated potential adverse outcomes, and risk-taking decision-making behavior.[113–116]

SVR-LSM results further revealed significant clusters in IFG. Cha *et al.*[117] found altered IFG dynamics linked to abnormal structural and functional prefrontal-limbic connectivity in clinically anxious individuals. The authors suggested that IFG plays a crucial role in modulating fear and anxiety in response to threats. Overall, lesions in the insula, IFG, central operculum, and parietal cortex play a role in developing anxious symptoms in acute stroke patients. A recent review reported evidence for an 'advanced fear network model' including these brain areas and hypothesized that fronto-limbic dysregulation is induced via sensory modalities from temporal, parietal, and occipital cortices.[118] Sensory information is filtered by the thalamus, processed by the insula, and further integrated into the fronto-limbic loop for cognitive and autonomic responses, including symptoms of anxiety.

Limitations

Despite the strengths of our study, it is crucial to address some limitations. One pertains to the inclusion of acute stroke patients, which introduces a potential confounding factor due to the progressive evolution of lesions over time, especially in the first 24 hours. Ischemic penumbra or diaschisis, representing regions of brain tissue surrounding and functionally connected to the lesion site, may exert an influence on the symptoms experienced by patients.[119] In our sample, the assessment of depressive symptoms occurred on average 8.43 days following MR scan. It is important to note that during this interval, the ongoing evolution of the lesion might have impacted the manifestation of symptoms. In addition, it is important to note that the patient sample exhibited on average mild depressive symptoms (mean MADRS score of 9.1). This places patients only on the brink of meeting criteria for mild depression The lack of

individuals with more severe depressive symptoms, warrants consideration of this potential influence. Furthermore, despite having a large patient sample, certain regions (such as those surrounding frontal and occipital poles, thalamus, cingulate gyrus, or medial prefrontal gyrus) were excluded in the analysis due to insufficient lesion overlap and cannot be concluded about. Consequently, conclusions are restricted to included regions.

Pathophysiology of PSD

PSD has been discussed as arising from a complex interplay of multi-dimensional biological, functional, and psychosocial aspects.[21,120] PSD severity and potential risk factors may vary considerably depending on the time post-stroke.[2,21] Some studies have revealed an association between PSD and neurological deficits, indicating that PSD may be a partial psychological reaction to, e.g., cognitive impairment, motor deficits (e.g., hemiplegia), and activities of daily living.[121,122] This view is challenged by studies conceptualizing PSD as a neurobiological consequence rather than an adjustment disorder. For example, stroke patients have been reported to be at a three to four times higher risk for developing depression than orthopedic patients or traumatic brain injury patients with comparable impairments or lesion volumes.[123,124] Singh *et al.*[125] identified both lesions in inferior frontal regions and functional impairment in activities of daily living assessed one month post stroke to predict PSD development, yet functional impairment was the strongest predictor. To the best of our knowledge, no previous study has investigated the relationship between specific depressive symptoms like motivational and emotional deficits, or anxiety and stroke severity (NIHSS). Importantly, our findings suggest no association between these specific depressive symptom domains and stroke severity in the acute stage post-stroke. Thus, our findings align with the notion that PSD symptoms primarily depend on anatomical causes rather than functional impairments. Nevertheless, our sample included patients in a very early stage after stroke, who participated in an early rehabilitation program and were embedded in frequent multidisciplinary therapies. As we did not evaluate PSD symptoms and stroke severity in later stages post-stroke, functionally impaired patients might develop increased PSD symptoms after discharge when they are confronted with impairments and drawbacks in their everyday life. Due to our eligibility criteria for early rehabilitation treatment, our study sample contained more severely affected patients than the average stroke population.[64] Furthermore, 55.5% of our patients showed at least mild depressive symptoms already in the acute stage after stroke,[63,126] which is substantially higher than the average prevalence of ~30% at any time up

to five years post-stroke.[3] Thus, we investigated the neuroanatomical correlates of PSD in a large sample of strongly impaired and prevalently depressive stroke patients. Accordingly, identifying the underlying pathophysiological mechanisms of PSD symptoms and potential risk factors in an average stroke population remains important to confirm our findings, identify patients at risk, and individualize PSD prevention and treatment.

While our current results support a symptom-specific view of anatomical correlates of PSD, depressive symptoms in MD have been suggested to arise from different risk factors and biomarkers.[127,128] Thus, while our findings may not be generalized to MD, they can inform future research on symptom-specific neural mechanisms underlying MD.

Crucially, the presence of a lesion does not necessarily indicate an increased risk for depression. Recent research by Trapp et al.35 conducted a large-scale LSM study on depression after focal brain damage and revealed that certain lesions can actually reduce the likelihood of developing depressive symptoms i.e., exhibiting a resilience to the manifestation of depressive symptoms. Especially, brain regions associated with the default mode network were identified as regions of resilience. These findings highlight an interesting factor to look at in the future of LSM.[35] As another outlook for future studies, it may be very promising to look at individual depressive symptom clusters from a functional and structural network perspective. This could be achieved by integrating normative connectome data and examining correlations with canonical resting state networks, which could potentially unveil network-level pathological mechanisms underlying PSD.

Conclusion

This relatively large-scale study reveals crucial aspects of the etiology of PSD by showing that distinct depressive symptoms (i.e., motivational symptoms, emotional symptoms, cognitive symptoms, somatic symptoms, and anxiety) in the acute stage post-stroke are related to specific lesion sites. These results extend the understanding of the etiology and pathophysiology of depression and the underlying functional and anatomical networks. Furthermore, we provide essential evidence of symptom-specific lesion lateralization in PSD, with symptoms of anxiety specifically being hemispheric. Our findings suggest that PSD arises from localized neural symptom clusters and does not solely represent a mere psychological adaptation following the functional impairment after stroke. Considering that stroke, and thus, PSD is a life-changing event with a substantial impact on the patient's health, multivariate approaches to lesion-

symptom mapping can reveal specific therapeutic targets for future interventions individually fitted to specific symptoms in post-stroke patients, thereby promoting optimal rehabilitative outcomes.

Acknowledgments

We thank the INM-7 team at Forschungszentrum Jülich, especially Prof. Simon Eickhoff, for establishing access to their HTC Cluster to compute our analyses. Furthermore, we thank Prof. Peter Weiss-Blankenhorn from University Hospital Cologne, Department of Neurology for granting us access to the patient's neuropsychological assessment records.

Funding

This research work has been funded by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG – Project-ID: 310098283). Gereon R Fink is funded by the DFG – Project-ID 431549029 – SFB 1451. Gereon R Fink acknowledges additional support from the Marga and Walter Boll Foundation.

Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain Communications* online

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Figure legends

Figure 1: Lesion coverage map

Overlap map of normalized lesions from patients included in the analysis (n= 200). Coordinates indicate corresponding z-value in Montreal Neurological Institute (MNI) space. Red indicates higher overlap, and pink indicates less overlap of lesions. Highest overlap was seen at the right putamen (n = 41). Please note, that small overlap into ventricles is due to co-registration for display purposes in MRIcron. L, left; R, right.

Figure 2: SVR-LSM results of the global depression sum score

SVR-LSM results and lesion locations associated with the global MADRS score with a voxel-wise significance threshold set to $p < 0.005$ (n= 200). Results were smoothed using a 2mm isotropic Gaussian smoothing filter. Classification of anatomical structures was performed using the Harvard-Oxford Cortical and Subcortical structural atlases. Coordinates indicate corresponding z-value in Montreal Neurological Institute (MNI) space. Predominant clusters are labeled. L, left; R, right; INS, insula; IFG, inferior frontal gyrus; dlPFC, dorsolateral prefrontal cortex; PreCG, precentral gyrus; PostCG, postcentral gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; PL, parietal lobe.

Figure 3: 3D renderings of SVR-LSM results

3D renderings of SVR-LSM results displaying the global MADRS score **(A)** and the five symptom domains based on the conceptual-empirical classification with a voxel-wise threshold set to $p < 0.005$ ($n = 200$) **(B)**. dlPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; STG, superior temporal gyrus; INS, insula; OFC, orbitofrontal cortex.

Figure 4: SVR-LSM results and lesion location associations of depressive symptom domains

SVR-LSM results and lesion location associations of depressive symptom domains based on the conceptual-empirical classification with a voxel-wise threshold set to $p < 0.005$ ($n = 200$). Results were smoothed using a 2 mm isotropic Gaussian smoothing filter. Coordinates indicate corresponding z-value in Montreal Neurological Institute (MNI) space. Blue: Anxiety. Pink: Somatic. Yellow: Emotional. Green: Cognitive. Red: Motivational. Classification of

anatomical structures was performed using the Harvard-Oxford Cortical and Subcortical structural atlases. Predominant clusters are labeled. L, left; R, right; AMG, amygdala; INS, insula; OFC, orbitofrontal cortex; TP, temporal pole; PAL, pallidum; PUT, putamen; IFG, inferior frontal gyrus; STG, superior temporal gyrus; FO, frontal operculum; CO, central operculum; PO, parietal operculum; TL, thalamus; PL, parietal lobe; dlPFC, dorsolateral prefrontal cortex; PreCG, precentral gyrus; PostCG, postcentral gyrus; MFG, middle frontal gyrus; LOC, lateral occipital cortex.

	Value
Demographics	
Sex (female:male)	114 : 86
Age (years), mean (±SD)	72.99 (12.77)
Lesion side (right:left:bilateral)	104 : 81 : 15
Examination NIHSS post-stroke (days), mean (±SD)	3.40 (2.01)
Examination NIHSS post-stroke (days), range	0 - 14
Examination MADRS post-stroke (days), mean (±SD)	8.43 (4.26)
Examination MADRS post-stroke (days), range	1 - 22
Examination MADRS post MR (days), mean (±SD)	7.55 (4.24)
Thrombectomy (*n*)	53
Thrombolysis (*n*)	67
Lesioned voxels (cm^3), mean (±SD)	33.58 (50.91)
Lesioned voxels (cm^3), range	0.01 – 268.11
Depressive symptom domains (MADRS)	
Global sum score, mean (±SD)	9.11 (7.09)
Anxiety domain, mean (±SD)	1.10 (1.39)[a]
Somatic symptoms domain, mean (±SD)	1.44 (1.37)[a]
Emotional symptoms domain, mean (±SD)	1.24 (1.18)[a]
Cognitive symptoms domain, mean (±SD)	0.51 (0.71)[a]
Motivational symptoms domain, mean (±SD)	0.55 (0.89)[a]
Global impairment	
NIHSS, mean (±SD)	12.85 (4.56)

Table 1 Overview of the demographic and clinical characteristics of the study sample (*n* = 200).

[a]Note that for the depressive symptom domains, each domain was standardized based on the number of MADRS items included in this domain to allow for a direct clinical comparison between domains. NIHSS: National Institute Health Stroke Scale; MADRS: Montgomery-Åsberg Depression Rating Scale

Brain region	Global MADRS	Motivational Symptoms	Emotional symptoms	Cognitive symptoms	Somatic symptoms	Anxiety
inferior frontal gyrus	R	R			R	L
middle frontal gyrus	R (dlPFC)	R (dlPFC)	R	R (dlPFC)	R (dlPFC)	
superior frontal gyrus	R	R		R	R	
insula	R	R (a)	R (av)		R	L
precentral gyrus	L/R	R	R	R	R	L
postcentral gyrus	L/R	R	R	R	R	L
middle temporal gyrus					R	
superior temporal gyrus	R		R		R	L
inferior parietal lobe			R		R	L
superior parietal lobe	R		R	R		L
amygdala					R	
frontal operculum					R	
central operculum			R		R	L
parietal operculum			R		R	L
putamen		R			R	
pallidum		R			R	
temporal pole				R	R	
thalamus			R (d)			
orbitofrontal cortex		R		R		
lateral occipital cortex						L
pons						L

Table 2 SVR-LSM results of the global MADRS score and the conceptual-empirical classification of depressive symptom domains. L(eft) or R(ight) indicate the hemisphere with significant clusters of voxels ($p < 0.005$) in a given brain region. Classification of anatomical structures was performed using the Harvard-Oxford Cortical and Subcortical structural atlases. dlPFC, dorsolateral prefrontal cortex; av, anterior-ventral; d, dorsal; a, anterior.

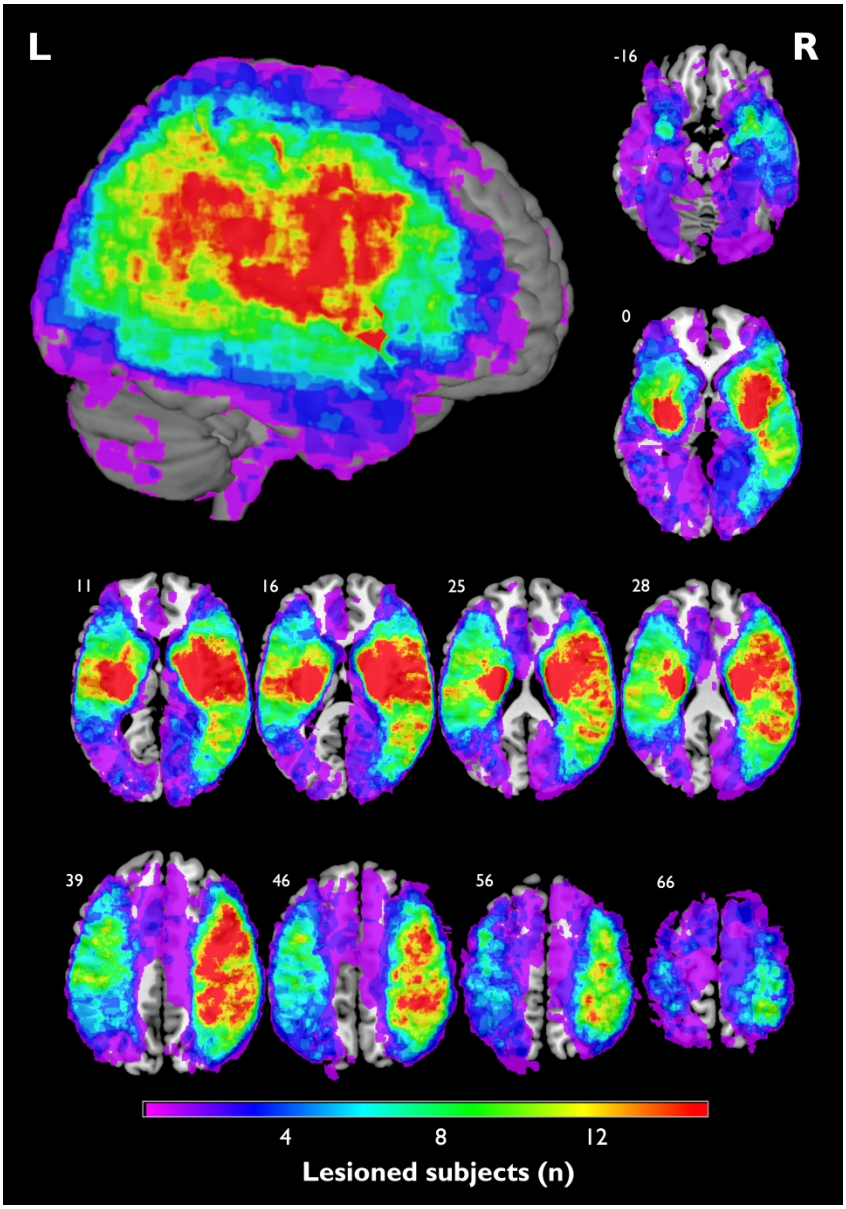


Figure 1

299x428mm (330 x 330 DPI)

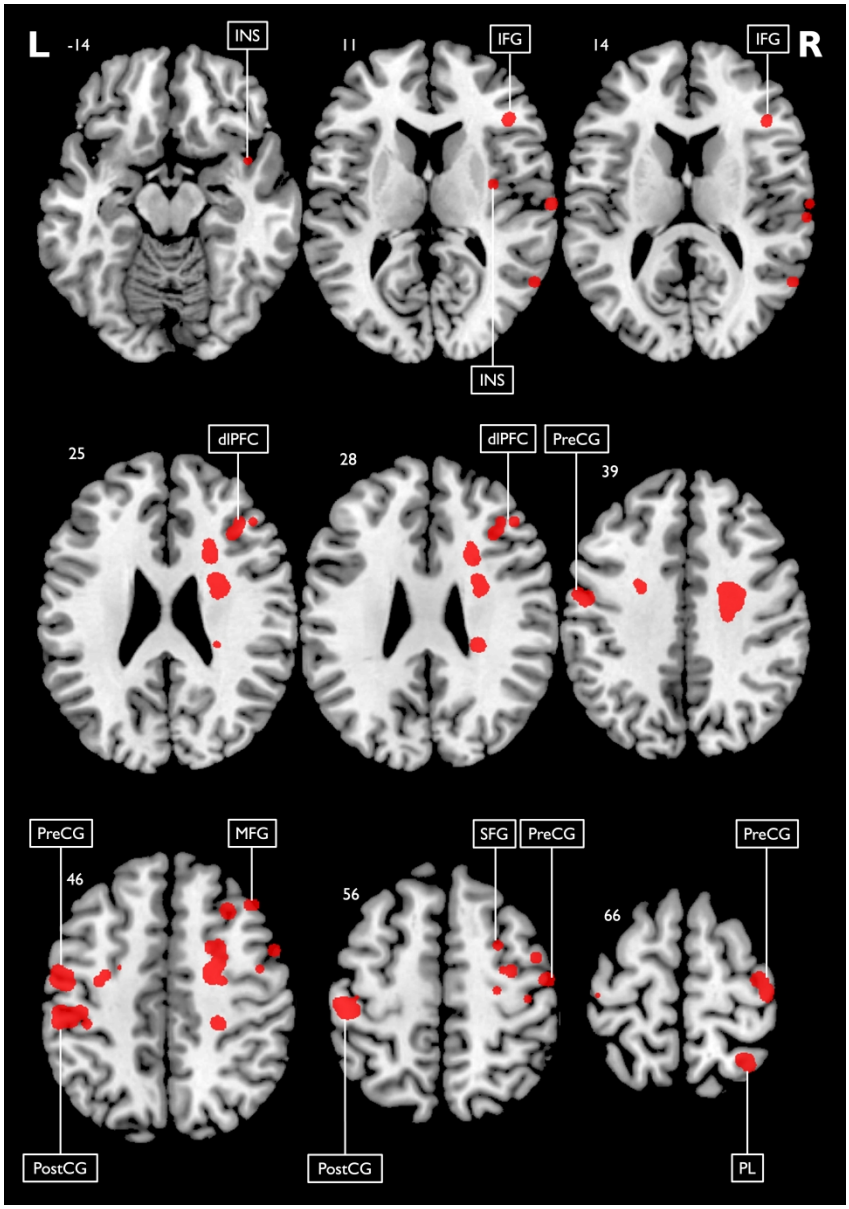


Figure 2

317x451mm (330 x 330 DPI)

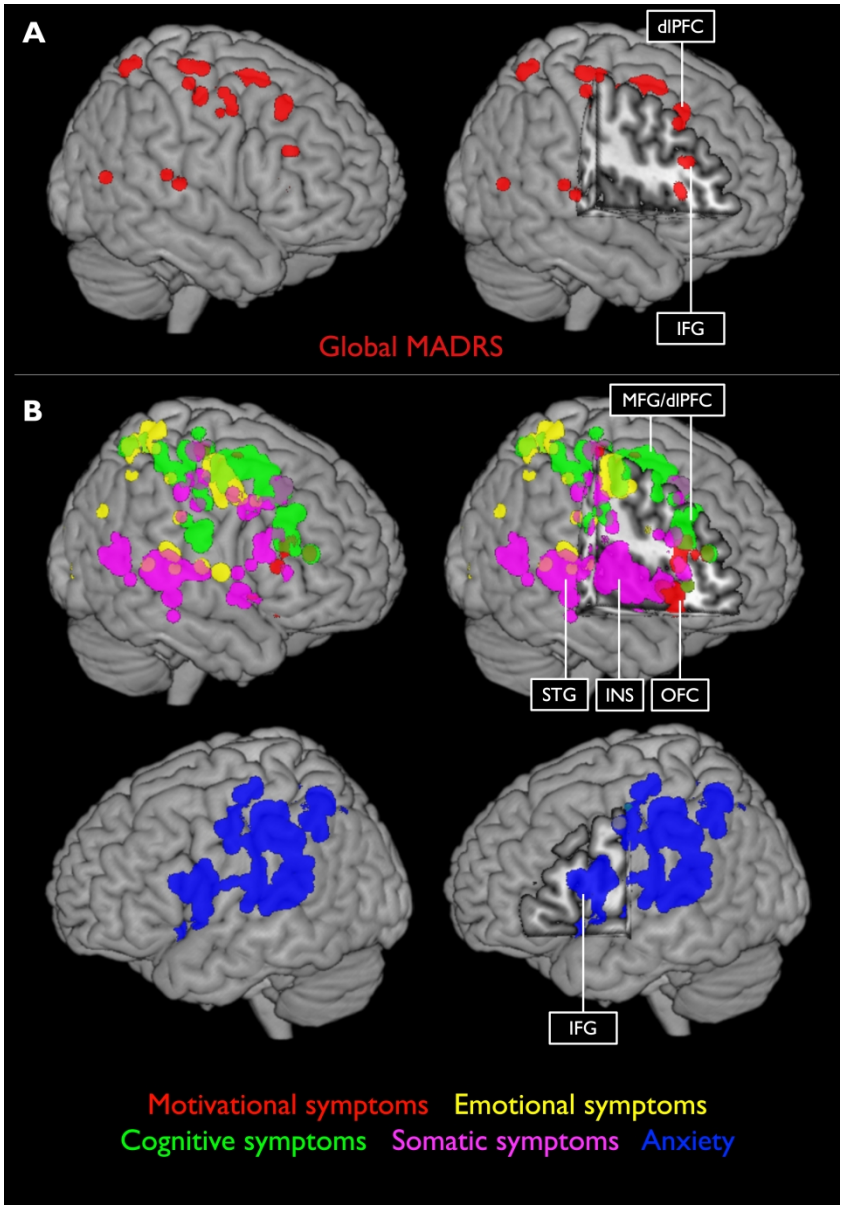


Figure 3

276x396mm (330 x 330 DPI)

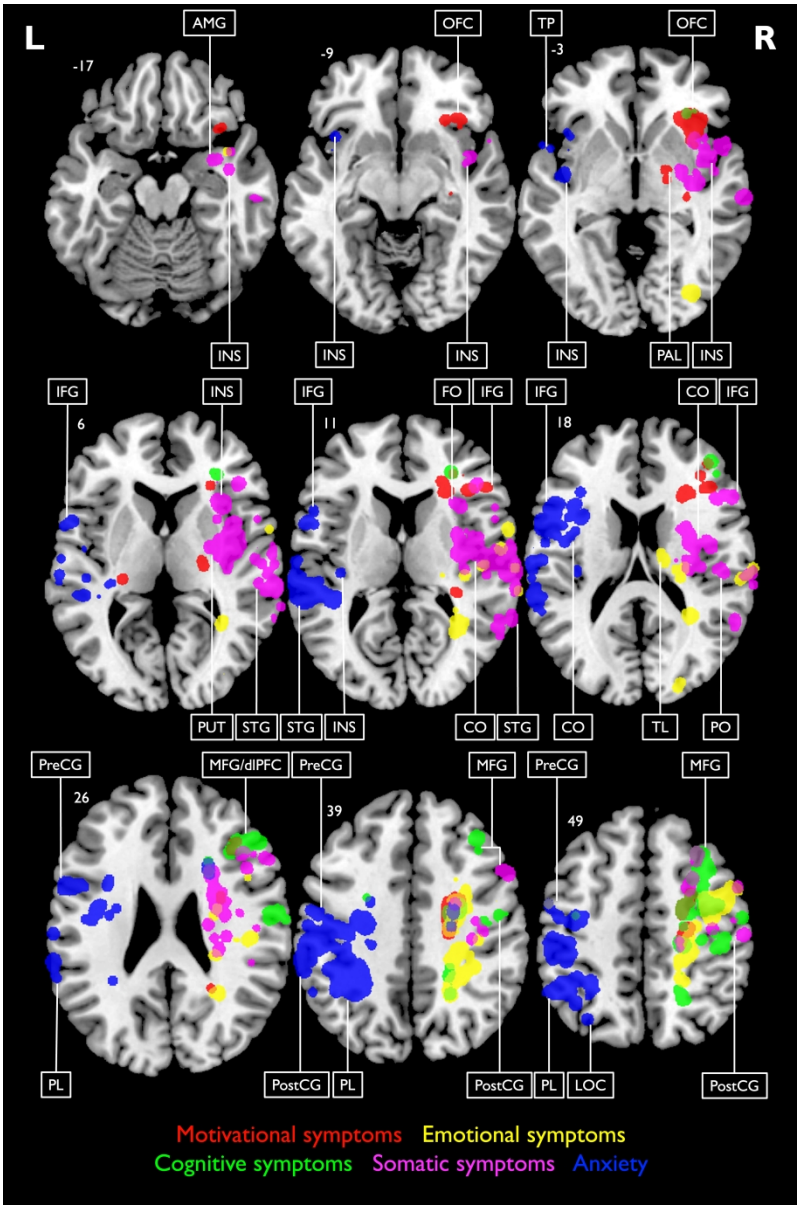


Figure 4

326x493mm (330 x 330 DPI)

Supplementary material

MRI protocols and scan parameters

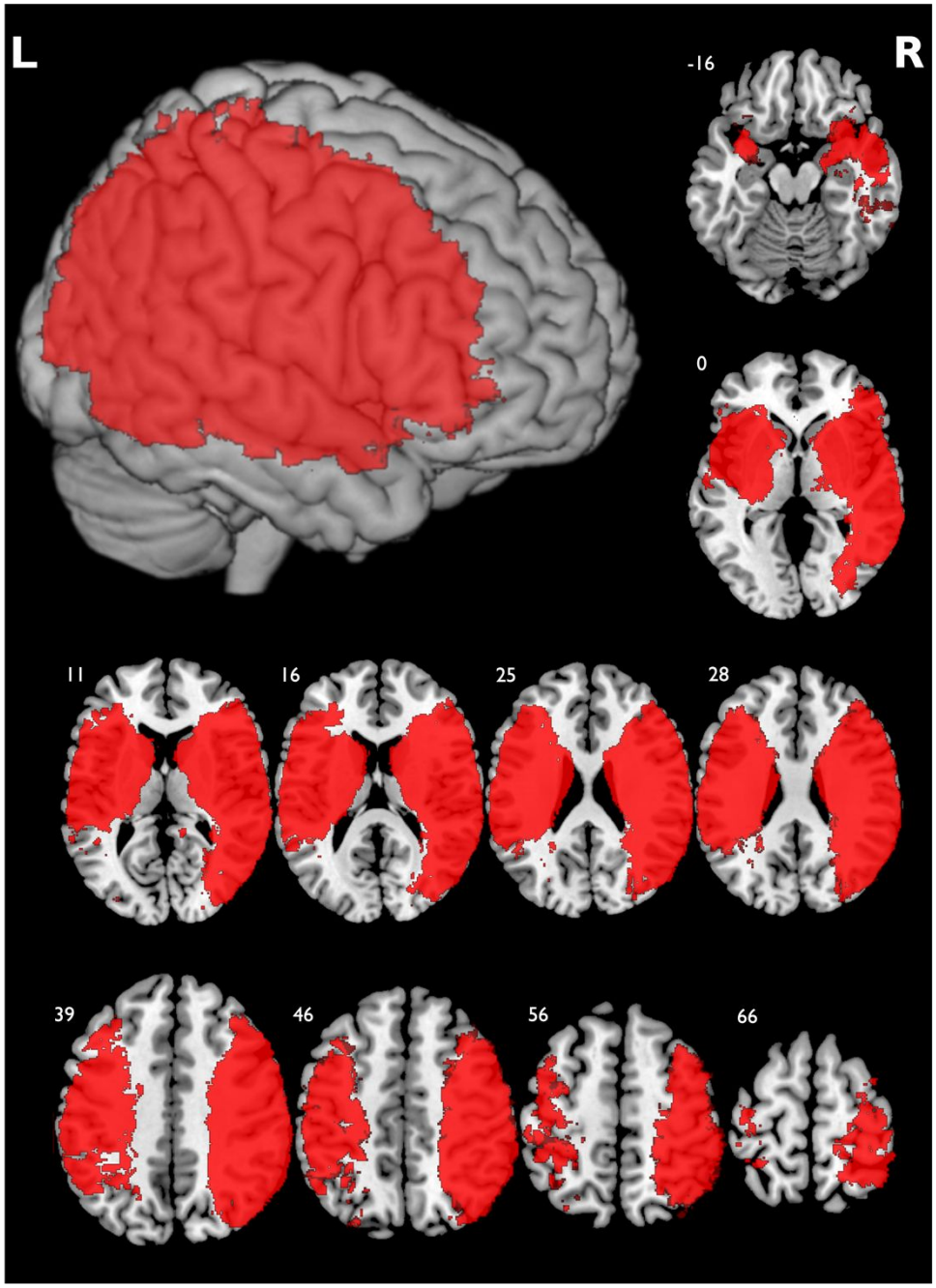
Stroke patients in the sample were scanned in the clinical routine over five years using three different MRI scanners. Following MRI protocols were used to assess diffusion-weighted imaging (DWI) and Fluid-attenuated inversion recovery (FLAIR) scans: First scanner Philips 1.5T: DWI: TR = 4126ms, TE = 95ms, voxel size 1.8mm (r-l) x 2.99mm (a-p) x 6mm, min. gap = 0.8mm, 22 to 24 axial slices. FLAIR: TR = 6000ms, TE = 100ms, voxel size 1.38mm (r-l) x 1.1mm (a-p) x 4mm, min gap = 0.8mm, 36 to 40 axial slices. Second scanner Philips 3T: DWI: TR = 3425ms, TE = 73ms, voxel size 1.5mm (r-l) x 2.19mm (a-p) x 5mm, min. gap = 0.5mm, min. 30 axial slices. FLAIR: TR = 8000ms, TE = 135ms, voxel size 1mm (r-l) x 0.65mm (a-p) x 4mm, min gap = 1mm, min. 33 axial slices. Third scanner Philips 1.5T: DWI: TR = 4421ms, TE = 110ms, voxel size 1.6mm (r-l) x 2.55mm (a-p) x 5mm, min. gap = 0.5mm, min. 28 axial slices. FLAIR: TR = 9000ms, TE = 120ms, voxel size 1mm (r-l) x 0.8mm (a-p) x 4mm, min gap = 0.5mm, min. 28 axial slices.

Lesion symptom mapping

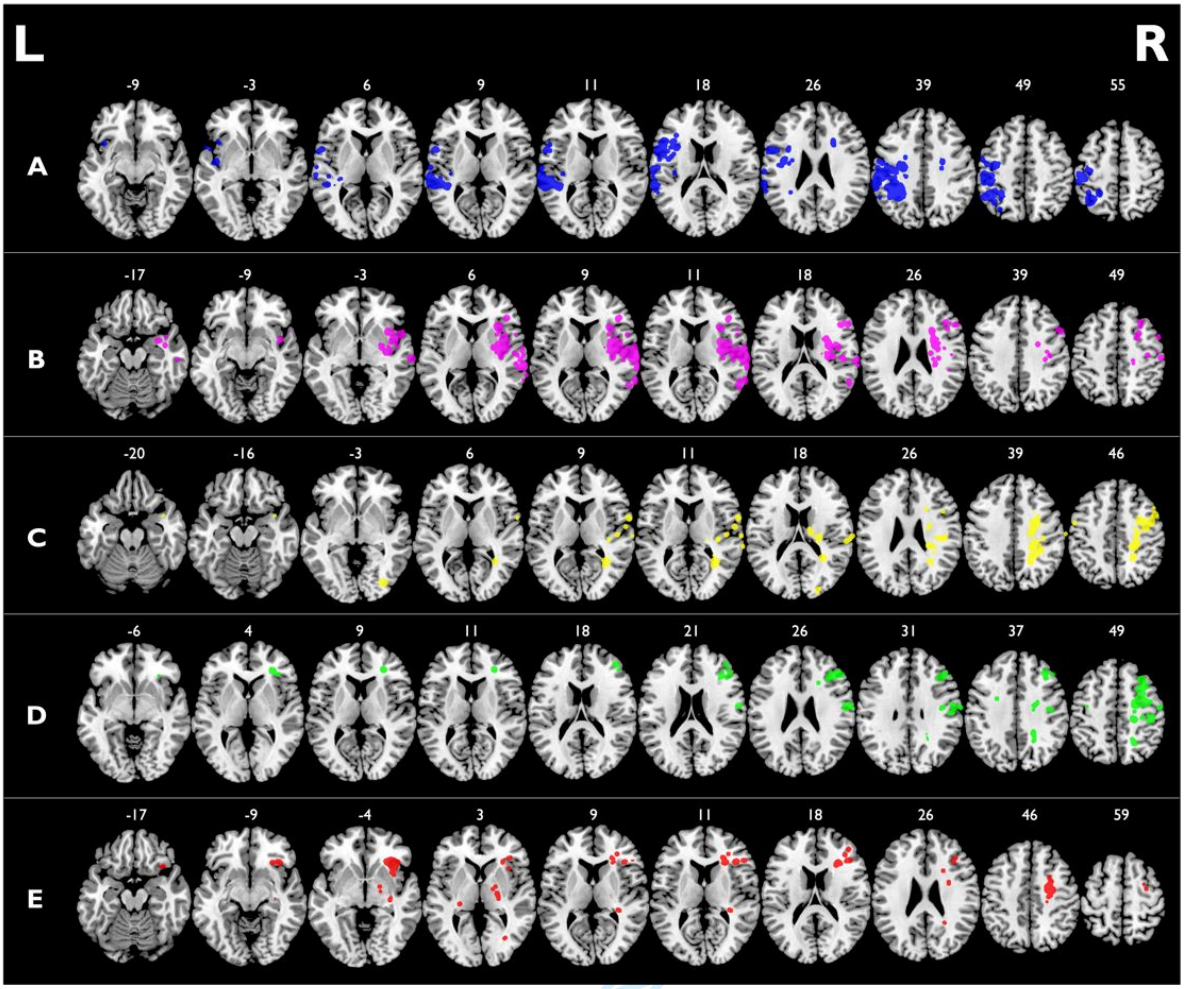
For our analyses, the MATLAB toolbox for the SVR-LSM[1], derived from the implementations for SVR-LSM by Zhang *et al*.[2], was used. It includes new features like a graphical user interface, parallel processing to speed up analyses, and a new way of removing lesion volume bias from both lesion and behavioral data. Furthermore, it uses the MATLAB Statistics and Machine Learning Toolbox implementation. We used the recommended default hyperparameters with a cost of 30, Sigma of 0.45, and Epsilon of 0.10.[2]

Five-fold cross-validation with ten replicates was used. The training was accomplished with 20% of the data left out for testing. During training, voxels were used as features, and the behavioral score was the training target. Each of the ten five-fold-cross-validation cycles resulted in SVR-LSM parametric β-maps. These were derived from the non-linear back projection from the infinite feature space to the original brain space to infer regional symptom-lesion relationships. The final β-map was derived from the average of the ten single β-maps generated during cross-validation. This map included raw β-values for each voxel, representing the strength of the relationship to the variable under examination before statistical testing. Of note, this multivariate approach of SVR-LSM has been extensively validated and has since then

been used in various studies.[3–7] After permutation testing, results were voxel-wise thresholded at $p < 0.005$, and resulting p-maps were smoothed using a 2mm Gaussian smoothing kernel. Lastly, lesions were projected on the ch2better template in MRIcron[8].



Supplementary Figure 1 Minimum lesion overlap map. Lesion overlap map of patients included in the SVR-LSM analyses displayed with the minimum lesion threshold of n ≥ 5 overlapping lesions. Coordinates indicate corresponding z-value in Montreal Neurological Institute (MNI) space. Please note, that small overlap into ventricles is due to co-registration for display in MRIcron. L, left; R, right.



Supplementary Figure 2 SVR-LSM results and lesion location associations of depressive symptom domains mapped individually. SVR-LSM results and lesion location associations of depressive symptom domains based on the conceptual-empirical classification with a voxel-wise threshold set to $p < 0.005$ ($n = 200$). Results were smoothed using a 2mm isotropic Gaussian smoothing filter. Coordinates indicate corresponding z-value in Montreal Neurological Institute (MNI) space. **(A)** Anxiety. **(B)** Somatic. **(C)** Emotional. **(D)** Cognitive. **(E)** Motivational. L, left; R, right.

PCA analysis

PCA with oblique rotation was used to analyze MADRS item scores by extracting five factors. The analysis results with factor loadings > 0.5 are presented in Supplementary Table 1. Except for suicidal thoughts (highest loading 0.44 on Factor 5), all items had significant factor loadings of >0.5, supporting the differentiation between the five factors. The goal of this additional data-driven approach was to receive five factors, which are clinically and item-wise concurring with the symptom domains derived in the conceptual-empirical approach. Thus, we expected to find a clinically related item structure in the five factors representing the depressive symptom domains of the conceptual-empirical approach. Both classification approaches showed an item-wise high correspondence. For example, the items 'reduced sleep' and 'reduced appetite' were attributed to 'somatic symptoms', and, accordingly, showed a high loading on Factor 2. Likewise, emotional symptoms of sadness were unambiguously classified together in Factor 3. When comparing conceptual-empirical and data-driven symptom domains, items representing the cognitive domain slightly differed between both approaches. In the data-driven approach, 'concentration deficits' represented a single Factor 4, whereas 'pessimistic thoughts' loaded high on Factor 5 together with 'lassitude'. Also, Factor 1 consisted predominantly of 'inner tension' and the item 'inability to feel', which was categorized as a motivational symptom in the conceptual-empirical rating approach. Notably, the items 'lassitude' and 'inability to feel', commonly considered motivational symptoms in the conceptual categorization, were related to different factors in the data-driven categorization. The item 'suicidal thoughts' was not well categorized by the PCA, failing to have significant factor loadings in any of the factors. This may be because patients indicated very few 'suicidal thoughts' in the interview (mean = 0.27) with relatively low variance (±0.788), as well as a high skewness (3.347) and kurtosis (11.160) compared to the other MADRS items. Thus, in this sample, the symptom could not be well represented in a factor.

In general, extracted factors in the PCA yielded factor loadings corresponding to the five depressive symptom domains formed in the conceptual-empirical classification approach. Likewise, the conceptual-empirical and data-driven classification approaches revealed strikingly similar lesion regions associated with the five specific depressive symptom domains, i.e., five factors (Supplementary Table 1, Supplementary Fig. 1). Please note that the aim of this paper was not primarily to compare two different classification methods. Instead, with the data-driven approach, we intended to support the results of our conceptual-empirical classification and wanted to show the robustness of a heterogeneous lesion-symptom association in PSD.

Items		Apparent sadness	Reported sadness	Innter Tension	Reduced Sleep	Reduced appetite	Concentration Deficits	Lassitude	Inability to feel	Pessimistic thoughts	Suicidal thoughts
Apparent sadness	R_{Sp} p (2-sided)	1									
Reported sadness	R_{Sp} p (2-sided)	0.438 <.001	1								
Inner tension	R_{Sp} p (2-sided)	0.297 <.001	0.308 <.001	1							
Reduced sleep	R_{Sp} p (2-sided)	0.002 0.978	0.182 0.01	0.216 0.002	1						
Reduced appetite	R_{Sp} p (2-sided)	0.19 0.007	.339 <.001	0.092 0.194	0.27 <.001	1					
Concentration deficits	R_{Sp} p (2-sided)	0.106 0.134	0.126 0.075	0.132 0.062	0.101 0.154	0.1 0.16	1				
Lassitude	R_{Sp} p (2-sided)	0.364 <.001	0.231 <.001	0.175 0.013	0.011 0.876	0.085 0.234	0.183 0.01	1			
Inability to feel	R_{Sp} p (2-sided)	0.2 0.004	0.206 0.003	0.328 <.001	0.079 0.263	0.029 0.684	0.246 <.001	0.326 <.001	1		
Pessimistic thoughts	R_{Sp} p (2-sided)	0.199 0.005	0.286 <.001	0.231 <.001	0.125 0.078	0.145 0.04	0.15 0.034	0.183 0.01	0.239 <.001	1	
Suicidal thoughts	R_{Sp} p (2-sided)	0.312 <.001	0.367 <.001	0.252 <.001	0.057 0.424	0.137 0.052	0.192 0.007	0.433 <.001	0.43 <.001	0.269 <.001	1

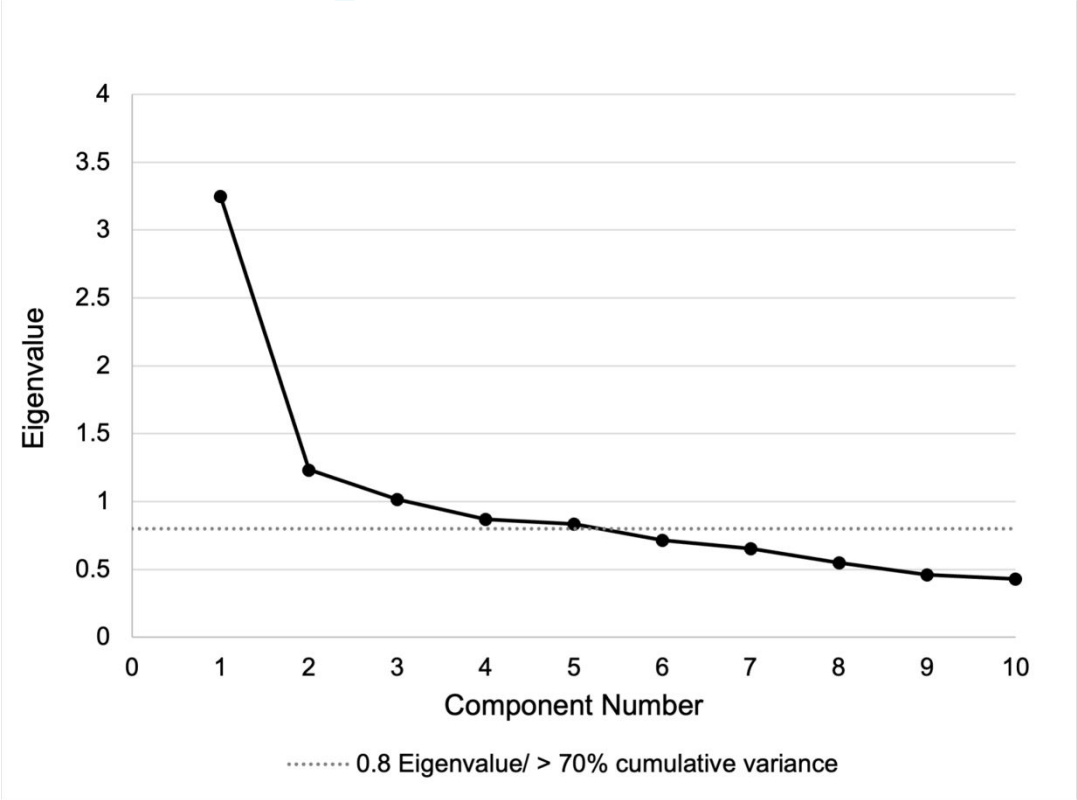
Supplementary Table 1 Inter-item correlations between the individual items of the MADRS interview

Items	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Apparent sadness			-0.809		
Reported sadness			-0.740		
Inner tension	0.820				
Reduced sleep		0.849			
Reduced appetite		0.517			
Concentration deficits				0.953	
Lassitude					0.562
Inability to feel	0.581				
Pessimistic thoughts					0.874
Eigenvalues	*3.248*	*1.233*	*1.014*	*0.867*	*0.835*
Cumulative variance (%)	*32.483*	*44.818*	*54.960*	*63.633*	*71.985*

Supplementary Table 2 MADRS factor analysis, including factor loadings >0.5 after oblique rotation.

Components	Eigenvalue	Explained variance (%)	Cumulative variance (%)
1	3.248	32.483	32.483
2	1.233	12.334	44.818
3	1.014	10.142	54.960
4	0.867	8.673	63.633
5	0.835	8.352	71.985
6	0.713	7.133	79.119
7	0.653	6.529	85.648
8	0.547	5.466	91.114
9	0.459	4.589	95.703
10	0.43	4.297	100,000

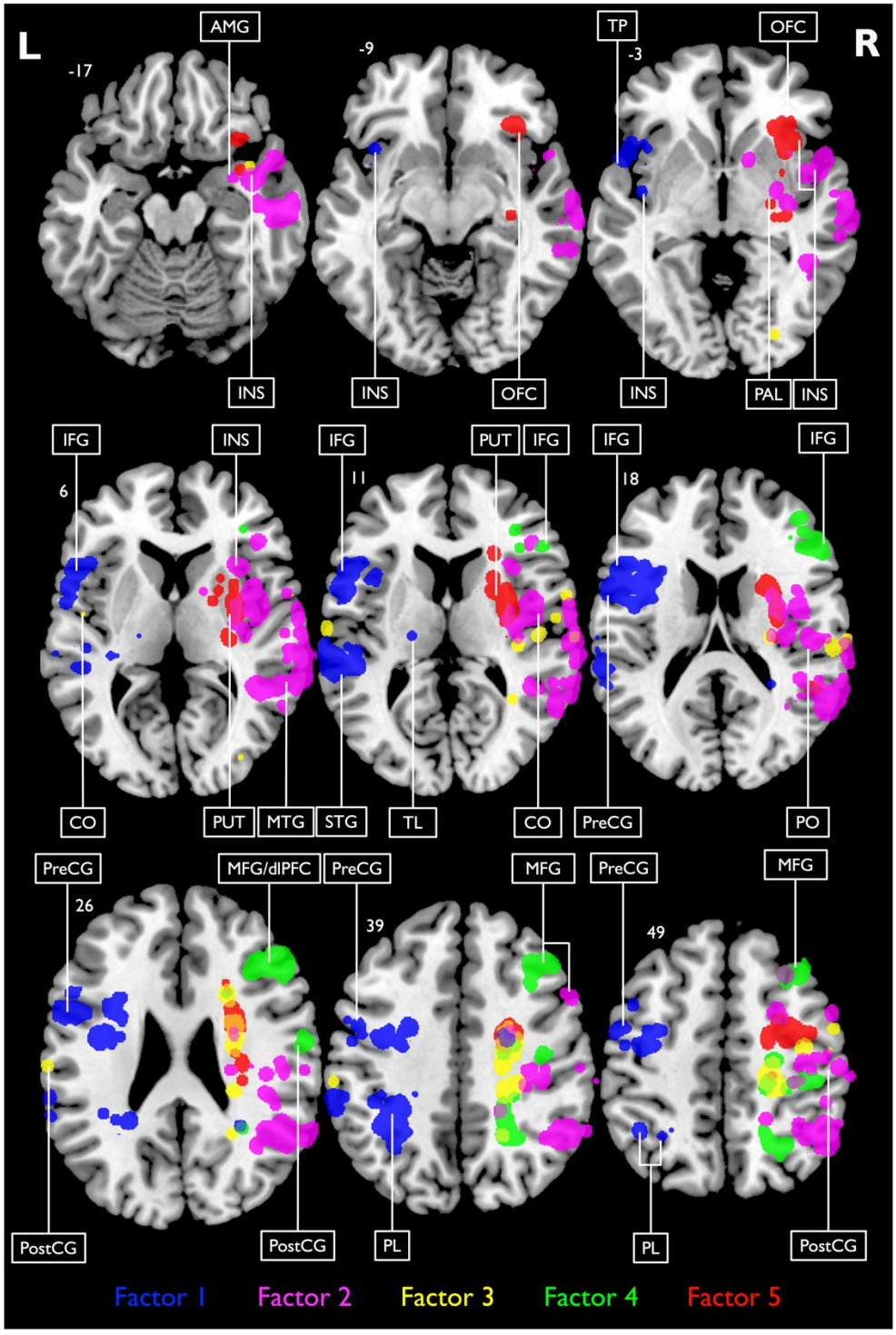
Supplementary Table 3 MADRS factor analysis, overview of total variance explained per component



Supplementary Figure 3 Scree plot of the PCA showing the derived factors with the corresponding Eigenvalues

Brain region	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
inferior frontal gyrus	L	R		R	
middle frontal gyrus	L	R		R (dlPFC)	R
superior frontal gyrus		R		R	R
insula	L	R	R (av)		R (a)
precentral gyrus	L	R	R	R	R
postcentral gyrus	L	R	L/R	R	
middle temporal gyrus		R			
superior temporal gyrus	L	R	R		
inferior parietal lobe	L	R	R		R
superior parietal lobe	L	R	R	R	
amygdala		R			
frontal operculum	L	R			
central operculum	L	R	L/R		
parietal operculum	L	R	R		
putamen		R			R
pallidum		R			R
temporal pole	L	R			
thalamus	L				
orbitofrontal cortex					R
lateral occipital cortex			R	R	
frontal pole				R	
pons	L				L

Supplementary Table 4 SVR-LSM results of data-driven categorization. L(eft) or R(ight) indicate the hemisphere with significant clusters of voxels ($p < 0.005$) in a given brain region. Classification of anatomical structures was performed using the Harvard-Oxford Cortical and Subcortical structural atlases. dlPFC, dorsolateral prefrontal cortex; av, anterior-ventral; a, anterior.



Supplementary Figure 4 SVR-LSM results of the data-driven approach. Voxel-wise threshold was set to $p < 0.005$ ($n = 200$). Results were smoothed using a 2mm Gaussian smoothing filter. Coordinates indicate corresponding z-value in Montreal Neurological Institute (MNI) space. Blue: Factor 1. Pink: Factor 2. Yellow: Factor 3. Green: Factor 4. Red: Factor 5. Please find the clinical interpretation of the five factors in the supplementary text. Classification of anatomical structures was performed using the Harvard-Oxford Cortical and Subcortical structural atlases. Predominant clusters are marked in white. AMG, amygdala; INS, insula; OFC, orbitofrontal cortex; TP, temporal pole; PAL, pallidum; PUT, putamen; IFG, inferior frontal gyrus; MTG, middle temporal gyrus; CO, central operculum; PO, parietal operculum; TL, thalamus; STG, superior temporal gyrus; PL, parietal lobe; PreCG, precentral gyrus; PostCG, postcentral gyrus; dlPFC, dorsolateral prefrontal cortex; MFG, middle frontal gyrus. L, left; R, right.

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5.2 To engage or not engage: Early incentive motivation prevents symptoms of chronic post-stroke depression–A longitudinal study.

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NeuroImage: Clinical, Volume 37, 2023
https://doi.org/10.1016/j.nicl.2023.103360

NeuroImage: Clinical 37 (2023) 103360

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

To engage or not engage: Early incentive motivation prevents symptoms of chronic post-stroke depression – A longitudinal study

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ARTICLE INFO

Keywords:
Reward
Motor impairment
Grip force
Prognosis
PSD
Corticostriatal network lesions

ABSTRACT

Background: Although post-stroke depression (PSD) is known to disrupt motor rehabilitation after stroke, PSD is often undertreated and its relationship with motor impairment remains poorly understood.
Methods: In a longitudinal study design we investigated, which factors at the early post-acute stage may increase the risk for PSD symptoms. We were especially interested in whether interindividual differences in the motivational drive to engage in physically demanding tasks indicate PSD development in patients suffering from motor impairments. Accordingly, we used a monetary incentive grip force task where participants were asked to hold their grip force for high and low rewards at stake to maximize their monetary outcome. Individual grip force was normalized according to the maximal force prior to the experiment. Experimental data, depression, and motor impairment were assessed from 20 stroke patients (12 male; 7.7 ± 6.78 days post-stroke) with mild-to-moderate hand motor impairment and 24 age-matched healthy participants (12 male).
Results: Both groups showed incentive motivation as indicated by stronger grip force for high versus low reward trials and the overall monetary outcome in the task. In stroke patients, severely impaired patients showed stronger incentive motivation, whereas early PSD symptoms were associated with reduced incentive motivation in the task. Larger lesions in corticostriatal tracts correlated with reduced incentive motivation. Importantly, chronic motivational deficits were preceded by initially reduced incentive motivation and larger corticostriatal lesions in the early stage post-stroke.
Conclusions: More severe motor impairment motivates reward-dependent motor engagement, whereas PSD and corticostriatal lesions potentially disturb incentive motivational behavior, thereby increasing the risk of chronic motivational PSD symptoms. Acute interventions should address motivational aspects of behavior to improve motor rehabilitation post-stroke.

1. Introduction

Stroke often leads to permanent disability, especially motor impairment (Virani et al., 2021). Patients suffering from stroke are also at risk of developing affective-depressive disorders, commonly described as post-stroke depression (PSD). To date, PSD often remains neglected, although it hinders rehabilitation and functional outcome (Medeiros et al., 2020; Robinson and Jorge, 2016). Depression includes heterogeneous symptoms such as emotional, cognitive, behavioral, and somatic disturbances, as well as motivational deficits or "apathy" (Hama et al., 2007a; Schmidt et al., 2008). Notably, stroke patients show a 3–4 times higher risk for depression compared to orthopedic patients or traumatic brain injury patients with comparable impairments or lesion volumes (Folstein et al., 1977; Robinson and Szetela, 1981). These findings suggest that PSD is a neurobiological consequence of the lesion rather than an adjustment to disability.

According to the monoamine hypothesis, depression may be caused by lesions of dopaminergic pathways in frontal and limbic structures constituting corticostriatal networks, which translate motivation into behavior (Loubinoux et al., 2012; Mayberg, 1997). Neuroimaging

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https://doi.org/10.1016/j.nicl.2023.103360
Received 5 January 2023; Received in revised form 22 February 2023; Accepted 24 February 2023
Available online 1 March 2023

studies showed consistent evidence that corticostriatal networks subserve reward-related motor behavior, and corresponding lesions correlated with motivational deficits that worsen motor rehabilitation (Hama et al., 2007b; Rochat et al., 2013; Schmidt et al., 2008). The translation of motivation into physical action can be studied in experiments where motor effort is modeled by the response to an expected reward, referred to as *incentive motivation* (Berridge, 2004). Previous fMRI studies with healthy participants reported reward-dependent increases of neural activity in the ventral striatum (VS) that predicted (pre-)motor activity and the amount of motor effort during subsequent motor execution (Pessiglione et al., 2007; Schmidt et al., 2012). In stroke patients, a recent fMRI study found reduced VS activation in processing monetary reward feedback after motor performance in a motor pointing task suggesting impaired skill learning (Widmer et al., 2019). Likewise, studies including unipolar depressed patients showed impaired reward-learning processes and reduced monetary outcome (Admon and Pizzagalli, 2015; Cléry-Melin et al., 2019), especially when task-dependent effort was required (Cléry-Melin et al., 2011; Treadway et al., 2012). It remains unclear how motor and PSD symptoms, especially motivational deficits or apathy, early after stroke impact on incentive motivation to engage into motor effort and how incentive motivation influences the prognosis of depression.

The goal of our study was to investigate incentive-driven motor effort in stroke patients early post-stroke to predict chronic symptoms of PSD within the first-year. We examined patients with unilateral hand motor impairment and healthy participants using a grip force task adapted from the 'classical' monetary incentive delay task (Knutson et al., 2000; Knutson et al., 2005). Our participants exerted motor effort (i.e., grip force) over an extended 15 seconds (s) period to earn a monetary incentive of either 1cent (low reward) or 1€ (high reward). Using this task, we assessed how motor impairment and PSD affect incentive motivational behavior, defined as (i) greater grip force during high reward relative to low reward trials ('reward effect') and (ii) higher monetary outcome. Symptoms of PSD were reassessed >3 months post-stroke during their usual peak (Hackett and Pickles, 2014).

We hypothesized that both groups show incentive motivation leading to greater grip force in high relative to low reward conditions (Widmer et al., 2019). It is further assumed that early PSD or lesions of ventral and dorsal corticostriatal networks correlate with reduced incentive behavior. Regarding stroke rehabilitation, our task allowed us to evaluate whether motor impairment decreases or increases incentive motivation and whether early-stage incentive behavior prevents development of PSD symptoms at the chronic stage.

2. Methods and materials

2.1. Participants

Twenty-two right-handed first-ever stroke patients were recruited from the Department of Neurology, University Hospital Cologne, Germany, in the early days post-stroke. Inclusion criteria were: (i) first-ever ischemic or hemorrhagic stroke, (ii) unilateral upper-limb motor deficit with a residual motor function of the affected hand to hold a grip force sensor with 10 kPa minimum grip force, (iii) right-handedness. Exclusion criteria were: (i) bilateral stroke lesions, (ii) cognitive impairment, neglect or aphasia according to neurological examination, (iii) insufficient visual acuity (as assessed by clinical-neurological assessment and verified by the ability to read and follow the instructions on printed screenshots of the experiment), (iv) severe comorbid neurological or psychiatric disorders including preexisting depression, (v) any other motor impairments affecting upper limb motor function (e.g., rheumatoid arthritis, missing limbs). Two stroke patients were excluded due to incorrect performance or inability to finish the task. This resulted in a final sample of n = 20 stroke patients who were assessed on average 7.7 days post-stroke (SD = 6.78). One stroke patient received antidepressant medication post-stroke onset of 20mg fluoxetine per day. Twenty-four healthy right-handed participants, matched in age and gender, were included as control group.

The experiment was performed at the Department of Neurology, Cologne. Stroke patients were examined at bedside during hospitalization. All participants gave informed written consent in accordance with the local ethics committee and the Declaration of Helsinki (revised in 2008). Participants received their task-related monetary outcome in Euro after task completion. Controls additionally received an expense allowance of 15€.

2.2. Apparatus

The experiment was designed using PsychToolbox (Brainard, 1997; Kleiner et al., 2007) implemented in MATLAB2019a (The MathWorks Inc., Natick, MA, USA) on Windows. Visual stimuli were presented on a 19″-monitor. Grip force signals were acquired with a strain-gauge based isometric dynamometer with a 0–800 Newton (N) range (MLT004/ST, AdInstruments Ltd, New Zealand). Grip force signals were sampled at 1000 Hz using PowerLab 26T data acquisition system and LabChart software (AdInstruments Ltd, New Zealand). Acquired signals were continuously transferred to a custom-written MATLAB interface that used the grip force signals to update the visual display in real-time.

2.3. Experimental design

The monetary incentive grip force task was designed following Pessiglione et al. (2007). Participants were seated in front of the screen in 1m distance, with both hands resting on their thighs and the grip force sensor in one hand. The grip force device was calibrated before the experiment to achieve a stable baseline. For calibration of the graphical representation, the maximum grip force was assessed by averaging the maximum force from three 3s intervals and used to represent 100% individual grip force. Calibration was done for the right and the left hand separately to control for differences in hand dominance or motor impairment. Each trial of the experiment was organized into an incentive phase, an effort phase, and a reward feedback phase (Fig. 1). Before the trial, participants were instructed to use either the left or right hand in alternating order between trials. During the incentive phase, subjects were informed about the money at stake by means of a picture showing either a one-cent or one-euro coin (3s). The picture resolution was 340x340 pixels with 8x8cm on the screen. The participants could earn the amount of money at stake using their grip force in the upcoming effort phase (15s). After a countdown of 3s, a thermometer bar appeared that turned green relative to the amount of grip force when pressing the device (Fig. 1). The thermometer level was updated in real-time based on the instantaneous grip force applied. In the reward feedback phase, the amount of money earned in each trial was presented in cents (3s). The monetary outcome was calculated based on the average grip force relative to the money at stake (1€ or 1ct) across the 15s effort phase. For example, a participant who squeezed on average 70% of his maximum grip force was rewarded with 70ct in a 1€-trial or 0.7ct in a 1-cent trial. A break was set after every five trials (30s). Prior to the experiment, participants were instructed to earn as much money as possible. The task consisted of a 2x2 factorial design with the factors HAND (levels: left, right) and REWARD (levels: low, high). The resulting four conditions were presented 10 times throughout the experiment, resulting in 40 identically structured trials. Using the right and left hand was required in an alternating order to control systematic hand fatigue effects. High and low reward trials were presented in a pseudo-random order with <4 equal reward trials in a row to prevent habituation.

2.4. Behavioral assessments

To assess motor deficits, we used the Jebsen-Taylor Hand-Function Test (JTT) (Jebsen et al., 1969), which evaluates the ability to perform hand movements of everyday life (e.g., picking up small items, lifting

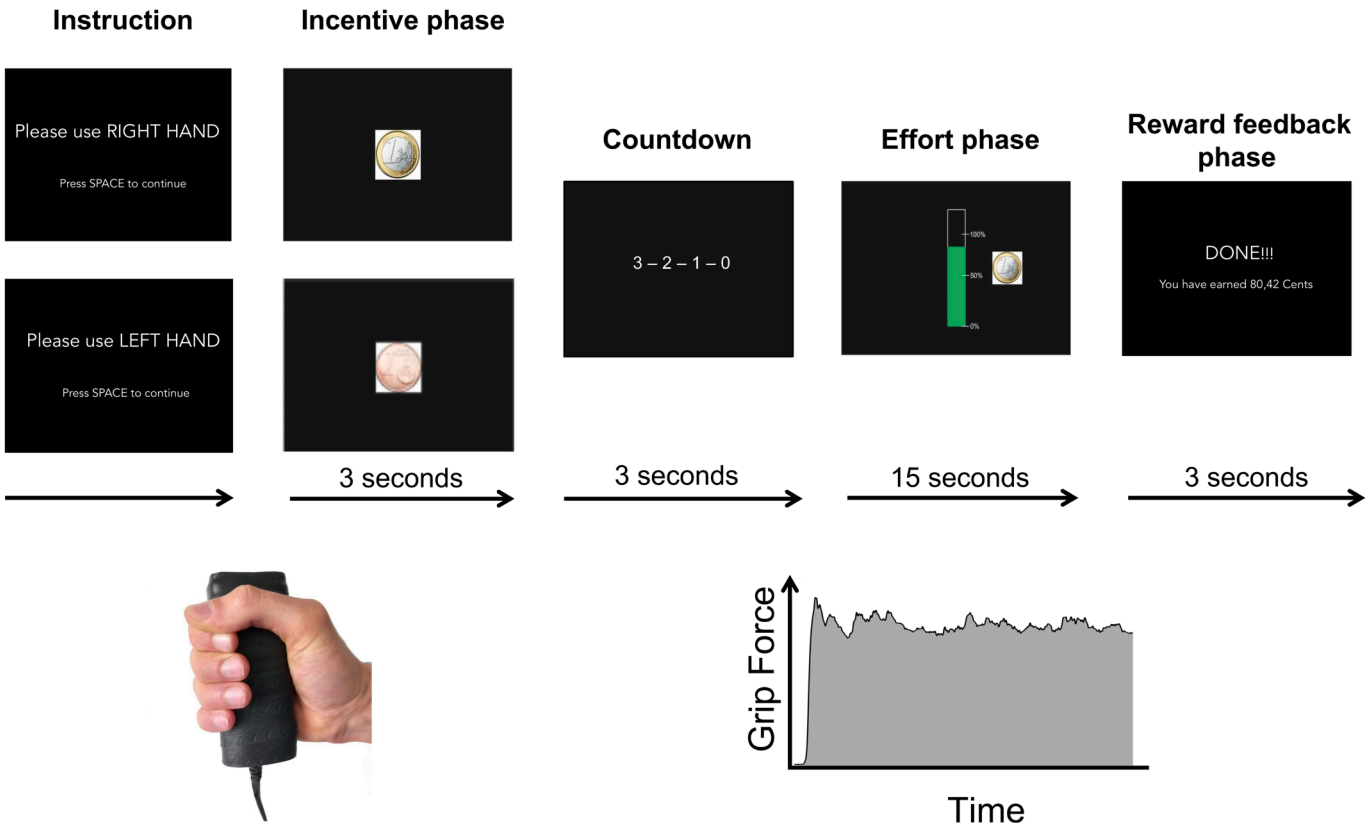

Fig. 1. Study design of the monetary incentive grip force task. Prior to the experiment, participants were instructed to earn as much money as possible by using their grip force. Instruction: Trials started with instruction of either using the left or right hand in alternating order. Incentive phase (3s): The money at stake was displayed (1€ or 1ct). Countdown (3s): A countdown led to the effort phase. Effort phase (15s): A thermometer bar appeared that turned green relative to the exerted amount of grip force in real-time. The money at stake was presented throughout the effort phase. Reward feedback phase (3s): The amount of money was calculated based on the average grip force during the effort phase relative to the money at stake (1€ or 1ct) and displayed on the screen. Bottom left: An exemplary picture of a hand squeezing the grip force dynamometer. Bottom right: An illustration of an exemplary grip force curve during a trial. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

cans) using reaction time (in s). We calculated an index score by using the time of the unaffected relative to the affected hand in percent to control for individual differences in motor speed. This means that a lower index (<100%) represents greater motor impairment. Additionally, the National Institutes of Health Stroke Scale (NIH-SS) (Brott et al., 1989), which is an observer rating to quantify neurological impairments in a global disability score, was obtained from the medical records. For quantifying depressive symptoms, we used the Montgomery-Åsberg Depression Rating Scale (MADRS) interview, which includes ten items to describe depression (Herrmann et al., 1998; Montgomery and Asberg, 1979). Importantly, each item must be answered based on several questions according to published guidelines (Williams and Kobak, 2008). As depression constitutes a heterogeneous syndrome and we were particularly interested in incentive motivational behavior, a *motivational* score was formed based on detailed interview questions for item 7 representing apathy, difficulties of getting started and perform daily activities and item 8 representing loss of interest and reduced ability to react with adequate emotion to circumstances. Previous studies showed that principal component analyses in elderly and stroke patients yielded a factor structure where these two items loaded on one factor named apathy/retardation/anhedonia (Farner et al., 2009; Parker et al., 2003). Furthermore, we tested the inter-rater reliability of items 7 and 8 included in a motivational score based on an independent rating of seven clinical psychologists, which resulted in substantial agreement (kappa = 0.625) (Landis and Koch, 1977).

2.4.1. Follow-up assessment

For follow-up assessment, patients were invited for a MADRS interview >3 months post-stroke (mean = 5.77 months, SD = 2.74). This time was referred to as the chronic stage when PSD symptoms peak (Hackett and Pickles, 2014). Data from n = 15 patients (75%) could be obtained. Reasons for dropouts were second strokes (10%), inability to perform the interview (5%), or disapproval (10%).

2.5. Grip force pre-processing

Grip force data were processed using MATLAB R2019a. Prior to the analysis, small negative grip force signals (in N) resulting from subtle oscillations were set to zero. Then, data were standardized using the maximum grip force per trial to yield relative values independent of the level of motor performance/impairment. No further filtering or smoothing was applied.

Data from patients with left-hemispheric stroke (45%) were flipped to assure that the affected hand corresponded to the left hand in all patients (Rehme et al., 2011a). Consequently, the same proportion of data was flipped in age- and gender-matched healthy controls. Thus, after flipping, the right hand did not correspond to the dominant hand in all participants and findings allow no conclusion on hand dominance effects. Please note that the left or right hand of the healthy participants is termed 'affected' or 'unaffected' compared to the respective hand of stroke patients.

We determined two parameters to depict incentive motivational behavior in the grip force task. First, the reward effect was calculated by subtracting the mean relative grip force in low from high reward trials to assess physical engagement for monetary incentives. Second, the monetary outcome was the accumulated win based on the overall motor

effort at the end of the experiment. There was no fixed upper limit of monetary gains. Whereas the reward effect depends on economical strategies to maximize monetary outcome by preserving the grip force for high versus low reward trials, the overall monetary outcome rather reflects the mere motivation for motor effort driven by monetary incentives.

Furthermore, we analyzed whether motor fatigue during the course of the experiment affects incentive motivational behavior. Therefore, we computed the difference in relative grip force between the first and second half of all trials.

2.6. Structural lesion analysis

For n = 14 patients (70%), anatomical MRI scans obtained during the clinical routine were available to map the stroke lesion based on diffusion-weighted imaging (DWI; TR = 4076ms, TE = 95ms, 22–24 axial slices, voxel size = 1.8x2.99x6mm^3) and fluid-attenuated inversion recovery images (FLAIR; TR = 6000ms, TE = 100ms, 36–40 axial slices, voxel size = 1.38x1.1x4mm^3). Lesion maps were manually drawn onto DWI images showing the extent of the ischemic lesion. These images were spatially co-registered to Montreal Neurological Institute (MNI) standard space, resampled to 1x1x1mm voxel size, and normalized using unified segmentation with masked lesions (Ashburner and Friston, 2005) in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) as implemented in MATLAB 2019a. Finally, lesion maps were binarized for further analyses using FMRIB Software Library (FSL, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). To test neuroanatomical correlates of depression, we generated binary maps of the online published diffusion tensor imaging (DTI) atlas based on data from 1065 healthy participants depicting the course of the ventral and dorsal corticostriatal tracts (Yeh et al., 2018). The binary atlas map was co-registered with the lesion maps. As the raw atlas tract showed small disruptions after normalization which was inappropriate for lesion-symptom mapping, the tract was smoothed using a 6mm Gaussian smoothing kernel in SPM12 (Fig. 4A). Percent overlaps between individual lesion maps and the corticostriatal atlas map were computed using SPM12 and FSL.

Twelve out of 15 patients (85%) examined in the follow-up assessment had anatomical MRI scans from the acute stage available for PSD prognosis.

2.7. Statistical analysis

Generally, group differences in age, JTT-index, and monetary outcome were analyzed using one-way ANOVA in SPSS version 26 (IBM Corp, Armonk, NY, USA). In case of ordinal scaled variables such as MADRS score and motivational score, Mann-Whitney U-rank tests were used. Significant effect sizes were determined by partial eta-squared (η_p^2) as provided by SPSS. For the experimental task, relative mean grip force and fatigue effects were analyzed using repeated-measures ANOVA and Bonferroni-corrected post-hoc t-tests with the within-subject factors HAND (affected vs. unaffected hand) and REWARD (high vs. low reward) and the between-subject factor GROUP including stroke patients and controls.

Correlations between two interval-scaled variables including JTT-index, reward effect, monetary outcome, and relative lesion volume were analyzed using Pearson correlations (R_P). For ordinal-scaled parameters including global MADRS and motivational score, Spearman correlations (R_{Sp}) were computed. All correlation analyses were two-sided ($p < 0.05$), except for correlations between incentive motivation and depression parameters based on previous evidence (Admon and Pizzagalli, 2015; Cléry-Melin et al., 2019; Cléry-Melin et al., 2011; Rochat et al., 2013; Schmidt et al., 2008; Treadway et al., 2012) (one-sided $p < 0.05$). We computed the following sets of correlation analyses with false-discovery-rate (FDR) correction applied for multiple testing (Benjamini and Hochberg, 1995). First, within the group of stroke patients, correlation analyses were computed between the incentive motivation parameters (i.e., reward effect, monetary outcome) and JTT-index, NIH-SS, global MADRS and motivational score. Second, for PSD prognosis at the chronic stage, correlations between initial behavioral scores including global MADRS, motivational score, and the reward effect and the follow-up assessment of global MADRS and motivational score were computed. For lesion-symptom analyses, we correlated the percent of lesion overlap in the ventral and dorsal corticostriatal tracts with the global MADRS or motivational score at initial and follow-up assessment as well as with the reward effect. Lastly, to investigate whether multiple predictors explain a higher amount of variance in post-stroke motivational deficits in the chronic stage, we computed stepwise linear regression models. MADRS motivational score at chronic stage was included as dependent variable and reward effect and lesion overlap in ventral and dorsal corticostriatal tracts as three different predictor variables.

3. Results

3.1. Demographics and group characteristics

Stroke patients (n = 20) were on average 71.55 (SD = 10.71) years old and control subjects (n = 24) were 66.96 (SD = 7.84) years old. This difference did not reach statistical significance ($F_{1,42} = 2.688$, $p = 0.109$). Furthermore, groups did not differ in the proportion of sex ($\chi_1^2 = 0.440$, $p = 0.507$). 12 female participants were included in the control group, 8 females in the patient group, as well as 12 male participants in both the control and patient group. Regarding the MADRS score and the motivational score, stroke patients showed on average more depressive symptoms (M = 11.20, SD = 6.83) than controls (M = 2.50, SD = 2.27; U = 36.500, $p < 0.001$, $\eta_p^2 = 0.527$), as well as stroke patients came with higher motivational deficits (M = 2.15, SD = 1.84) than controls (M = 0.33, SD = 0.56; U = 85.500, $p < 0.001$, $\eta_p^2 = 0.349$). Similarly, groups significantly differed in their motor impairment score (JTT index; stroke patients: M = 37.35, SD = 30.01, controls: M = 98.04, SD = 10.41; $F_{1,42} = 86.074$, $p < 0.001$, $\eta_p^2 = 0.672$). Stroke patients were assessed on average 7.7 days after stroke onset (SD = 6.78), with nine patients had left-hemispheric lesions (11 patients right-hemispheric), and 18 patients suffered from ischemic strokes (two patients had hemorrhagic strokes). One stroke patient received antidepressant medication post-stroke onset of 20mg fluoxetine per day. See Table 1 for all demographics and group characteristics.

3.2. Monetary incentive grip force task

The repeated-measures ANOVA yielded a significant interaction between HAND and GROUP ($F_{1,42} = 30.030$, $p < 0.001$, $\eta_p^2 = 0.417$) (Fig. 2A). Overall, stroke patients showed lower relative grip force as compared to controls. Likewise, there was a significant main effect of GROUP ($F_{1,42} = 31.519$, $p < 0.001$, $\eta_p^2 = 0.429$) and HAND ($F_{1,42} = 37.783$, $p < 0.001$, $\eta_p^2 = 0.474$). There was a main effect of REWARD, that is, all participants showed greater grip force for high compared to low reward trials ($F_{1,42} = 17.332$, $p < 0.001$, $\eta_p^2 = 0.292$) (Fig. 2B). However, there was neither an interaction between GROUP and REWARD ($F_{1,42} = 0.155$, $p = 0.696$), nor a difference between groups in their monetary outcome ($F_{1,42} = 2.238$, $p = 0.142$), so the magnitude of incentive motivation parameters was not statistically different between groups. Importantly, there was no significant correlation between the reward effect and the monetary outcome, neither in the overall sample ($R_P = -0.010$, $p = 0.947$), nor in the subgroup of stroke patients ($R_P = -0.316$, $p = 0.175$), reflecting two different aspects of incentive motivation.

The repeated-measures ANOVA of experimental fatigue yielded a significant main effect of HAND ($F_{1,42} = 7.102$, $p = 0.011$, $\eta_p^2 = 0.145$). That is, the affected hand showed stronger muscular fatigue over the course of the experiment. Furthermore, there was no statistically significant interaction between HAND and GROUP ($F_{1,42} = 2.931$, p =

Table 1
Overview of the demographic and clinical characteristics of the sample.

	Stroke patients n = 20 mean (SD)	Controls n = 24 mean (SD)	Statistical test
Demographics			
Sex (f:m)	8:12	12:12	χ^2_1=0.440, p=0.507
Mean age (years) (±SD)	71.55 (10.71)	66.96 (7.84)	$F_{1,42}$=2.688, p=0.109
Days post-stroke (±SD)	7.7 (6.78)		
Lesion side (left:right)	9:11		
Stroke (ischemic:hemorrhagic)	18:2		
Motor impairment			
JTT-index (%) (±SD)	37.35 (30.01)	98.04 (10.41)	$F_{1,42}$=86.074, p<0.001**, η^2_p=0.672
Global impairment			
NIH-SS	8.48 (4.63)		
Depressive symptoms			
MADRS global score $_{early}$ (±SD)	11.20 (6.83)	2.50 (2.27)	U=36.500, p<0.001**, η^2_p= 0.527
Motivational score $_{early}$ (±SD)	2.15 (1.84)	0.33 (0.56)	U=85.500, p<0.001**, η^2_p=0.349
MADRS global score $_{follow\text{-}up}$ (±SD)	7.93 (5.86)		
Motivational score $_{follow\text{-}up}$ (±SD)	2.86 (2.83)		

JTT: Jebsen-Taylor Hand Function Test, NIH-SS: National Institutes of Health Stroke Scale, MADRS: Montgomery-Åsberg Depression Rating Scale, χ^2: chi square, η^2_p: Partial eta-squared effect size, U: Mann-Whitney U. One patient received antidepressive medication of 20mg fluoxetine/day. MADRS scores in the early stage post-stroke were: no depression (n = 7), mild depression (n = 11), moderate depression (n = 2). MADRS scores in the chronic stage were: no depression (n = 10), mild depression (n = 4), moderate depression (n = 1) (Herrmann et al., 1998).

0.094), nor a significant main effect of REWARD ($F_{1,42}$ = 2.900, p = 0.096), yet significance trends could be noticed. Importantly, there was neither an interaction effect between REWARD and GROUP ($_{F1,42}$ = 0.386, p = 0.538), nor a main effect of GROUP ($F_{1,42}$ = 0.260, p = 0.613). The experimental variables of the monetary incentive grip force task are summarized in Supplementary Table S1.

3.3. Stroke subgroup analysis

The correlation analysis in the group of stroke patients showed that the reward effect correlated negatively with the JTT-index (R_P = -0.630, p = 0.024, FDR-corrected) (Fig. 3A). This means that patients with more severe hand motor impairment exhibit greater incentive motivation as assessed by stronger grip force at high versus low reward trials. Likewise, the NIH-SS correlated positively with the reward effect (R_{Sp} = 0.592, p = 0.024, FDR-corrected), which indicates that more severe global impairment is associated with greater incentive motivation.

The global MADRS correlated negatively with the overall monetary outcome (R_{Sp} = -0.490, p = 0.037, FDR-corrected) (Fig. 3B). That is, more depressed stroke patients earned less money in the experiment based on their overall motor performance than less depressed patients. Likewise, there was a non-significant trend between the global MADRS score and the reward effect (R_{Sp} = 0.372, p = 0.084, FDR-corrected). Interestingly, the MADRS score did not correlate with the JTT-index (R_{Sp} = -0.343, p = 0.158, FDR-corrected), thus, in our sample of stroke patients with residual hand motor function, depressive symptoms were not associated with motor impairment early post-stroke. Yet there was a non-significant trend for a correlation between MADRS and NIH-SS indicating greater depression among more severely impaired patients (R_{Sp} = 0.435, p = 0.073, FDR-corrected).

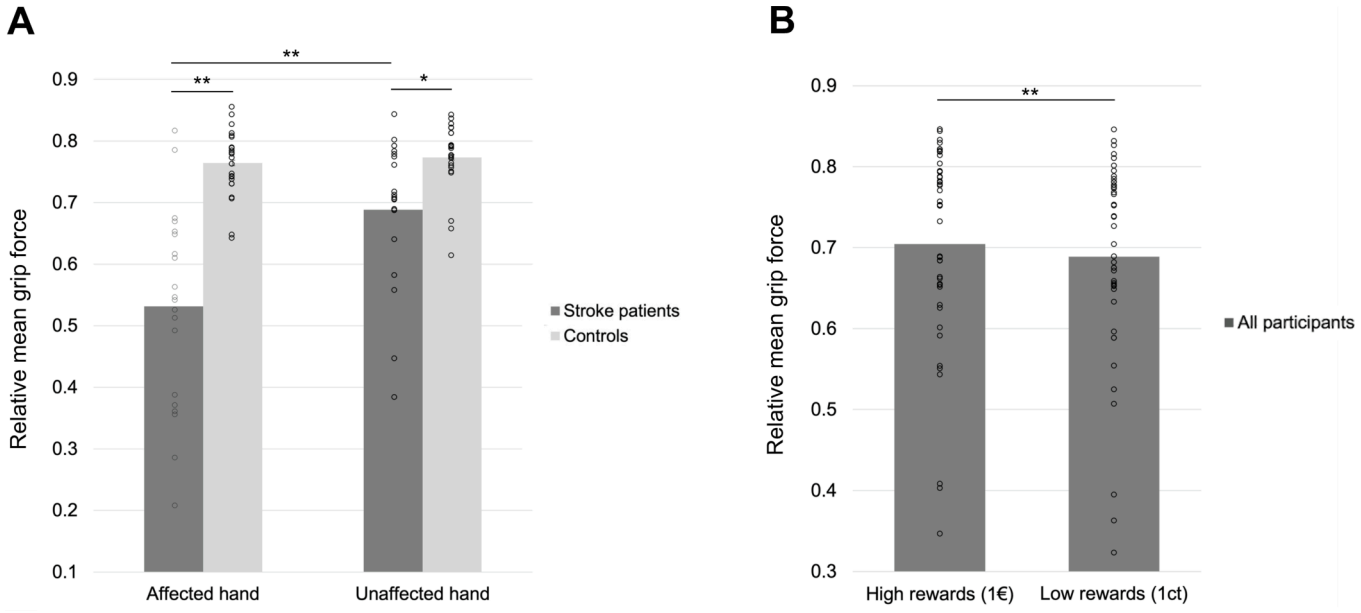

Fig. 2. Monetary incentive grip force task. A: Relative mean grip force of stroke patients and controls in the monetary incentive grip force task per hand. B: Relative mean grip force of all participants in the high compared to low reward condition. (**= p < 0.01, *= p < 0.05).

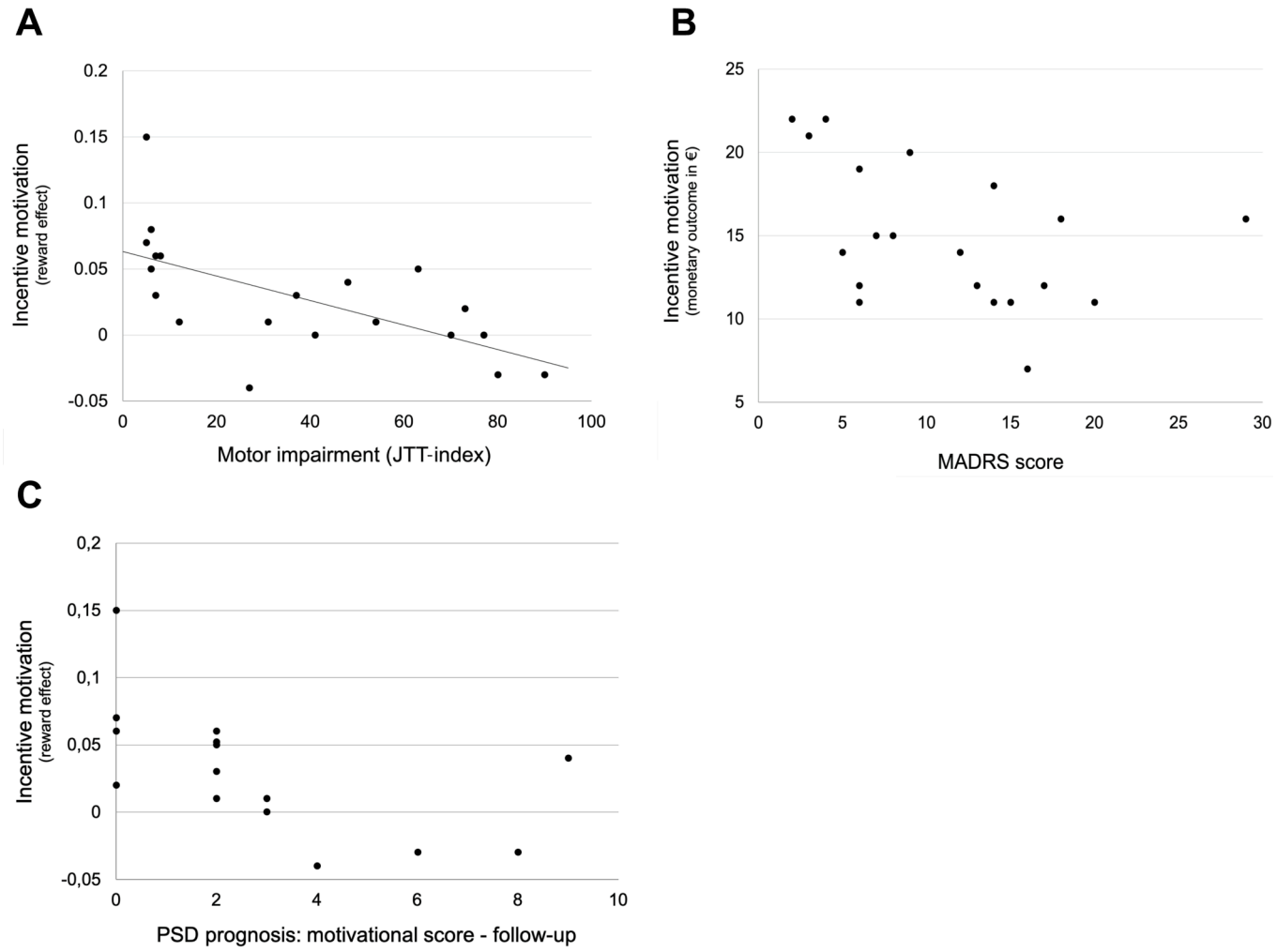

Fig. 3. Relationships with incentive motivational behavior. A: Negative correlation between the reward effect in the monetary incentive grip force task and the motor impairment (JTT-index) in stroke patients (n = 20; R_P = -0.630, p = 0.024). Lower JTT-index scores indicate higher motor impairment. More severely impaired stroke patients showed a higher reward effect. B: Negative correlation between the monetary outcome in the task and the global MADRS score in stroke patients (n = 20; R_{Sp} = -0.490, p = 0.037). More depressed stroke patients earned less money in the task. C: Prognosis of PSD. Negative correlation between the reward effect in the monetary incentive grip force task and the motivational score at follow-up (n = 15; R_{Sp} = -0.718, p = 0.015). Stroke patients who showed higher reward effects in the monetary grip force task were less prone to motivational deficits at the chronic stage.

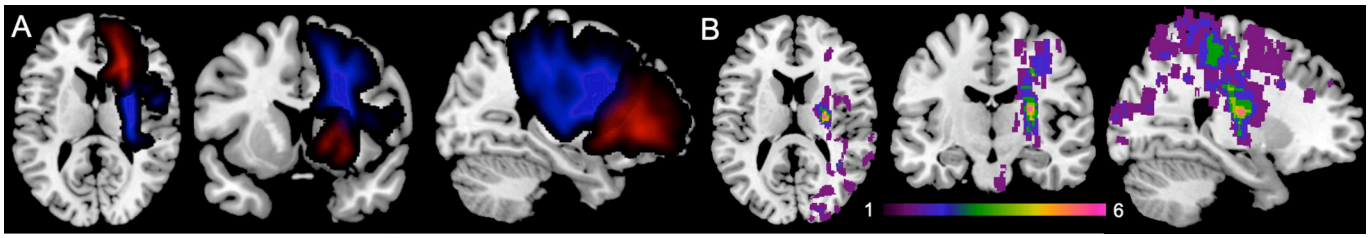

Fig. 4. Structural lesion analysis. A: Anatomical DTI tract template of the corticostriatal tracts (Yeh et al., 2018) with a 6mm Gaussian smoothing. Red: ventral corticostriatal tract. Blue: dorsal corticostriatal tract. B: Lesion overlap map. The highest overlap was at the level of the internal capsule. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3.1. *PSD prognosis*

In stroke patients, there was a negative correlation between the experimental reward effect and the motivational score at follow-up (R_{Sp} = -0.718, p = 0.015, FDR-corrected) (Fig. 3C). That is, patients with initially higher incentive motivation showed less motivational deficits at the chronic stage. There were no correlations between initial and follow-up global MADRS scores (R_{Sp} = -0.369, p = 0.352, FDR-corrected), motivational scores (R_{Sp} = 0.009, p = 0.974, FDR-corrected), and between the reward effect and the follow-up MADRS (R_{Sp} = -0.069, p = 1.000, FDR-corrected).

3.3.2. *Structural lesion analysis*

The anatomical DTI template of the dorsal and ventral corticostriatal tracts (Yeh et al., 2018) are shown in Fig. 4A. Stroke patients had the highest lesion overlap at the level of the internal capsule (30%) (Fig. 4B). The percent of the lesion in the ventral corticostriatal tract correlated

negatively with the reward effect (R_P = -0.711, p = 0.012, FDR-corrected). This indicates that patients with more extended lesions of the ventral corticostriatal tract were less likely to be motivated by reward to engage in physical activity. Furthermore, the follow-up motivational score correlated positively with lesions in the dorsal tract (R_{Sp} = 0.684, p = 0.042, FDR-corrected), which suggests that patients with more extended lesions of the dorsal tract were more likely to develop motivational deficits at the chronic stage. There were no correlations between initial MADRS or motivational score and corticostriatal lesions (p > 0.207).

To test whether multiple predictors improve the prognosis of motivational deficits in the chronic stage, we additionally performed stepwise regression models. Overall, reward effect, lesion overlap of dorsal and ventral corticostriatal tract did not explain more variance in stepwise executed regressions than the reward effect and the dorsal corticostriatal tract alone (coefficients of correlation in regression models ranged from R = 0.484 to R = 0.516).

4. Discussion

Incentive motivation early after stroke is influenced by different factors, including the degree of motor impairment, damage in corticostriatal networks, and PSD. Importantly, incentive motivation was increased in patients with more severe motor impairments and decreased in patients with greater PSD symptoms. In our sample, early incentive motivation served as one prognostic factor of reduced risk for motivational deficits or apathy at the chronic stage, whereas patients with lesions of dorsal and ventral corticostriatal tracts showed reduced incentive motivation and a higher risk for motivational deficits at the chronic stage. This is one of the first longitudinal studies showing that behavioral parameters of incentive motivation preceded motivational deficits at the chronic stage post-stroke. An overview of the main study results is provided as Supplementary Fig. S2.

4.1. Monetary incentive motivation and motor impairment

Both groups showed similar incentive motivational behavior in the task. Another study investigating reward-modulated motor performance post-stroke reported similar findings (Widmer et al., 2019). Interestingly, we found that stroke patients with greater motor impairment maximized their monetary outcome by preserving their grip force for high versus low reward trials. Importantly, as the relative grip force is higher despite limited resources, this economical behavior may reflect a general psychological phenomenon of the underlying motivational state of the patients rather than an effect of the lesion and concomitant motor impairment. This motivational state might represent an adaptive coping strategy considering that task difficulty of holding one's grip force is increased given restricted physical abilities (Raghavan, 2015).

Importantly, post-stroke fatigue is a prevalent condition in the acute and chronic stages after stroke and can negatively affect rehabilitation outcome (De Groot et al., 2003; Nadarajah and Goh, 2015). Generally, it can be differentiated between motor fatigue, which indicates a muscular exhaustion after physical effort, and chronic fatigue as a strong feeling of tiredness and lethargy or apathy, which typically does not improve with rest and represents motivational fatigue (de Doncker et al., 2018; De Groot et al., 2003; Tseng et al., 2010). In our sample, muscular fatigue was stronger for the affected hand, probably because recruitment of motor units was reduced due to the ischemic lesion to motor tracts. Notably, as there were no interactions and effects of the reward conditions on experimental fatigue, we assume that incentive motivation was not driven by fatigue.

4.2. Monetary incentive motivation and PSD

Early symptoms of PSD showed a correlational trend for a reduced reward effect in the monetary grip force task. Nevertheless, considering the monetary outcome, patients with greater depression earned significantly less money in the task. Of note, the potential monetary gain had no upper limit to motivate subjects with normal reward processing to try to further increase their grip force. Hence, our finding of less monetary outcome in more depressed patients suggests that they were less motivated to generally engage in reward-related physical effort, independent of the money at stake. This is in line with previous studies including unipolar depressed or apathetic stroke patients (Cléry-Melin et al., 2011; Rochat et al., 2013; Schmidt et al., 2008). Nevertheless, this is the first study showing that depressive symptoms correlate with incentive motivational behavior early after stroke.

4.2.1. Prognosis of PSD

Various clinical studies reported a higher risk for PSD at chronic stages 3–12 months post-stroke (Medeiros et al., 2020; Robinson and Jorge, 2016). A novel finding of our study is that the reward effect as a measure of incentive motivation had predictive power for later motivational PSD symptoms or apathy. Here, increased motivation to engage in incentive-driven motor activity may potentially prevent later motivational deficits. Interestingly, other studies found an antidepressant effect of motor activity in patients (Cuijpers et al., 2007; Loubinoux et al., 2012; Yuan et al., 2015). According to the reinforcement model (Lewinsohn, 1974), depression results from a lack of positive reinforcement based on reduced behavioral activity, which in turn may increase the experience of 'learned helplessness', which is also triggered by stroke (Seligman, 1972). Thus, in terms of a vulnerability-stress model, the stroke lesion may induce a vulnerability that can lead, driven by psychological factors including loss of positive reinforcement and learned helplessness, into PSD. Due to the relatively small sample size, results must be considered as preliminary, and effects may be underpowered. However, given the difficulty to assess early-stage stroke patients with a high risk of later drop-outs, the results reveal important aspects of the symptomatology of PSD. Please also note that control subjects did not receive a follow-up assessment in our study and thus, due to a lack of comparability, our findings of incentive motivation as a prognostic factor for later motivational deficits cannot assuredly be assigned to a patient-specific phenomenon. However, as healthy control participants were included only in absence of any neurological or psychiatric disorders, we assumed no change in depressive symptoms or motivational deficits over time, so control subjects were assessed only once (Rehme et al., 2011b).

Importantly, chronic MADRS scores were not associated with initial MADRS scores suggesting that the monetary incentive grip force task represents a covert but more specific measure of the underlying motivational state and for prognosis of chronic motivational deficits. As our task required patients with residual hand motor function and consent, patients with different impairments might develop greater PSD or less incentive motivation. Furthermore, our sample comprised patients with relatively mild depressive symptoms and good recovery thereof. In comparison to our findings, other studies found that PSD during the first-year post-stroke depend on earlier MADRS scores (Fuentes et al., 2009; Mikami et al., 2021). This difference may partly result from different sample sizes, but also different examination stages or impairment levels. For example, Mikami et al. (2021) assessed 48 patients within the first 6 weeks post-stroke with lower impairment severity (NIH-SS: mean 3.9) compared to our sample (NIH-SS: mean 8.48) assessed on average 7.7 days post-stroke. Thus, chronic PSD may be reliably predicted by the presence of depressive symptoms in the subacute stage rather than the early stage post-stroke.

4.2.2. Structural lesion sites and PSD

We found that ventral corticostriatal tract lesions were specifically associated with impaired incentive motivation in task performance, whereas lesions of the dorsal corticostriatal tract were associated with prognosis of motivational PSD symptoms at later stages. Corticostriatal projections have been shown to be involved in goal-directed behaviors,

including the motivation and cognitions leading to these actions (Haber, 2016). As the *dorsal* tract connects higher-order sensorimotor areas with dorsal striatum (Alexander and Crutcher, 1990; Draganski et al., 2008; Haber and Knutson, 2010), our finding corroborates that this circuit plays a vital role for motivated behaviors and that apathy following stroke may impair motor rehabilitation (Hama et al., 2007b; Rochat et al., 2013; Schmidt et al., 2008). Interestingly, a multicenter study showed that the antidepressant selective serotonin-reuptake-inhibitor fluoxetine improves motor performance independent of changes in PSD symptoms (Chollet et al., 2011). The *ventral* tract connects primarily ventro-medial prefrontal and orbitofrontal cortices with the VS, including nucleus accumbens, that has been shown to be involved in translating motivation into action and reward learning (Haber and Knutson, 2010). It has been frequently reported that reduced fMRI activity in dorsolateral prefrontal cortex and VS correlates with reduced incentive motivation in unipolar depressed patients (Cléry-Melin et al., 2011; Knutson et al., 2008; Robinson et al., 2012). Additionally, incentive motivation has been shown to be reduced by apathy post-stroke, resulting from damage to bilateral basal ganglia including VS (Rochat et al., 2013; Schmidt et al., 2008). Our preliminary findings of a prognosis for motivational deficits suggest – in line with extensive evidence from structural and functional neuroimaging studies – that incentive motivation requires an intact reward system as prerequisite for motor recovery and prevention of motivational PSD symptoms.

4.3. Conclusion

This study demonstrates for the first time that early-stage incentive motivation might reduce the risk for motivational PSD symptoms or apathy at the chronic stage. Thus, early motivation post-stroke may be a key target for interventions to improve rehabilitation and individual life quality while reducing public healthcare costs (Robinson and Jorge, 2016; Widmer et al., 2022). Additional studies of early-stage stroke patients are warranted to identify further PSD predictors and determine valuable treatment approaches.

CRediT authorship contribution statement

Janusz L. Koob: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Shivakumar Viswanathan:** Conceptualization, Formal analysis, Writing – review & editing. **Maike Mustin:** Data curation, Formal analysis, Writing – review & editing. **Imon Mallick:** Data curation. **Sebastian Krick:** Data curation. **Gereon R. Fink:** Writing – review & editing. **Christian Grefkes:** Conceptualization, Funding acquisition, Supervision, Resources, Writing – review & editing. **Anne K. Rehme:** Conceptualization, Funding acquisition, Data curation, Investigation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

This research work has been funded by a grant of the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, grant number: 310098283).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103360.

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Supplementary material

Supplementary table S1: Sample characteristics in grip force performance in the monetary incentive grip force task.

	Stroke patients n = 20 mean (SD)	Controls n = 24 mean (SD)	Statistical test
Mean relative grip force (±SD)	0.61 (0.13)	0.77 (0.05)	$F_{1,42} = 31.519$, $p < 0.001$**, $\eta_p^2 = 0.429$
Mean relative grip force $_{AffH}$ (±SD)	0.53 (0.16)	0.76 (0.05)	$F_{1,42} = 43.774$, $p < 0.001$**, $\eta_p^2 = 0.510$
Mean relative grip force $_{UnaffH}$ (±SD)	0.69 (0.12)	0.77 (0.06)	$F_{1,42} = 9.919$, $p = 0.003$**, $\eta_p^2 = 0.191$
Mean absolute grip force (in N) (±SD)	118.79 (81.30)	215.73 (54.29)	$F_{1,42} = 22.261$, $p < 0.001$**, $\eta_p^2 = 0.346$
Mean absolute grip force$_{AffH}$ (in N) (±SD)	68.28 (82.00)	213.06 (63.00)	$F_{1,42} = 43.838$, $p < 0.001$**, $\eta_p^2 = 0.511$
Mean absolute grip force$_{UnaffH}$ (in N) (±SD)	169.30 (91.22)	218.39 (50.21)	$F_{1,42} = 5.111$, $p = 0.029$*, $\eta_p^2 = 0.108$
Reward effect (±SD)	0.03 (0.04)	0.03 (0.05)	$F_{1,42} = 0.155$, $p = 0.696$
Reward effect $_{AffH}$ (±SD)	0.01 (0.03)	0.02 (0.03)	$F_{1,42} = 0.823$, $p = 0.370$
Reward effect $_{UnaffH}$ (±SD)	0.01 (0.03)	0.01 (0.03)	$F_{1,42} = 0.136$, $p = 0.714$
Fatigue effect (±SD)	-0.015 (0.045)	-0.009 (0.033)	$F_{1,42} = 0.260$, $p = 0.613$
Fatigue effect $_{AffH}$ (±SD)	-0.057 (0.118)	-0.024 (0.069)	$F_{1,42} = 1.340$, $p = 0.254$
Fatigue effect $_{UnaffH}$ (±SD)	-0.002 (0.091)	-0.012 (0.068)	$F_{1,42} = 0.154$, $p = 0.697$
Monetary outcome (in €) (±SD)	14.95 (4.25)	16.83 (4.08)	$F_{1,42} = 2.238$, $p = 0.142$

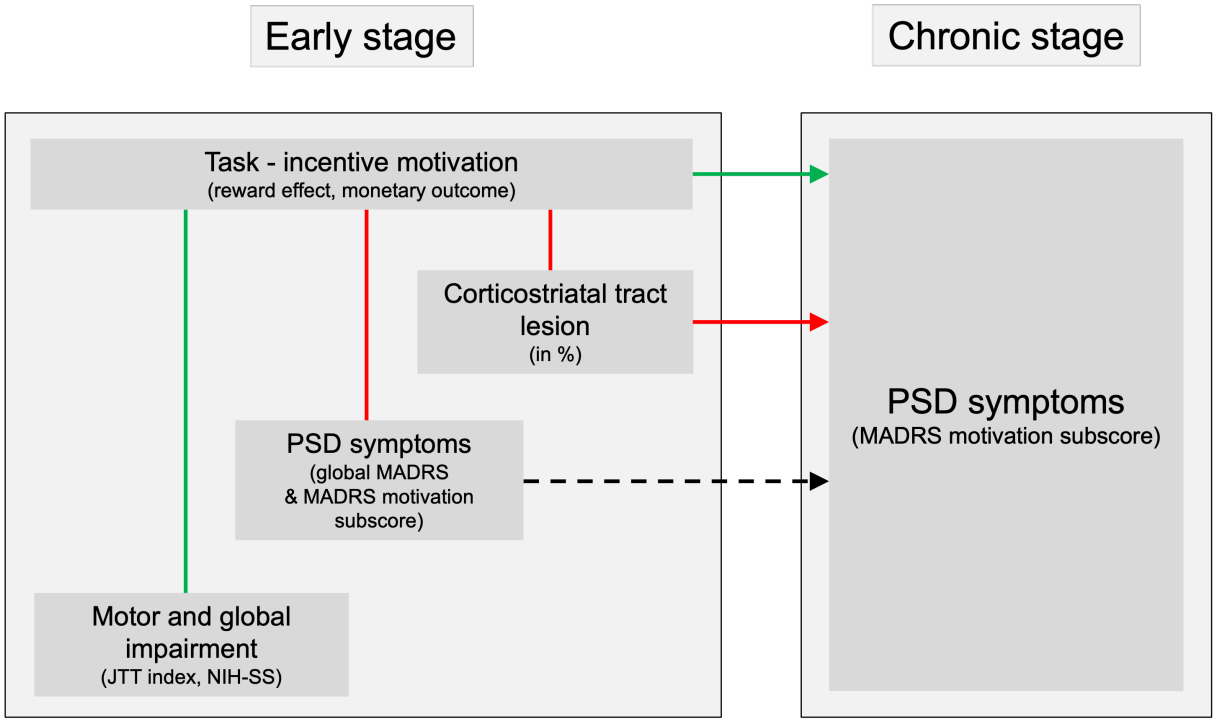
AffH: affected hand, UnaffH: unaffected hand.

As an additional motor impairment indication, we performed the ‘Hand’ and ‘Sensation’ subtests of the upper limb extremity functions of the Fugl-Meyer Assessment (FMA) (Fugl-Meyer, Jääskö, Leyman, Olsson & Steglind, 1975). Stroke patients performed significantly worse in the FMA (M = 21.5, SD = 5.07) compared to controls (M = 26, SD = 0) ($F_{1,42} = 18.974$, $p < 0.001$**, $\eta_p^2 = 0.490$).

An additional questionnaire was the German version of the Aspiration Index (AI) of current life goals. The AI assesses the priority of specific current life goals and needs as well as the perceived probability of achieving them in the dimensions of monetary wealth, personal growth, social relationships, and physical health (Kasser & Ryan, 1993). Between stroke patients and controls, the dimensions of the Aspiration Index (AI) of momentary values and needs showed no significant differences (all $p > 0.098$). Within the stroke patients subgroup, the AI showed a correlation between the expectation of physical health in the future and MADRS score ($R_{Sp} = -0.646$, $p = 0.012$, FDR-corrected) as well as between the importance of health and the JTT index ($R_{Sp} = 0.513$, $p = 0.033$, FDR-corrected). Hence, higher depression and greater motor impairment reflected less confidence or less importance in physical health. Furthermore, there was a negative correlation between the JTT-index and the perceived probability of achieving monetary wealth ($R_{Sp} = -0.543$, $p = 0.032$, FDR-corrected). That is the confidence into monetary wealth as a behavioral marker of

motivation was greater in those patients with stronger motor deficits. Likewise, the reward effect correlated positively with expected monetary wealth (R_{Sp} = 0.511, p = 0.025, FDR corrected).

Supplementary figure S2: Overview of the main study results. Green arrow lines indicate a supportive association, red arrow lines indicate a detrimental association, and the dotted black line indicates no significant correlation. In the early stage post-stroke, reduced incentive motivation in the monetary grip force task was related to less motor and global impairment, a greater percentage of corticostriatal tract lesions, and more pronounced PSD symptoms. Initially higher incentive motivation in the task predicted a decreased risk of motivational deficits in PSD symptoms in the chronic stage post-stroke. Furthermore, greater damage of the dorsal tract predicted later PSD symptoms. PSD symptoms in the early stage post-stroke had no predictive value for PSD symptoms in the chronic stage.



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5.3. Lesion-symptom mapping and negative attentional bias of facial emotion processing in post-stroke depression.

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In preparation, final draft prior to submission (September 11, 2023)

Lesion-symptom mapping and negative attentional bias of facial emotion processing in post-stroke depression

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Abstract

Background: Emotion processing deficits are common after stroke and are also known to accompany depressive symptoms. Few is known about the influence of symptoms of post-stroke depression (PSD) and specific brain lesions on altered emotion processing abilities. In a longitudinal study design, we investigated how PSD affects emotion processing abilities in the early and chronic stages post-stroke.

Methods: Twenty-six ischemic stroke patients performed an emotion processing task with shown videos of emotional faces ('happy,' 'sad,' 'anger,' 'fear,' and 'neutral') at different intensity levels (20%, 40%, 60%, 80%, 100%). Recognition accuracies and response times were measured, as well as scores of depressive symptoms (Montgomery-Åsberg Depression Rating Scale). Twenty-eight healthy participants matched in age and sex were included as a control group. Whole-brain lesion-symptom mapping (LSM) analyses were performed to investigate whether specific lesion locations were associated with recognition accuracy of specific emotion categories.

Results: Stroke patients performed worse in overall recognition accuracy compared to controls, specifically in the recognition of happy, sad, and fearful faces. Importantly, more depressed stroke patients showed an attentional bias towards specific negative emotions, as they responded significantly faster to angry faces and recognized sad faces of low intensities significantly more accurately. These effects remained stable at follow-up. SVR-LSM analyses revealed that inferior and middle frontal regions (IFG/MFG) and insula and putamen were associated with emotion recognition deficits. Specifically, recognizing happy facial expressions was associated with the anterior insula, putamen, IFG, MFG, orbitofrontal cortex, and rolandic operculum. Lesions in the posterior insula, rolandic operculum, and MFG were further related to reduced recognition accuracy of fearful facial expressions, whereas recognition deficits of sad faces were associated with frontal pole, IFG, and MFG damage.

Conclusion: PSD facilitates processing negative emotional stimuli, indicating a preference for mood-congruent emotions. The recognition accuracy of different emotional categories was linked to brain lesions in emotion-related processing circuits, including insula, basal ganglia, IFG, and MFG. We provide support for psychosocial and neural factors underlying emotional processing after stroke, contributing to the pathophysiology of PSD. As disrupted emotion processing abilities deteriorate social relationships and can promote depressive symptoms, interventions and therapies after stroke should aim at stabilizing socio-emotional networks and coping strategies.

Keywords: PSD, emotion processing, dynamic faces, longitudinal, multivariate SVR-LSM

1. Introduction

Deficits in emotion processing are a common complication in patients suffering from a stroke (Abbott et al., 2014; Aben et al., 2020; Adams et al., 2019; Luo et al., 2022; Yuvaraj et al., 2013). Accurately recognizing and reacting to social and emotional cues, such as facial expressions, is essential for interactions and social bonding (Adolphs, 2008). Importantly, depressive-affective disorders are also known to hinder specific socio-emotional processing (Bourke et al., 2010). Notably, about 30% of stroke patients suffer from depressive symptoms, commonly described as post-stroke depression (PSD) (Hackett & Pickles, 2014; Robinson & Jorge, 2016). Selective negative attentional bias, which involves an enhanced sensitivity to emotionally negative stimuli (such as sad or angry faces), is known to promote the mood-congruent emotional state of sadness in depression (Bourke et al., 2010; Peckham et al., 2010). Yet, to date, it is not well established whether stroke patients suffering from PSD show this attentional bias towards negative, mood-congruent faces and whether lesions in specific brain areas may facilitate disturbed emotion recognition.

There is broad literature investigating biased emotion processing towards negative facial expressions in MD, e.g., impaired recognition accuracy, longer response times, and selective attention for emotionally valenced stimuli. While evidence for a general impairment of emotion processing in depression is less abundant, reviews and meta-analyses rather indicate preferred processing of negative stimuli (e.g., sad and angry faces), reduced processing of positive stimuli (e.g., happy faces), as well as a tendency to attribute more negative meaning to neutral stimuli (Bourke et al., 2010; Leppänen, 2006; Peckham et al., 2010). In the research of emotion processing, cognitive models of depression propose that mood-congruent processing and a selective attentional bias towards negative stimuli affect the development, maintenance, and recurrence of depressive episodes (Beck, 1964; Lewinsohn, 1974). Studies showed that selective attention to sad facial expressions, in the sense of faster response times, greater accuracy, and enhanced memory, were predominant in MD (Gilboa-Schechtman et al., 2002; Gotlib, Kasch, et al., 2004; Gotlib, Krasnoperova, et al., 2004; Van Vleet et al., 2019) especially in subtle expressions (Bomfim et al., 2019; Surguladze et al., 2004) and even after recovery (Joormann & Gotlib, 2007). Likewise, findings also suggested that depressive patients exhibit a greater attentional bias towards angry faces in reaction time and eye-tracking indices (Leyman et al., 2007; Woody et al., 2016). Furthermore, a study by Domes et al. (2016) found that the administration of oxytocin, as an enhancing hormone of social bonding, reduced the allocation of attention toward angry faces and increased attention toward happy faces in chronically depressed patients. Concerning the relevance of sad and angry facial stimuli, Gilboa-

Schechtman et al. (2004) reasoned that for depressed people, sad emotions signal the more 'mood-congruent' emotional state of another person. Yet, it involves only indirect relevance to the observer. 'Mood-eliciting' stimuli, such as angry faces, might be even more relevant to depressed patients, given that they express personal rejection and failure. It is evident that depressed persons are often less socially skilled than non-depressed persons (Coyne, 1976). Thus, exposure to interpersonal disappointment or resentment may cause a higher sensitivity to socially aversive information, which can influence the evaluation of one's behavior (Leyman et al., 2007).

Of note, stroke patients are also often impaired in their emotion recognition (Yuvaraj et al., 2013). Importantly, in contrast to MD patients, it is suggested that stroke patients show an overall deficit in recognition compared to healthy controls (Braun et al., 2005; Luo et al., 2022; Nijsse et al., 2019; O'Connell et al., 2021; Tippett et al., 2018; van den Berg et al., 2021). To date, only a few studies have investigated the question of to what extent PSD symptoms are associated with deficits in emotion processing. Montagne et al. (2007) demonstrated in an emotion recognition task including dynamic face stimuli with different intensity levels that depressed stroke patients showed lower accuracy than those without depressive symptoms in recognizing anger, disgust, happiness, and sadness. Furthermore, stroke patients with depressive symptoms required more intense emotions to correctly identify angry, sad, and happy faces compared to patients without depressive symptoms. Likewise, de Souza et al. (2021) observed a significant correlation between a better recognition of sad faces and increasing levels of depression in stroke patients. To date, we found no study investigating the effect of PSD on emotion processing abilities in the early stage post-stroke and how these develop over time.

Notably, most emotion-processing studies in stroke patients found impaired emotion recognition accuracy in patients with right-hemispheric lesions compared to left-hemispheric lesions (Yuvaraj et al., 2013). A neural network is suggested to be responsible for the cognition and processing of emotions, constituting cortical and subcortical regions including occipital-temporal cortices, which play a role in forming perceptual representations of the facial signal, as well as amygdala, hippocampus, orbitofrontal cortex (OFC), basal ganglia, insula, cingulum, striatum, and somatosensory cortex for representing the emotional value of the expression (Craig, 2009; A. Damasio, 2003; Gasquoine, 2014; Leppänen, 2006; Palomero-Gallagher & Amunts, 2022; Pessoa & Adolphs, 2010; Phan et al., 2002). Neuroimaging studies in depressed patients have demonstrated both structural and functional brain changes (Davidson et al., 2002; Phillips, 2003) as well as altered neural responses to emotional faces (Fu et al., 2008; Lee et al.,

2008; Peluso et al., 2009; Surguladze et al., 2005) in parts of those networks. This suggests that these brain regions may also mediate emotion recognition deficits. A structural MRI study reported that acute stroke patients with lesions in the right amygdala or right anterior insula showed a significantly worse recognition accuracy of happy and angry faces than patients with other lesion locations (Tippett et al., 2018). Nevertheless, whether lesions of specific regions are related to a recognition deficit of specific emotional valence contributing to a general emotion recognition network is poorly examined.

To our knowledge, only one lesion-symptom mapping study investigated which specific emotion processing deficits are related to which lesion site in stroke patients. The recent study by van den Berg et al. (2021) investigated facial emotion recognition and found significant lesion-symptom associations in right-hemispheric regions, including the insula, putamen and rolandic operculum, as well as the middle and superior frontal gyrus (anger), caudate nucleus (disgust), superior corona radiata white matter tract, superior longitudinal fasciculus and middle frontal gyrus (happiness), and inferior frontal gyrus (sadness). The authors concluded that emotion recognition is represented in the brain within a network, including nodes and interconnections of specific basic emotions (van den Berg et al., 2021).

This study aimed to investigate emotion processing abilities (e.g., recognition accuracy, response time) in stroke patients early post-stroke and to assess how PSD symptoms influence the bias of attending toward negative emotions. Healthy participants were included as a control group. We used an emotion processing task, where real-life evolving dynamic face stimuli were presented to the participants. The videos expressed faces of four basic emotions (happiness, sadness, anger, fear, and a neutral expression) in different intensity levels (e.g., 20%, 40%, 60%, 80%, 100%). Furthermore, we performed multivariate lesion-symptom analyses to explore which specific lesioned brain sites are associated with specific emotion recognition deficits (van den Berg et al., 2021). In a follow-up assessment (3-6 months), where PSD symptoms are thought to peak (Hackett & Pickles, 2014), patients replicated the experimental task, and depressive symptoms were examined again to evaluate how emotion processing abilities developed over time.

We hypothesized that stroke patients show an overall worse emotion recognition accuracy in the task compared to controls. It is further assumed that increased PSD symptoms will lead to a greater selective attentional bias towards negative emotions (specifically sad and angry faces) in the sense of increased recognition accuracy and a faster response time in the task as well as impaired processing of positive stimuli (i.e., happy faces). Moreover, on a neural

basis, we hypothesize to detect brain lesions related to recognition deficits of distinct emotion categories.

2. Methods

2.1 Participants

Right-handed first-ever stroke patients were recruited from the Department of Neurology, University Hospital of Cologne, Germany. Examination took place on average ten days post-stroke (range 3 – 20 days). Inclusion criteria were: (i) legal capacity, (ii) no severe comorbid neurological or psychiatric disorders including preexisting depression, (iii) sufficient sight, (iv) no severe cognitive impairment, neglect, or aphasia according to neurological examination. Healthy participants matched in age and sex were recruited as a control group. Seven stroke patients were excluded due to inability to finish the task or incorrect performance. Three healthy controls were excluded due to currently mild depressive symptoms. The final sample included 54 participants (n = 26 stroke patients, n = 28 healthy controls). Twelve stroke patients had lesions in the left hemisphere (LH), and 14 lesions were on the right hemisphere (RH). All stroke patients were right-handed, and one control participant was left-handed (see Table 1 for demographics and sample characteristics).

Assessments took place at the Department of Neurology, Cologne. Stroke patients were examined at the bedside during hospitalization. All participants gave informed written consent in accordance with the local ethics committee and the Declaration of Helsinki (revised in 2008). Controls received an expense allowance of 15€.

2.2 Design of dynamic face stimuli

For the emotion processing task, dynamic face stimuli of different intensities were designed using the static pictures from the FACES database, Center for Lifespan Psychology, Max Planck Institute for Human Development, Berlin, Germany (Ebner et al., 2010). We selected four model stimuli (2 females) showing the facial expression of happiness, sadness, anger, fear, and a neutral expression. We chose middle-aged models as older raters recognized these most accurately (Holland et al., 2019), and these were the most age-related group to our sample. Then we morphed the stimuli out of the static images to create a video presenting an evolving facial emotion expression using the software MorphAge (v5.0.3) for MacOS, similar to the creation of the Dynamic FACES, an extension of the original FACES database (Holland et al., 2019). The neutral facial expression and the final expression (e.g., happiness at 100% intensity) were used to create the morph. In this way, we created facial expressions of different intensities by terminating the transition at 20%, 40%, 60%, 80%, and 100%. Each video lasted 3 seconds (sec). Emotion expressions started with the neutral image and evolved linearly, reaching the final expression within 1 sec (Holland et al., 2019) - shown for 2 sec. Neutral faces

did not have intensity levels, so we morphed the transition from the same neutral in two data sets provided by the database to create the dynamic video. A total of 100 videos were created in 2048 x 2560-pixel resolution with a frame rate of 30 fps.

2.3.1 Experimental design

The experiment was designed using PsychoPy3 v.2020.2.0 based on Python (Peirce et al., 2019) and implemented on a 17' Lenovo touch-screen Windows laptop. The picture resolution was 1920 x 1080 pixels with 19.7 x 355.2 cm on the screen. In the task, participants gave their answers by tapping on the touch-screen.

The experimental design of the emotion processing task is presented in Figure 1. Participants were seated in front of the screen at 1 m distance. Each trial started with a countdown of three seconds, followed by the dynamic facial expression stimuli. Before the task, participants received written and oral instruction and completed a training run of five trials. Participants could choose the appropriate emotion on the touch-screen after the stimuli appeared. Answer buttons were shown in fixed order beneath the stimulus: happy, sad, angry, fearful, neutral. The stimulus of facial expression disappeared after 3 sec, and participants had an additional 6 seconds to choose the appropriate emotion category, resulting in a maximum of 9 seconds for answering per trial. Importantly, as participants were asked to correctly identify the emotion category (even if relatively uncertain), they were further instructed to respond as fast as possible. For task execution, participants used the dominant/non-affected hand. A break of individual length was set after every ten trials.

The task consisted of a 5x5 factorial design with the factors of emotional expression (happy, sad, angry, fearful, neutral) and intensity level (20%, 40%, 60%, 80%, 100%). Note that four stimuli models from the FACES database were chosen to express the facial emotions at different intensity levels. This resulted in 100 identically structured trials. Further, neutral emotional expressions did not contain any intensity levels. Thus, five equal neutral video stimuli were presented per stimuli model for an equal number of all emotion categories. Trials were presented in a pseudo-random order, with consecutive trials never showing the same model and the same emotion category to prevent habituation.

Figure 1: Experimental design of the emotion processing task. Trials started with a countdown (3s) leading to the stimuli presentation phase in which the video displayed the evolvement of the facial expression (3s). When starting with the presentation phase, participants were allowed to select the corresponding emotion category (happy, sad, angry, fearful, neutral) up to 6s after the presentation (3s). Participants were instructed to respond as fast as possible. The stimuli in the figure illustrate an evolvement of an ANGRY facial expression with a final intensity of 80%.

2.4 Behavioral assessments

To quantify depressive symptoms, we used the Montgomery-Åsberg Depression Rating Scale (MADRS) interview, which includes ten items of depression rated by an experimenter (Herrmann et al., 1998; Montgomery & Asberg, 1979). According to published guidelines, each item must be answered based on several questions (Williams & Kobak, 2008). To quantify neurological impairments after stroke, we used the National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989).

2.5 Follow-up assessment

For follow-up assessment, patients were re-invited >3 months post-stroke (mean = 155.04 days, SD = 34.11). This time was referred to as the chronic stage when PSD symptoms peak (Hackett & Pickles, 2014). Follow-up assessment included the same experimental assessments as during hospitalization. Data from n = 26 patients (100%) could be obtained, yet four patients disapproved or could not attend in person, so depression scores (MADRS) were assessed via telephone interview.

2.6 Data pre-processing

Data from the emotion processing task were processed using SPSS 28 (IBM Corp, Armonk, NY, USA). First, we created variables, including information about emotion category (EMOTION) and intensity level (INTENSITY). Neutral stimuli did not include any intensity levels. Variables were created for the dependent variables: (i) recognition accuracy (in %) and (ii) response time. The response time variables were formed relative to the average response time over all trials for each participant. Thus, the reported response times are normalized to the

participant's individual speed, which might be impaired due to the stroke, e.g., as a consequence of hemiparesis. This allows a more accurate comparison of response time effects independent of stroke severity.

In an additional task, we provided a scale for each video to measure the participant's explicit emotional intensity rating. Moreover, we computed confusion matrices to illustrate which emotion categories were mistaken for which other emotion categories (type of mistakes) during emotion recognition in the task. See the Supplementary for this additional information.

2.8 Statistical Analysis

For the emotion processing task, recognition accuracy and response time were analyzed using mixed-design ANOVA and Bonferroni-corrected post-hoc t-tests with the within-subject factors EMOTION (happy, sad, angry, fearful) and INTENSITY (20%, 40%, 60%, 80%, 100%) and the between-subject factor GROUP including stroke patients and controls. As neutral facial expressions did not involve any intensity levels, a separate t-test was calculated to compare effects between groups in the dependent variables (i.e., recognition accuracy and response time). Significant effect sizes were determined by partial eta-squared (η_p^2) as provided by SPSS. To assess potential sex differences in emotion processing (Alaerts et al., 2011; Hoffmann et al., 2010; Lambrecht et al., 2014), we computed mixed-design ANOVAs with Bonferroni corrections per experimental group with the between-subject factor SEX including females and males and the within-subjects factors EMOTION and INTENSITY (see Supplementary material).

To investigate associations between task performance parameters and depression in the stroke subgroup, further correlational analyses were computed. Of note, we observed that emotional expressions within the subgroup with intensities of 60% - 100% were recognized as equally accurate. Therefore, to increase statistical power for the correlational analyses, we combined the scores for recognition accuracy of 20% and 40% to 'low-intensity level' and the scores of 60%, 80%, and 100% to 'high-intensity level' for each emotional category. For example, the variable for the recognition accuracy of happy faces of low intensities included the average of both accuracies of 20% and 40% in recognizing happy faces. Spearman correlations (R_{SP}) were computed for the ordinal scaled dependent variable' recognition accuracy' (low intensity and high intensity), and Pearson correlations (R_P) were calculated for the interval scaled dependent variable' response time.' Correlations were considered significant at $p<0.05$ (two-sided), except for associations between depression (MADRS) and parameters including negative emotions (sad, angry, fearful) according to the hypothesis of negative

attentional bias, where more depressed patients show a better performance in mood-congruent emotional stimuli (one-sided $p<0.05$) (Bourke et al., 2010; Gilboa-Schechtman et al., 2002, 2004; Gotlib, Kasch, et al., 2004; Gotlib, Krasnoperova, et al., 2004; Lee et al., 2008; Leyman et al., 2007; Takizawa et al., 2020; Van Vleet et al., 2019). False discovery rate (FDR) correction for multiple testing was applied for each set of a dependent variable correlation analysis (Benjamini & Hochberg, 1995).

To compare emotion processing parameters in the early stage and chronic stage post-stroke (>3 months), we performed paired-sample t-tests of both time points' overall recognition accuracy and the overall absolute response time. To further evaluate the potential effects of specific emotion categories and intensity levels over time, we executed a mixed-design ANOVA per parameter similar to the above-described mixed-design ANOVA with the extra within-subjects factor TIME (early stage, chronic stage). Additionally, we aimed to substantiate the effects of early depressive symptoms on task performance parameters in the chronic stage. Therefore, we performed correlational analyses for significant behavioral parameters and depressive symptoms between the early and the chronic stage ($p < 0.05$, one-sided). FDR correction was applied to all correlation analyses in the follow-up computations.

In six different multivariate SVR-LSM analyses, we investigated lesion-recognition deficit associations between each specific emotion category's recognition accuracy and overall recognition accuracy.

2.7.1 Lesion mapping and pre-processing

For all patients, anatomical MRI scans obtained during the clinical routine were available to map the stroke lesion based on diffusion-weighted imaging (DWI; TR = 4076ms, TE = 95ms, 22-24 axial slices, voxel size = 1.8x2.99x6mm^3) and fluid-attenuated inversion recovery images (FLAIR; TR = 6000ms, TE = 100ms, 36-40 axial slices, voxel size = 1.38x1.1x4mm^3). Lesion maps were manually drawn onto DWI images, showing the extent of the ischemic lesion. Lesion drawings underwent quality control by a second reviewer. DWI, FLAIR, and lesion masks were then spatially normalized to a standard template (1x1x1 mm) in the space of the Montreal Neurological Institute (MNI) by using the unified segmentation approach with masked lesions in SPM12 (https://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB R2020a (The MathWorks Inc, Natick, MA, USA) and FMRIB Software Library (FSL). Unlike many other lesion-symptom mapping studies in stroke research, lesions were not systematically flipped to a particular hemisphere, i.e., information on inter-hemispheric differences in lesion location was preserved.

2.7.2 Support-vector regression lesion-symptom mapping (SVR-LSM)

A MATLAB-based toolbox was used for multivariate lesion-symptom mapping (DeMarco & Turkeltaub, 2018) based on an SVR-LSM implementation introduced by Zhang et al. (2014). Support vector regression (SVR) is a special case of support vector machines, which are employed to solve binary classification problems, e.g., whether a disease is either present or absent (Rehme, Volz, Feis, Bomilcar-Focke, et al., 2015; Rehme, Volz, Feis, Eickhoff, et al., 2015). In contrast, SVR allows the prediction of continuous variables (and their variability) based on the lesion status of multiple voxels.

Controlling for lesion volume is essential in lesion-symptom mapping because patients with larger lesions tend to show more significant deficits (DeMarco & Turkeltaub, 2018; Price et al., 2017). Thus, after correcting both the behavioral scores and the lesioned voxels for lesion volume, the interpretation of SVR-LSM results allows answering questions about whether the behavior of interest is more strongly related to lesions in a particular brain area relative to all other brain regions rather than a mere correlative interpretation of whether lesions are associated with the behavior of interest (DeMarco & Turkeltaub, 2018). Therefore, lesion volume was regressed from both the lesion maps and the behavioral variables for all SVR-LSM analyses. A minimum lesion threshold of three lesions per voxel was used, as 10% of the sample size is suggested as the minimum threshold to ensure sufficient lesion overlap (Sperber & Karnath, 2017). Importantly, the analysis design is one-tailed. Thus, the analyses were set to be negatively tailed based on the assumption that lesion presence was associated with a greater deficit, i.e., worse emotion recognition accuracy.

For model estimation, five-fold cross-validation was used. Statistical significance was determined by a non-parametric approach using 10,000 permutations. A voxel was considered significant when passing a threshold of $p < 0.005$. Final permutation-based voxel-wise thresholded p-maps were smoothed using a 2mm isotropic Gaussian smoothing kernel in SPM12 to reduce cluster independence of neighboring lesion voxels. Significant anatomical structures were classified using the Harvard-Oxford Cortical and Subcortical structural atlases as implemented in FSL and the SPM Anatomy Toolbox.

3. Results (1098 words)

Demographic and clinical characteristics of the sample are summarized in Table 1.

Table 1: Overview of the demographic and clinical characteristics of the sample.

	Stroke patients n = 26 mean (SD)	Controls n = 28 mean (SD)	
Demographics			
Sex (f:m)	14:12	11:17	$\chi^2_1 = 1.150$, p = 0.284
Mean age (years) (±SD)	67.312 (12.05)	69.46 (8.5)	$F_{1,52} = 0.693$ p = 0.409
Examination post-stroke (days) (range)	10.27 (3-20)		
Lesion Side (left:right)	12:14		
Handedness (left:right)	0:26	1:27	$\chi^2_1 = 0.946$, p = 0.331
Neurological impairment			
NIHSS $_{early}$ (±SD)	5.31 (4.25)		
NIHSS $_{follow\text{-}up}$ (±SD)	2.64 (2.17)		
Depressive symptoms			
MADRS global score $_{early}$ (±SD)	9.42 (8.01)	0.96 (1.37)	F = 30.302, p < 0.001, $\eta^2 = 0.368$
MADRS global score $_{follow\text{-}up}$ (±SD)	8.69 (7.18)		

NIHSS: National Institutes of Health Stroke Scale, MADRS: Montgomery-Åsberg Depression Rating Scale, χ^2: chi-square, η^2: Eta-Square effect size, U: Mann-Whitney U. One patient received anti-depressive medication (Citalopram 20mg/day) due to acute depressive symptoms. MADRS scores in the early stage post-stroke were: no depression (n = 13), mild depression (n = 10), moderate depression (n = 3), and severe depression (n = 0). MADRS scores in the chronic stage were: no depression (n = 13), mild depression (n = 12), moderate depression (n = 1), and severe depression (n = 0) (Herrmann et al., 1998).

3.1 Emotion processing task

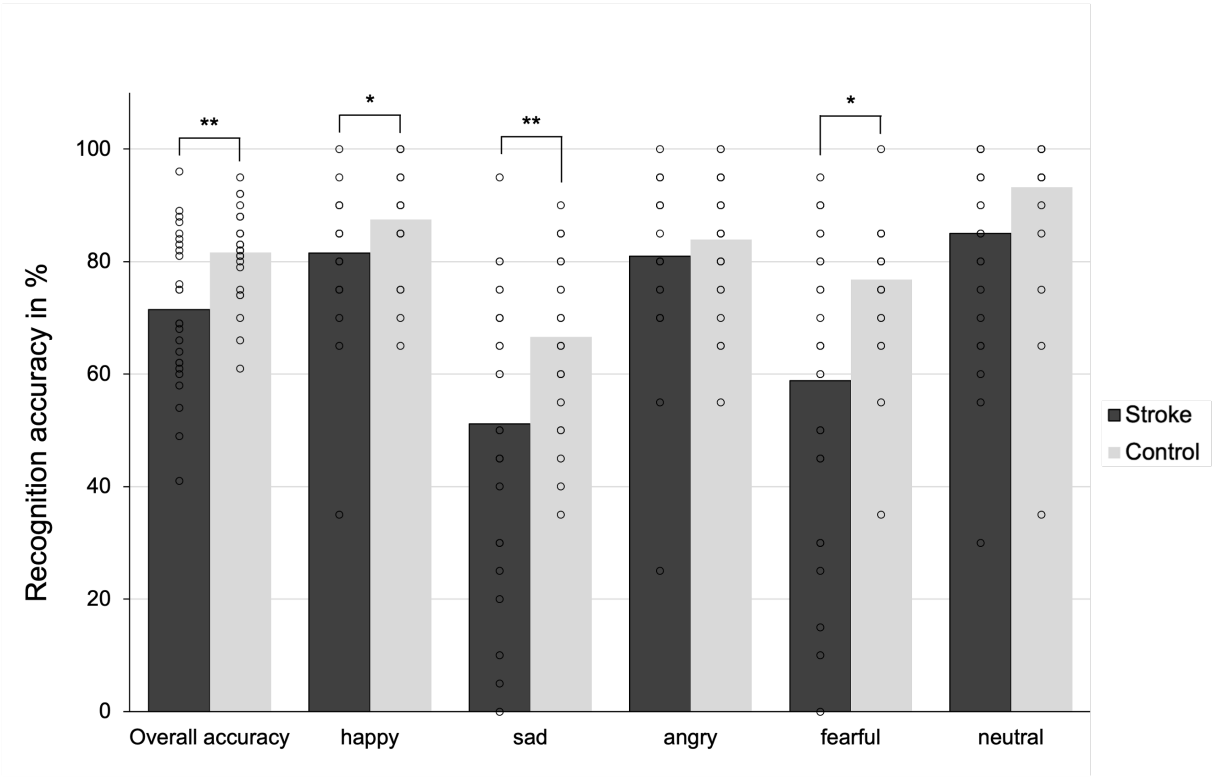
3.1.1 Recognition accuracy

When analyzing the accuracy of emotion recognition, the mixed model ANOVA yielded a main effect of INTENSITY ($F_{1,52}$= 330.768, p < 0.001, η_p^2= 0.864). That is, all participants recognized stimuli better with increasing emotion intensity. Furthermore, a significant main effect of EMOTION ($F_{1,52}$= 37.674, p < 0.001, η_p^2= 0.420) showed that happy expressions were most accurately recognized (mean = 84.63%, SD = 11.15), followed by angry (mean = 82.5%, SD = 13.38), fearful (mean = 68.15%, SD = 22.35), and sad expressions (mean = 59.17%, SD = 21.65).

Moreover, we observed a main effect of GROUP ($F_{1,52}$= 12.110, p = 0.001, η_p^2= 0.189), with stroke patients recognizing emotions significantly less accurately than controls. Likewise, a significant interaction effect between GROUP and EMOTION ($F_{1,52}$= 3.309, p = 0.030, η_p^2= 0.060) indicates a worse recognition accuracy of stroke patients than controls in sad ($F_{1,52}$= 7.744, p = 0.007, η_p^2= 0.130), fearful ($F_{1,52}$= 10.197, p = 0.002, η_p^2= 0.164), and happy emotional expressions ($F_{1,52}$= 4.075, p = 0.049, η_p^2= 0.073) (Figure 2). Besides, there was a trend for statistical significance in the correct recognition of neutral faces between groups (t_{52}

= 1.871; p = 0.067). We identified a significant three-way interaction, where stroke patients recognized specific emotions of different intensity levels significantly worse than controls. These results are reported in the supplementary material. There was neither a significant interaction between GROUP and INTENSITY (p = 0.622) nor between EMOTION and INTENSITY (p = 0.130). An overview of the effects of the mixed model ANOVA on the recognition accuracy, response times, and subjective intensity rating are provided in Supplementary Table 1.

Figure 2: Emotion recognition accuracy scores for stroke patients and controls. Overall accuracy and per emotion category. Stroke patients showed significantly worse overall performance, especially in recognizing happy, sad, and fearful facial expressions. ** $p < 0.01$, * $p < 0.05$



3.1.2 Response time

When analyzing the differences in relative response time between groups, we found a significant main effect of EMOTION ($F_{1,52}$= 32.020, p < 0.001, η_p^2= 0.381) showing that happy faces were recognized the fastest (mean = 3.73s, SD = 0.34), followed by angry (mean = 3.79s, SD = 0.33), sad (mean = 4.12s, SD = 0.29), and fearful facial expressions (mean = 4.36s, SD = 0.40). Response times to neutral facial expressions were not significantly different between groups (t_{52}=1.466, p = 0.149). The response time analyses indicated a significant main effect of INTENSITY ($F_{1,52}$= 43.949, p < 0.001, η_p^2= 0.458) with higher intensity levels corresponding to reduced response time. There was neither a significant main effect of GROUP (p = 0.149)

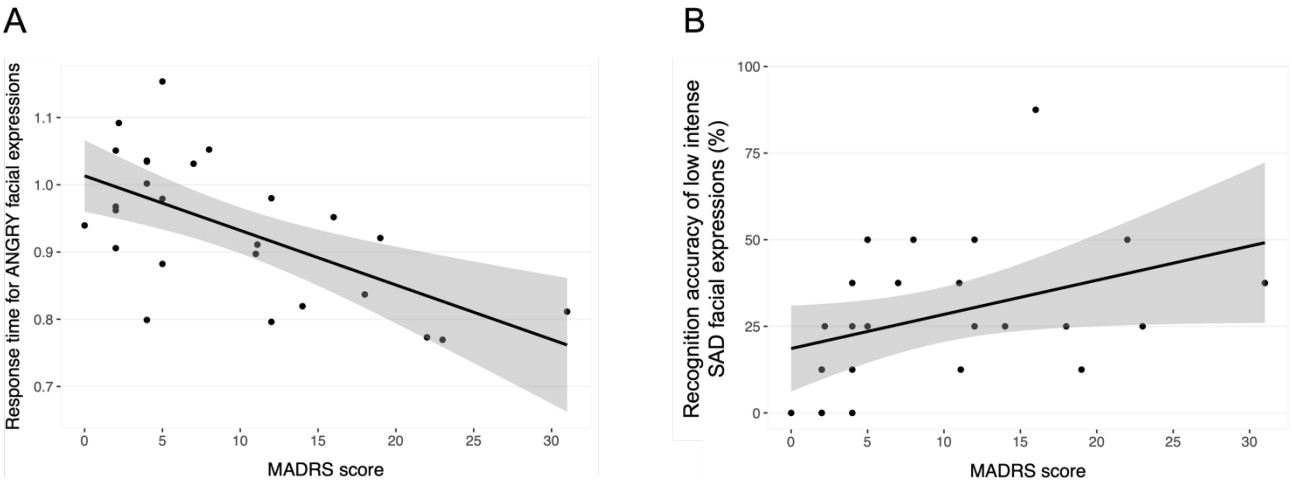
nor a significant interaction between EMOTION and GROUP ($p = 0.594$) for relative response time. Thus, independent of stroke impairment and potential motor disabilities, controls and stroke patients did react differently to emotional face stimuli and specific emotions.

3.2 Stroke subgroup analysis

The number of days between the stroke and examination date did not correlate with depressive scores or performance in the task (i.e., recognition accuracy and response time). Stroke severity, as assessed by the NIHSS, did not affect depressive symptoms (MADRS) in the stroke sample ($p = 0.213$), and neither stroke severity nor depression influenced overall recognition accuracy (all $p > 0.267$).

Correlation analyses within the stroke subgroup showed a negative association between the MADRS score and the response time to angry emotions (irrespective of intensity level) (R_P=-0.620, $p = 0.005$, FDR-corrected). This indicates that more depressed patients responded significantly faster to angry faces (Figure 3A). Interestingly, we also observed a positive correlation between the MADRS score and the recognition accuracy of low intense, sad facial expressions (R_{Sp}=0.527, $p = 0.027$, FDR-corrected), indicating a better recognition performance of more depressed stroke patients (Figure 3B). There was no effect of lesion side (LH/RH) on depression, overall recognition accuracy, and overall absolute response time (all $p > 0.310$).

Figure 3: Relationships between performance in the emotion processing task and depressive symptoms (MADRS score) in stroke patients. A: Negative correlation between the response time to angry facial expressions and the MADRS score (R_P: -0.620, p = 0.005), with more depressed patients responding faster. B: Positive correlation between the recognition accuracy of sad facial expressions in low-intensity levels (in %) and the MADRS score in stroke patients (R_{Sp}: 0.527, p = 0.027). More depressed patients showed better accuracy.



Overall, in the chronic stage, stroke patients performed significantly better in the emotion processing task (overall recognition accuracy and overall absolute response time) compared to the early stage (recognition accuracy: t_{21}=2.887, p = 0.009, early stage: 71.14% correct responses, chronic stage: 76.27% correct responses; absolute response time: t_{21}=2.355, p = 0.028, early stage: 3.30 sec, chronic stage: 3.01 sec). This went along with significantly reduced stroke impairment (NIHSS) (t_{21}=4.692, p < 0.001) but not with a different MADRS score (p = 0.587) in the chronic stage compared to the early stage post-stroke. In the mixed-models ANOVA, no interaction between EMOTION or INTENSITY and TIME could be observed for recognition accuracy and response times (all p > 0.229). Thus, the task performance did not improve for a specific emotion or intensity level.

We performed additional correlational analyses to investigate characteristics of task performance parameters in the chronic stage based on previous behavioral results. We found faster response times to angry facial expressions in the early stage as well as in the chronic stage to be negatively associated with MADRS scores in the chronic stage (R_P= -0.542, p = 0.012, FDR-corrected; R_P= -0.435, p = 0.042, FDR-corrected, respectively). Moreover, the recognition accuracy of low intense, sad faces in the chronic stage showed a significant positive association with MADRS scores in the early stage (R_{Sp}= 0.467, p = 0.042, FDR-corrected). These findings suggest that behavioral effects remained stable over time.

3.3 SVR-LSM

The average lesion volume was 33.12 cm^3 (±62.40 cm^3, range: 0.46 cm^3 - 291.43 cm^3). There was no effect of lesion side (left, right) on task performance parameters (i.e., overall recognition accuracy, overall absolute response time), depression symptoms (MADRS), or stroke severity (NIHSS) and no associations between lesion volume (in cm^3) and NIHSS or task performance parameters.

To investigate lesion-symptom associations of emotion recognition abilities, we performed several multivariate SVR-LSM analyses. In Figure 4, we depicted the overlap map of the lesion coverage included in the analyses. The analyses revealed that deficits in *overall* recognition accuracy were associated with damage in the insula (anterior and posterior), OFC, inferior frontal gyrus (IFG), middle frontal gyrus (MFG), putamen, frontal operculum, and pre- and post-central gyri (Figure 5). Also, deficits in correctly identifying *happy* facial expressions were associated with damage in the frontal pole, anterior insula, OFC, inferior frontal gyrus (IFG), middle frontal gyrus (MFG), putamen, frontal operculum, and pre- and post-central gyrus (Figure 5). Furthermore, reduced recognition accuracy for *fearful* expression was related to lesions in the posterior insula, frontal pole, central operculum, and MFG. Recognition deficits of *sad* faces were associated with damage in the frontal pole, IFG, and MFG. No significant lesion voxels were related to reduced recognition of *angry and neutral* faces. Brain regions of lesion-symptom associations are provided in Table 2.

Table 2: SVR-LSM results for the recognition accuracy deficits of happiness, fear, sadness, and overall accuracy in the emotion processing task. Brain regions are provided with corresponding Z-values at peak lesion-symptom associations and MNI coordinates. Regions are labeled using the Harvard-Oxford Cortical Structure Atlas and the SPM Anatomy Toolbox.

		MNI coordinates		
Region	Z-value	x	y	z
Happiness				
Inferior frontal gyrus (IFG)	3.54	50	13	10
Middle frontal gyrus (MFG)	3.53	48	15	34
Precentral gyrus	3.52	55	8	26
Orbitofrontal cortex (OFC)	3.51	35	24	-6
Anterior insula	3.39	33	23	-3
Putamen	3.27	32	4	1
Frontal operculum	3.18	45	24	1
Frontal pole	2.75	44	49	2
Fear				
Rolandic Operculum	3.70	46	-12	17
Posterior insula	3.32	37	-16	16
Frontal pole	2.49	44	49	2
Middle frontal gyrus (MFG)	1.37	43	24	43
Sadness				
Inferior frontal gyrus (IFG)	2.44	48	23	19
Frontal pole	2.40	44	49	2
Middle frontal gyrus (MFG)	1.63	40	20	43
Overall				
Rolandic operculum	3.70	46	-12	17
Posterior insula	3.50	37	-17	16
Inferior frontal gyrus (IFG)	2.84	55	13	9
Middle frontal gyrus (MFG)	2.80	48	18	36
Orbitofrontal cortex (OFC)	2.76	37	27	-6
Frontal pole	2.59	44	49	2
Anterior insula	2.58	33	23	-1
Putamen	2.39	31	4	1
Frontal operculum	2.14	43	20	0

Figure 4. Overlap map of the lesions included in the SVR-LSM analyses (n=26) on axial slices. Colors indicate the number of overlapping lesions. Analyses included voxels only when a minimum of three patients had a lesion in this voxel. Blue voxels were not included in the SVR-LSM. MNI coordinates are displayed next to corresponding slices. L, left; R, right.

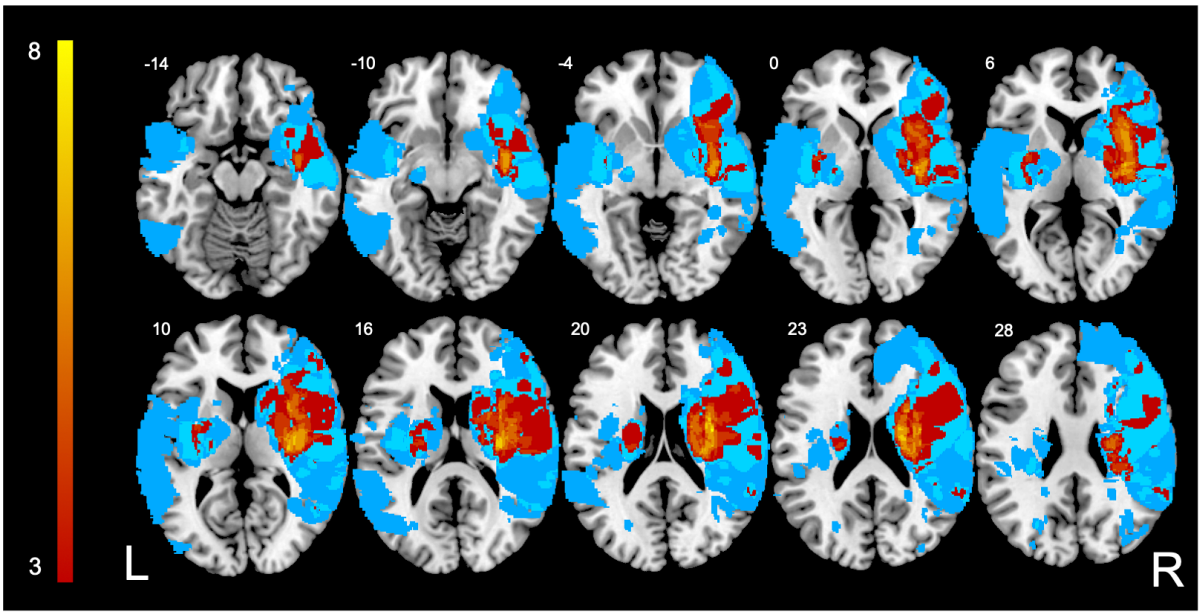


Figure 5. Results of the SVR-LSM analyses depicting lesion-symptom associations of the overall emotion recognition accuracy in the emotion processing task (blue). Results are thresholded with a voxel-wise threshold set to $p < 0.005$. MNI coordinates are displayed next to corresponding slices. L, left; R, right.

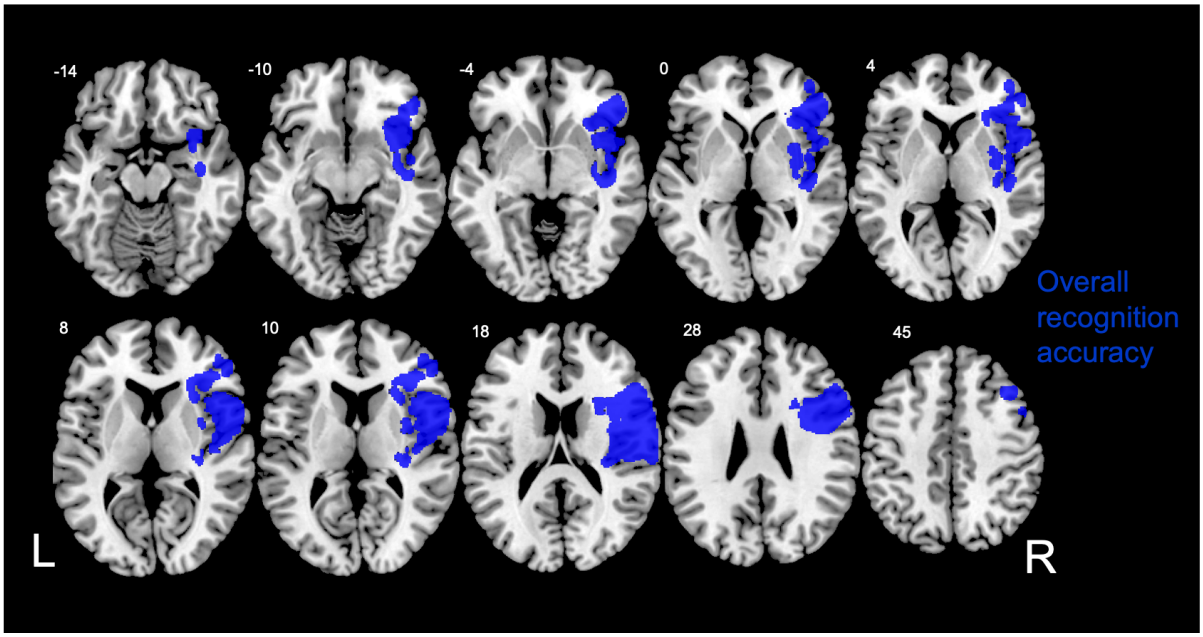
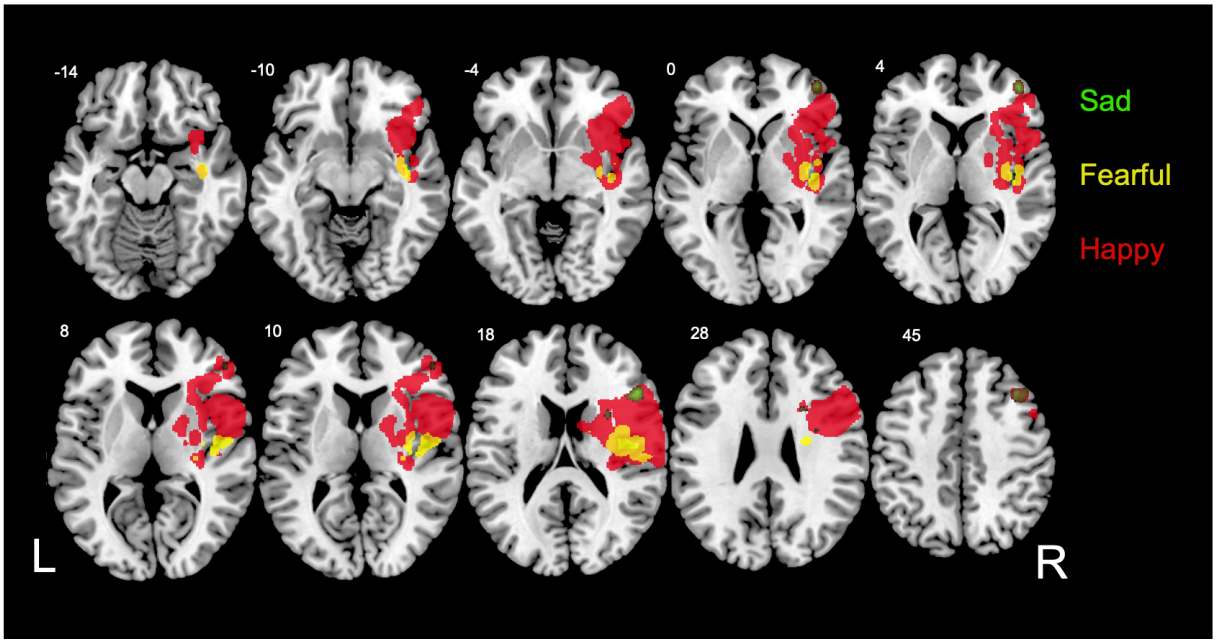


Figure 6. Results of the SVR-LSM analyses depicting lesion-symptom associations of emotion recognition accuracy in happy (red), fearful (yellow), and sad (green) faces in the emotion processing task. Results are thresholded by 10,000 permutations, and a voxel-wise threshold is set to $p < 0.005$ for each emotion. MNI coordinates are displayed next to corresponding slices. L, left; R, right.



4. Discussion (2200 words incl. cit.)

We compared the emotion processing of dynamic face stimuli at different emotion intensity levels in stroke patients and healthy controls. We revealed specific lesion-symptom associations for the overall emotion recognition accuracy and distinct emotion categories. Mainly, we found that greater symptoms of PSD were correlated with an attentional bias towards rather negative emotions, including sadness and anger. Thus, we observed that depressive symptoms after stroke facilitate processing socially negative valenced/mood-congruent face stimuli. Our findings support the model of the negative emotional attentional bias in major depression disorder (Bourke et al., 2010; Leppänen, 2006; Peckham et al., 2010). Importantly, analog to behavioral findings of emotional recognition deficits, SVR-LSM further revealed that lesions of an emotion processing network, including inferior and middle frontal regions and insula and parts of basal ganglia, were associated with these deficits. Generally, our findings suggest that behavioral, psychological, and neural aspects after stroke are potential risk factors for developing and maintaining PSD.

Emotion recognition

We found that stroke patients showed worse overall recognition accuracy compared to controls. This finding supports previous literature on emotion recognition of facial emotion

expressions in stroke patients (Abbott et al., 2014; Aben et al., 2020; Adams et al., 2019; Luo et al., 2022; Yuvaraj et al., 2013). After stroke, cognitive functions such as executive dysfunction, attention, processing speed, and visuospatial functioning are frequently disrupted (Hachinski et al., 2006; Nys et al., 2007). Impairments in emotional or social recognition often accompany cognitive dysfunctions (Aben et al., 2020). Although it is well established that impaired emotion recognition and processing are important predictors of rehabilitation outcome and quality of life after stroke (Blonder et al., 2012; Cooper et al., 2013; Dombovy et al., 1986; Langer et al., 1998; Yeates et al., 2016), as well as markers of depression (Bourke et al., 2010), these are frequently not detected by clinicians (Henry et al., 2015). This might be due to the unawareness of clinicians and the patient's inability for introspection, but impairments could also be too subtle to notice (Aben et al., 2020; Henry et al., 2015; Spikman et al., 2013). Therefore, examining patients regarding potential impairments in emotional recognition and social dysfunction is important in clinical practice. Acknowledging neural correlates of emotional recognition deficits can facilitate the consideration of early interventions such as medication treatment, social skills training, psychotherapy, and psychoeducation.

Negative attentional bias in PSD

Our findings demonstrated a negative attentional bias in more depressed stroke patients, especially regarding the emotions of anger and sadness. Precisely, higher depression induced a stronger reactivity towards angry persons. This result aligns with findings that MD patients showed stronger emotional responses to an expression of rejection (i.e., mood-eliciting cues) (Domes et al., 2016; Leyman et al., 2007; Woody et al., 2016). Furthermore, the response was facilitated for sadness in more depressed stroke patients, which is well in line with previous literature showing that MD patients are more prone to mood-congruent cues, representing someone's congruent emotional state (Bomfim et al., 2019; Surguladze et al., 2004; Van Vleet et al., 2019). Our findings suggest that attentional bias in emotion processing may be a characteristic feature of PSD similar to MD. Interestingly, these findings of a negative attentional bias were stable at the chronic stage post-stroke.

Montagne et al. (2007) demonstrated in a facial emotion recognition task with different emotion intensity levels that chronic stroke patients (> 5.5 months post-stroke) with depressive symptoms showed lower accuracy than stroke patients without depressive symptoms in recognizing the emotions anger, disgust, happiness, and sadness. Furthermore, stroke patients with depressive symptoms require more intense emotions to correctly recognize anger, sadness, and happiness. In contrast, we found a lower emotion threshold to accurately respond to sad

emotions in more depressed patients. Another study assessed individuals with subthreshold depression (i.e., significant depressive symptoms not fulfilling the diagnostic criteria for depression) and healthy controls using a recognition task with faces distorted by different levels of visual noise (Mei et al., 2020). The study found that individuals with depressive symptoms showed lower recognition thresholds for sad faces (i.e., more effective discrimination of images with higher visual noise intensity) than controls. Importantly, this finding was observed two months later, too, and individuals with lower recognition thresholds for sadness were less likely to show improvements in depressive symptoms at follow-up. As the sample in our study showed, on average, only mild depressive symptoms, too, the recognition of subtle sad emotions might be a tipping point in developing and maintaining depression.

Importantly, PSD symptoms early after stroke may also represent an adjustment to the critical life event than a depressive disorder. Nevertheless, the attentional bias towards mood-congruent and mood-eliciting cues may result in socially negative interactions that maintain depression, as postulated by the interpersonal theory of depression (Coyne, 2016). This theory suggests that people's communication, even with mild depressive symptoms, seeks excessive demands and causes rejection of other people. Studies have shown that in this vicious cycle, negative emotions can be promoted by negative interpersonal relationships and by increasing feelings of loneliness and helplessness (D'Angelo & Wiekzbicki, 2003; Hames et al., 2013; Joiner, 1994; Joiner et al., 1992). In our sample, the presentation of mood-eliciting and mood-congruent faces, respectively, might induce interpersonal feedback seeking in patients with a higher proneness to PSD.

Furthermore, the over-processing of negatively valenced emotional cues is in line with the reinforcement model of depression (Lewinsohn, 1974). This theory postulates that depression arises and preserves due to insufficient reinforcement directly associated with a behavior, which may further increase the experience of learned helplessness (Seligman, 1972). Due to the expected lack of positive reinforcers after stroke and vast negative reinforcers (e.g., motor impairment or cognitive deficits), the extinction of positive behavior occurs, and an attentional bias towards negative cues manifests (Lewinsohn, 1974). This results in an increased reactivity to negative emotional cues (i.e., mood-eliciting and mood-congruent). Overall, these behavioral results prove that psychological processes rather than the biological consequences of the stroke contribute to PSD. Furthermore, the SVR-LSM approach unraveled some biological causes that may contribute to worse emotion processing.

Lesion-symptom mapping of the recognition accuracy

A worse recognition accuracy of happy, sad, and fearful faces after stroke could be observed in the emotion recognition task (Figure 2) and in the SVR-LSM analyses, where deficits in recognition accuracy were associated with distinct lesioned brain areas (Figure 6). Results indicated that emotion recognition depended predominantly on the right-hemispheric frontal and insular regions and the putamen. Moreover, distinct emotion categories were linked to certain brain regions and emotion-overlapping regions, including brain regions involved in overall recognition capabilities. Significant overlapping regions included the frontal pole, IFG, and MFG (related to overall emotion recognition, including happiness, sadness, and fear), the putamen (related to happiness and fear), and the insula (happiness, fear). The more anterior part of the insula, as well as the OFC and frontal operculum, were related to poorer happiness recognition, whereas the posterior insula and the Rolandic operculum were related to fear recognition. As our results showed that poorer overall recognition accuracy of emotions highly overlapped with lesion-symptom associations for specific emotions, we likely revealed parts of an emotion-processing network. This network consists of a distributed network with reciprocal interactions between cortical and subcortical regions, including occipito-temporal cortices for perceptual face representations, as well as amygdala, hippocampus, OFC, basal ganglia, insula, cingulum, striatum, and somatosensory cortex for representing the emotional value (Leppänen, 2006; Palomero-Gallagher & Amunts, 2022; Pessoa & Adolphs, 2010). Especially the insula is suggested to play a major role in processing socio-emotional stimuli (Harrison et al., 2010; Kurth et al., 2010; Phillips et al., 1998). It has many interconnections with other brain structures, such as frontal cortex areas and subcortical structures, including the amygdala (A. Damasio, 2003; Gasquoine, 2014). A structural MRI study by Tippett et al. (2018) observed that acute stroke patients with lesions in the right amygdala or right anterior insula performed significantly worse in happy and angry facial emotion recognition than patients with other lesion locations. As it is suggested that emotional impressions are represented in the insula (Craig, 2009; Phan et al., 2002), our results support the view that lesions to insular regions are accompanied by distorted emotion recognition.

To our knowledge, this is the first study using a multivariate voxel-based lesion-symptom mapping approach to examine emotion recognition of dynamic emotional stimuli in early-stage stroke patients. A recent large-scale study investigating subacute and chronic ischemic stroke patients used a multivariate lesion-symptom method, too, and identified recognition accuracy deficits in anger, happiness, sadness, and disgust to be related to fronto-temporal regions, including the insula, Rolandic operculum, and putamen (van den Berg et al.,

2021). In our sample, we observed a poorer recognition of sad faces related to frontal regions, including the frontal pole, IFG, and MFG. Van den Berg et al. (2021) also identified a poorer recognition of sadness as exclusively associated with the IFG. Likewise, a fMRI study observed cortical hyperactivity (medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC)) in patients with anxiety disorder when confronted with sad faces compared to controls (Labuschagne et al., 2012). Interestingly, this exaggerated regional activity was attenuated after oxytocin. Also, damage to the right mPFC, ACC, and temporal areas, including IFG and MFG, was related to a worse ability to recognize negative emotions in traumatic brain injury patients (Dal Monte et al., 2013). Together with our findings, this suggests that specifically frontal cortical areas might play a key role in processing sadness. As we found PSD is related to altered processing of sadness, too, it is likely that an interplay of frontal lesions, depressive symptoms, and mood-congruent emotional processing might affect each other and facilitate the development and persistence of PSD. Furthermore, negative attentional bias of facial recognition in healthy and depressed populations is associated with rumination tendencies involving repetitive thinking about negative feelings and their consequences (Owens & Gibb, 2016; Raes et al., 2006; Suslow et al., 2019), while rumination in depression is further related to altered frontal activation and volume encompassing IFG, cingulum, PFC, and OFC (Burkhouse et al., 2017; Cooney et al., 2010; Kühn et al., 2012). Our results demonstrate recognition deficits of sadness showed lesion-symptom associations in frontal regions only, suggesting that altered processing of sadness might influence rumination predispositions, potentially exacerbating depressive states.

In contrast to van den Berg et al. (2021), we found a worse fear recognition related to lesions in the posterior insula. Likewise, in a PET study, fear processing in healthy controls induced a decreased activation in the posterior insula (Damasio et al., 2000). While broad literature and early studies reported the amygdala to be crucial in the processing and recognition of fearful faces (Adolphs et al., 1995; McFadyen et al., 2019; Morris et al., 1996), we did not identify such a lesion-symptom association. This might be because our lesion coverage in the sample was too little to assess the potential effects of an amygdala lesion on facial recognition abilities (van den Berg et al., 2021).

Our SVR-LSM results showed lesion-symptom associations between recognition accuracy and damaged voxels in the RH only, regardless of emotion category. Although lateralization in emotion processing remains a topic of debate, a large meta-analysis found evidence for the right lateralization, especially for facial stimuli (Yuvaraj et al., 2013). Yet, our results must be interpreted cautiously, as lesion coverage was lower in the left hemisphere

(Figure 3). This might be because left-hemispheric strokes can induce severe aphasia, which was an exclusion criterion for our study. Overall, our important SVR-LSM findings extend the literature on neural correlates of emotional face recognition in stroke patients, especially on studies using multivariate lesion-symptom approaches. According to our findings regarding emotional processing, it seems likely that a combination and interconnection of psychosocial (worse emotional responsiveness and negative attention bias) and neural factors play a role in the pathophysiology of PSD. Further research should aim at disentangling the effects of both parameters (depression and stroke lesion network) on emotional processing. This would give important insights into therapeutic approaches regarding social interactions and emotional bonding for stroke patients, especially in the acute stage after stroke.

Conclusion

The findings extend previous literature on behavioral and neural aspects of PSD. Depression after stroke facilitates processing socially negative valenced emotional stimuli, thus suggesting a proneness to a mood-congruent and mood-eliciting emotion processing in PSD. As negative attentional bias maintains depressive symptoms and deteriorates rehabilitation, interventions, and therapies after stroke, one should aim at stabilizing socio-emotional networks and coping strategies. Additionally, we identified an emotional-processing network including the insula as well as inferior and middle frontal regions and parts of basal ganglia related to deficits in the recognition of distinct emotions. Our findings yield important insights into how lesions in certain brain regions early after stroke can selectively affect the recognition abilities of particular emotions. These may, in turn, promote specific behavioral disturbances (e.g., depressive symptoms and negative attentional bias), which should be investigated in future studies on lesion-symptom mapping and PSD.

Funding & Acknowledgements

This research work has been funded by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, grant number: 310098283). We thank Christian Bordin for providing a script to pseudo-randomize the experimental trials in the task design.

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Supplementary material

Design of the dynamic face stimuli

For the emotion processing task as well as the intensity rating, dynamic face stimuli of different intensities were designed using the static pictures from the FACES database, Center for Lifespan Psychology, Max Planck Institute for Human Development, Berlin, Germany (Ebner et al., 2010; Holland et al., 2019). We selected four model stimuli (2 females) from 'Dataset A,' showing the facial expression of happiness, sadness, anger, fear, and a neutral expression. For this study, we morphed the stimuli out of the static images to create a video presenting an evolving facial emotional expression using the software MorphAge (v5.0.3) for MacOS. Morphing the stimuli was done as described in the manuscript, and similarly to the creation of the Dynamic FACES, an extension of the original FACES database and validated by 1822 raters (Holland et al. 2018). MorphAge software allows the use of two input pictures to create a transition between these static images. For a smooth transition of the images and a realistic emotional evolvement, sufficient corresponding points in both images outlining the head and curves of the faces need to be set. The neutral facial expression and the final expression (e.g., happiness at 100% intensity) were used to create the morph. Different intensities of each facial expression were created by terminating the transition at 20%, 40%, 60%, and 100%. For example, 20% intensity would mean the final image consists of 80% of the neutral image and 20% of the target facial expression. Videos of facial expressions in different intensities (4 models x 4 emotions x 5 intensities + 4 x neutral expressions) were rendered to 2048 x 2560 pixels with a frame rate of 30 fps.

Subjective intensity rating of emotional stimuli

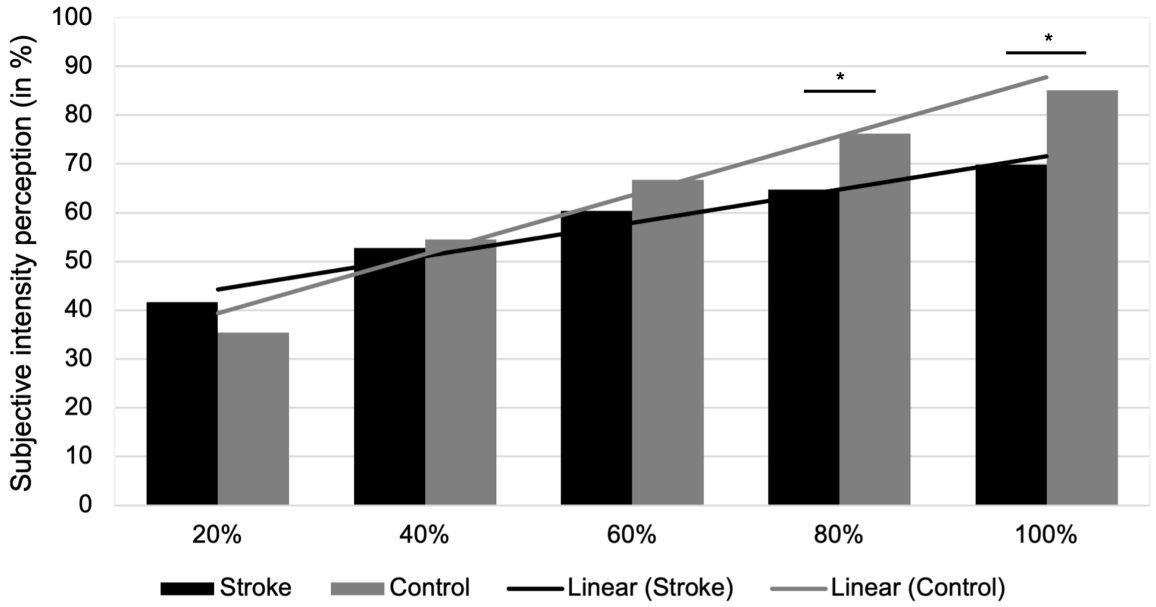
Furthermore, we investigated the participant's subjective perception of the emotional intensity of provided stimuli (explicit perception). Thus, participants were presented with the facial expression videos again and were asked to rate the self-perceived intensity of each stimulus' expression on a visual-analogue scale (VAS) from 0 ('not intensive at all') to 10 ('very intensive'). Importantly, the specific emotion was not important here, but to indicate the individual perceived intensity. These subjective intensity ratings aimed to obtain a more explicit perception of the emotional stimuli than rather implicit perception parameters (i.e., recognition accuracy, relative response time) during the emotion processing task. The subjective intensity rating data were processed using SPSS 28 (IBM Corp, Armonk, NY, USA). Dependent variables, including information about emotion category (EMOTION) and intensity level

(INTENSITY), were created similarly to the emotion recognition accuracy and response times variables. Neutral stimuli did not include any intensity levels. Subjective intensity rating scores were analyzed using mixed-design ANOVA and Bonferroni-corrected post-hoc t-tests with the within-subject factors EMOTION (happy, sad, angry, fearful) and INTENSITY (20%, 40%, 60%, 80%, 100%) and the between-subject factor GROUP including stroke patients and controls.

We observed a significant interaction between INTENSITY and GROUP ($F_{1,52}$= 11.378, $p < 0.001$, η_p^2= 0.180), showing that stroke patients perceived facial expressions in higher intensities as less intense compared to controls (80% intensity: $F_{1,52}$= 11.134, $p = 0.002$, η_p^2= 0.176; 100% intensity: $F_{1,52}$= 20.072, $p < 0.001$, η_p^2= 0.279) (Figure 4). Supplementary Figure 1 illustrates that patients perceive emotions with increasing intensity as subjectively less intense than healthy controls. GROUP had no main effect ($F_{1,52}$= 2.774, $p = 0.102$) nor an interaction with EMOTION ($F_{1,52}$= 1.706, $p = 0.187$).

Since stroke patients perceived emotions with medium to high intensities as less intense than healthy controls, it is likely that the presence of the stroke possibly led to this lower subjective intensity perception at higher intensity levels, as there was no association between depressive symptomatology (MADRS) and subjective intensity perception (across all intensity categories per emotion) in patients (all $p > 0.142$). Moreover, situational circumstances could have also contributed to lower intensity perception in stroke patients. In fact, from an investigator's perspective, stroke patients' affect appeared to be flattened, and they tried to suppress emotional outbursts. This could be because they were processing the life-changing experience and their physical impairment. They seemed to have a general feeling of shame, potentially because they depended on other people's help and were bedridden.

Supplementary Figure 1: Subjective intensity perception (in %) of stroke patients and controls over all four emotion categories for each intensity. When confronted with emotions of higher intensities (80% and 100% - regardless of emotion), stroke patients perceived the respective emotions as more intense than controls.

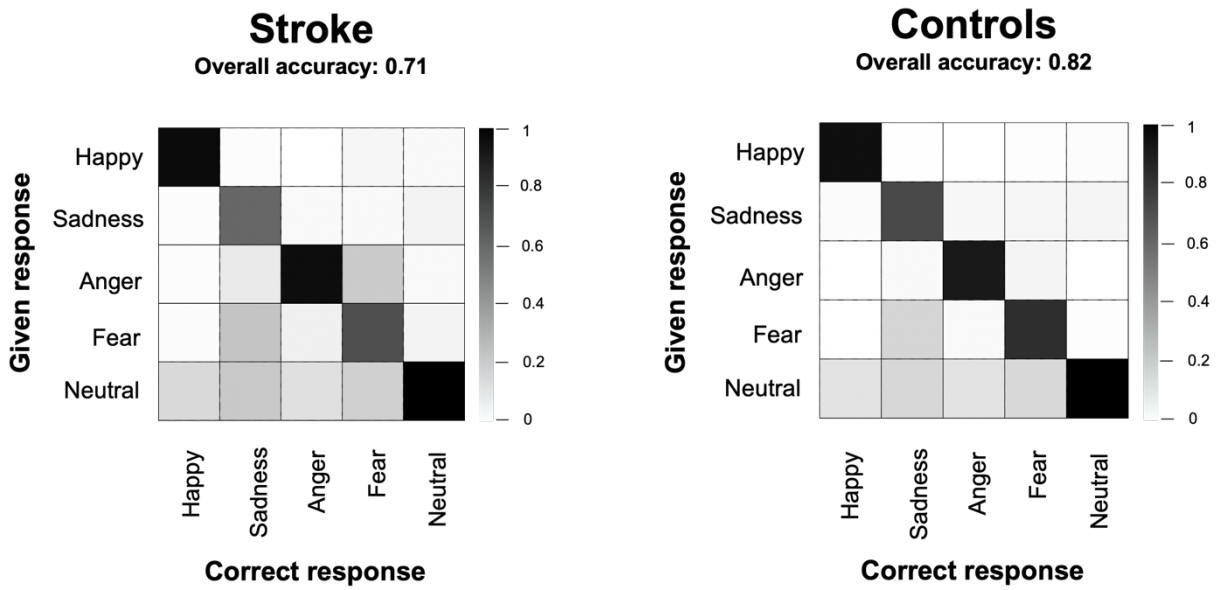


Error types

Moreover, we computed confusion matrices to illustrate the type of mistakes made during emotion recognition. These indicate an accuracy score of how participants responded to each emotion and thus display which emotion categories were mistaken for which other emotion categories. To test mood-congruent response performance within the stroke subgroup, we correlated the accuracy scores of confusing neutral face stimuli with sad or angry emotion responses and the depressive symptomatology (MADRS score). Likewise, the accuracy scores of confusing happy face stimuli with neutral emotion responses and the MADRS score.

Importantly, stroke patients had a higher proportion of responses off the diagonal, indicating lower overall accuracy. Of note, there were no correlations between depressive symptomatology (MADRS score) and the number of confused answers of neutral face stimuli to another given emotion response, e.g., sad or angry emotion response, according to the mood congruency hypothesis. Furthermore, no correlations existed between the MADRS score and the number of confused answers of happy face stimuli to neutral given responses.

Supplementary Figure 2: Confusion matrices of the emotion recognition accuracy for stroke patients and controls separately. Darker black on the diagonal axis indicates higher accuracy, while darker black off the diagonal indicates errors (0 equals 0% of responses, 1 equals 100%). Plots reveal that stroke patients and control subjects made similar mistakes (i.e., mislabeling sadness as fear), but overall performance was worse for patients (stroke patients = 0.71 accuracy: controls = 0.82 accuracy).



Additional mixed model ANOVA results

Supplementary Table 1: Results of the mixed design ANOVA analyses for emotion recognition accuracy, response times, and the subjective intensity rating scores. The * marks significant effects at a 0.05 significance level.

2 (group) x 4 (emotions) x 5 (intensity) mixed-design ANOVA						
	Recognition accuracy		Response Time		Subjective intensity rating	
	F	p	F	p	F	p
Main effects						
Group	12.110	**0.001***	2.149	0.149	2.774	0.102
Emotion	37.674	**<0.001***	32.020	**<0.001***	14.490	**<0.001***
Intensity	330.768	**<0.001***	43.949	**<0.001***	147.609	**<0.001***
Two-way interactions						
Group x emotion	3.309	**0.030***	0.634	0.580	1.706	0.187
Group x intensity	0.543	0.622	0.706	0.483	11.378	**<0.001***
Emotion x intensity	1.644	0.130	8.721	**<0.001***	2.191	**0.027***
Three-way interactions						
Group x emotion x intensity	3.440	**0.002***	2.933	**0.003***	1.125	0.345

Three-way interactions

For the accuracy of emotion recognition, we identified a significant three-way interaction where stroke patients recognized specific emotions in different intensity levels significantly worse than controls ($F_{1,52}$= 3.340, p = 0.002, η_p^2= 0.062). This effect was pronounced in the lowest intensity level of 20% in happy faces ($F_{1,52}$=4.903, p = 0.008, η_p^2= 0.127), and in low to middle intensity levels of sad expressions (20%: $F_{1,52}$= 4.261, p = 0.044, η_p^2= 0.076; 40%: $F_{1,52}$= 10.567, p = 0.002, η_p^2= 0.169; 60%: $F_{1,52}$= 4.931, p = 0.031, η_p^2= 0.086). This indicates that stroke patients needed higher intensity levels to correctly identify the emotional expressions of happy and sad faces. Furthermore, for fearful expressions stroke patients recognized the faces of all intensity levels worse than controls (40%: $F_{1,52}$= 5.722, p = 0.020, η_p^2= 0.099; 60%: $F_{1,52}$= 10.636, p = 0.002, η_p^2= 0.170; 80%: $F_{1,52}$= 14.183, p < 0.001, η_p^2= 0.214; 100%: $F_{1,52}$= 8.588, p = 0.005, η_p^2= 0.142), except for the 20% intensity level. There were no differences between intensity levels in angry expressions.

For response times, there was also a significant three-way interaction GROUP x EMOTION x INTENSITY ($F_{1,52}$= 2.933, p = 0.003, η_p^2= 0.053). Yet, regarding differences between groups for emotions in specific intensity levels, there was a difference only in angry

face stimuli with 40% intensity, in which stroke patients responded significantly slower than controls.

Sex differences

When analyzing the effect of sex per group for the task performance parameters, no significant differences could be found in the recognition accuracy (stroke patients: $F_{1,24} = 2.959$, $p = 0.098$; controls: $F_{1,26} = 0.805$, $p = 0.378$), response time (stroke patients: $F_{1,24} = 0.127$, $p = 0.724$; controls: $F_{1,26} = 0.001$, $p = 0.978$), and subjective intensity perception (stroke patients: $F_{1,24} = 1.066$, $p = 0.312$; controls: $F_{1,26} = 0.620$, $p = 0.438$) between female and male participants. Likewise, there were no interaction effects of EMOTION or INTENSITY with SEX for either of the task performance parameters.

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6. General discussion

The present thesis aims at improving our understanding of underlying psychological and neural mechanisms in post-stroke depression. Three studies investigated behavioral and neuroanatomical correlates of PSD and their significance for symptom specificity, motivational incentives, and socio-emotionally valenced cues. Thereby, we gained important insights into the emergence and development of PSD characteristics on different pathological levels. In this section, I will discuss the relevance of our study-specific findings, considering the existing literature and how these contribute to the general understanding of PSD. I will summarize each study's main findings and discuss their clinical implications. Furthermore, I will address the limitations of our studies, applied methods, and conclusions. Lastly, I will illustrate how unipolar depression and PSD research can complement each other and outline suggestions for future research in the field of PSD.

6.1 Discussion of key findings

6.1.1 Neuroanatomical substrates of distinct PSD symptoms

This study aimed to identify the neuroanatomical substrates of distinct PSD symptom domains, representing a heterogeneous clinical condition. Through a comprehensive analysis of clinical-empirical and data-driven evidence using a multivariate lesion-symptom mapping approach, five sub-clusters of symptom domains were identified (motivational, emotional, cognitive, somatic symptoms, and anxiety) and linked to specific lesion regions in the brain characterizing different functional brain networks.

Our findings emphasize that PSD is less related to the lateralization of the lesions than to a "depression network" of functionally specific and interrelated regions. In this context, lesions in specific cortical regions contribute to the manifestation of distinct symptoms. Notably, insula lesions are strongly associated with the development of somatic but also emotional and anxious symptoms of depression. This assigns a particular role to the insula in developing and maintaining depressive symptoms. For processing several kinds of socio-emotional stimuli, specifically, the anterior insula is an essential neural correlate (Chang et al., 2011; Harrison et al., 2010; Koelsch et al., 2006; Phillips et al., 1997; Sanfey et al., 2003; Wright et al., 2004). Furthermore, the posterior insula integrates interoceptive signals such as fatigue, hunger, pain, or sexual drive, linking them with emotionally salient information gradually represented by the anterior insula (Craig, 2009). Evidence indicates that these interoceptive sensations are disturbed in unipolar depressed patients (Paulus & Stein, 2010; Wiebking et al.,

2010). It is postulated that diminished insula activation, possibly mediated by connections with somatosensory regions within the parietal cortex, contributes to these disturbances (Avery et al., 2014; Nagai et al., 2007). Moreover, insular regions have been recognized as critical neural correlates in modulating anxious traits (Baur et al., 2013; Paulus & Stein, 2010). Notably, a study involving stroke patients with frontal brain lesions highlighted a strong link between structural insular abnormalities and heightened anxiety sensitivity (Shi et al., 2017). Thus, the insula is assigned a central involvement in stress and anxiety states linked to uncertain circumstances, exaggerated potential adverse outcomes, and risk-taking decision-making behavior (Critchley et al., 2001; Paulus et al., 2003; Sarinopoulos et al., 2010).

Furthermore, our neuroimaging findings provide support for the frontal-limbic model of depression (Lai, 2021; Pan et al., 2022a). This model postulates that frontal and limbic brain regions, including ACC, dlPFC, OFC, hippocampus, amygdala, thalamus, and caudate nucleus, are related to the top-down and bottom-up mechanisms in the emotion regulation processes. While depressed mood can be a typical response to adversity, individuals vulnerable to MDD are impaired in their ability to effectively regulate negative mood (Johnstone et al., 2007). Heightened emotional reactions and consequent depressive symptoms stem from changes in limbic regions such as the hippocampus and amygdala (Lai, 2021). Depressed individuals show increased amygdala activation in response to negative stimuli, leading to stronger connectivity between the amygdala and frontal regions, such as the ACC and dlPFC (bottom-up) (Johnstone et al., 2007; Lai, 2021). Frontal regions, such as the ACC and dlPFC, are involved in emotional regulation, cognitive control, and goal-directed behavior (top-down). ACC-dlPFC connectivity rises and regulates amygdala-driven emotions to resolve conflicts. Dysfunction of these top-down processes in response to the amygdala's elevated negativity is crucial in the pathogenesis of MDD (Johnstone et al., 2007; Lai, 2021). PSD-lesion associations provide insight into depression from a basic research perspective by serving as a lesion model. Hence, it can be inferred that affective symptoms are influenced by the dysfunction of the lesioned brain areas and may be addressed by psychopharmacological treatment.

From a clinical perspective, pharmacological treatments targeting specific neurotransmitters may improve affective symptoms associated with PSD. Generally, there is consensus that antidepressive medication can alleviate PSD symptoms (Chollet et al., 2011; Medeiros et al., 2020; Robinson & Jorge, 2016). For instance, selective serotonin reuptake inhibitors (SSRIs) may enhance motivation and mood, selective noradrenaline reuptake inhibitors (SNRIs) can be employed to address attention deficits (cognitive symptoms), and sedating neuroleptics can effectively target sleep disturbances, including insomnia. However,

various antidepressant medications vary in effectiveness for each patient, address distinct symptoms, and often require changes due to side effects (Medeiros et al., 2020). Importantly, there remains uncertainty regarding the side effects of antidepressants, including SNRIs, SSRIs, and tricyclic antidepressants (TCA), referring to the increased risk of recurring stroke. Some studies found that only TCAs increase the prevalence of second strokes (Wang et al., 2015). Others found a generally increased independent risk across different antidepressant medications (Juang et al., 2015; Trajkova et al., 2019). Finally, some studies reported no association, but SSRIs may even be protective for recurrent stroke (Alqdwah-Fattouh et al., 2022). Generally, the prescription of pharmacological medications should be well-considered based on the patient's specific circumstances and possible benefits (Medeiros et al., 2020; Robinson & Jorge, 2016).

Furthermore, stroke patients with lesions in the identified regions from our study results need appropriate psychological treatment to address the depressive symptomatology and enable participation in rehabilitative treatments. To achieve this, integrating specific psychological treatment components into physiotherapy may be an essential tool to improve functional outcomes and quality of life. Until today, the focus in rehabilitation settings remains on motor activation, including physiotherapy and speech training (Kuriakose & Xiao, 2020; Langhorne et al., 2011). To address the alleviation of specific depressive symptoms, strategies may include, for instance, discussions on sleep hygiene (Im et al., 2010) and structuring daily activities, validation of sad feelings, practicing affirmative exercises, psychoeducation, regulation of behaviors, activation of social support networks, and cognitive training based on cognitive-behavioral therapy (CBT) for depression (Medeiros et al., 2020; Starkstein & Hayhow, 2019). CBT addresses cognitive distortions, enhances coping skills, provides guidance on beneficial activities for improved functioning and symptom relief, and enhances emotional regulation. A meta-analysis by Wang et al. (2018) revealed that CBT, whether used alone or in conjunction with antidepressants, effectively alleviated PSD symptoms. Such tailored interventions can enhance the effectiveness of rehabilitation and promote overall well-being in affected individuals.

In summary, understanding the clinical implications of lesion lateralization and the central role of specific cortical regions in specific PSD symptom domains opens opportunities for personalized interventions that consider both psychological and pharmacological approaches. By implementing comprehensive treatment strategies, healthcare professionals can better support stroke patients with lesions in critical areas, ultimately improving their quality of life and promoting successful rehabilitation outcomes. Prospective research is warranted to

validate and refine these approaches and explore additional opportunities for effective PSD management.

6.1.2 The influence of incentive motivation on post-stroke depression

In study 2, we investigated, in a longitudinal design, whether interindividual differences in the motivational drive to engage in physically demanding tasks indicate PSD development in patients suffering from motor impairments. In this relatively simple experimental design of a monetary incentive grip force task, we identified that incentive motivation parameters are shown to be related to motor impairment and PSD symptoms in the early stage post-stroke. More specifically, patients with stronger motor impairments showed stronger motivation for reward-dependent motor engagement, whereas chronic motivational deficits were predicted by initially reduced incentive motivation and larger corticostriatal lesions in the early stage post-stroke.

Interestingly, in study 1, we found that pronounced motivational deficits were primarily related to damage in OFC, dlPFC, pre- and postcentral gyrus, and basal ganglia, including putamen and pallidum. As described in the paper, these regions constitute the human cortico-striatal reward network, which subserves incentive motivational behavior by transforming motivations and cognitions into actions (Haber, 2016). This motivational system can further be differentiated into ventral and dorsal cortico-striatal tracts, organized by reciprocal loops to translate motivations into actions, regulate emotions, and mediate goal-directed behavior (Draganski et al., 2008). Although study 1 and study 2 comprise distinct study approaches, it seems crucial to note that the findings from the incentive grip force task fit well with the SVR-LSM results. First, similar responsible brain regions were identified in two different lesion models to describe neural involvements of motivational aspects in PSD, i.e., the drive to physically engage in tasks for a reward. Second, it underlines the importance of viewing symptoms of post-stroke depression in a more differentiated manner, in the sense of specific sub-symptoms. In study 2, corticostriatal lesions were particularly linked to motivational deficits. Moreover, when examining PSD sub-symptoms in study 1, including motivational deficits, we found a more differential neural pattern compared to using the global depression sum score. This allows narrowed therapeutic interventions for motivational deficits specifically, enhancing rehabilitation outcomes.

Importantly, the brain regions within these networks describe effects on affective and motor levels. The corticospinal tract is responsible for voluntary motor function and projects from frontoparietal cortical regions, including the primary and secondary motor cortex, and

somatosensory cortex, via the midbrain, including the internal capsule and cerebral peduncles to the brainstem and the spinal cord (Jang, 2014). This demonstrates structural and functional overlaps and interactions between corticostriatal and corticospinal loops. Thus, motivational depressive symptoms are closely linked to motor volition (Schmidt et al., 2008; Widmer et al., 2019), compared to other symptoms of depression, e.g., cognitive or somatic symptoms. We observed that lesions in the corticostriatal tracts induce reduced motivation in physical engagement for incentives. It may be the case that patients with lesions in corresponding regions are not only impaired in their motivation but also their motor engagement (e.g., JTT score). For instance, antidepressant therapy improves mood and enhances motor recovery post-stroke (Chollet et al., 2011; Gainotti et al., 2001; Mikami et al., 2011). Even in non-stroke-related major depression, connections between affective and motor systems can be observed (Sobin & Sackeim, 1997; Walther et al., 2012). Therefore, motor retardation is reported to be a core symptom in the presence of severe major depression. Integrating these systems offers insight into novel treatments, e.g., such as integrating motivation-enhancing features into motor rehabilitation therapies.

6.1.3 Emotional-attentional bias and neuroanatomical substrates after stroke

Study 3 dealt with emotion processing abilities and how PSD influences these in an emotion recognition task. Using the same lesion-symptom mapping toolbox as in study 1, the association between structural brain lesions and specific emotion recognition deficits was further investigated. Particularly, we observed that stroke patients showed an overall impairment in emotional recognition accuracy, while PSD specifically facilitates the processing of negative emotional stimuli (i.e., angry and sad faces). We further identified that recognition accuracy of distinct emotions was linked to brain lesions in an emotion-related processing network, including fronto-cortical and insular regions. In this study specifically, we provide support for psychosocial and neural factors underlying altered emotion processing after stroke, thus contributing to the pathophysiology of PSD.

It is important to notice that disrupted social and emotional processing abilities are important markers for dysfunctional social interactions and interpersonal networks, thereby facilitating the development of depressive symptoms (Bourke et al., 2010). Most post-stroke behavioral or character changes result from impaired emotional and social cognition, i.e., the perception, processing, and interpretation of socially valenced information (Henry et al., 2015; Nijsse et al., 2019a). This also contributes to higher caregiver burden and distress (Luker et al., 2017; Schönberger et al., 2010). Attending to these changes and recognizing post-stroke social

cognitive deficits could offer caregivers tools to effectively cope with their partner's challenges, possibly through interventions like psychoeducation and training (Kootker et al., 2019). Furthermore, compensatory training exists for impairments in emotional recognition and social interactions, which can be effectively applied to patients (Westerhof-Evers et al., 2019). For instance, this training includes exercises like perspective taking, asking others about their thoughts and feelings, bodily language, listening, the reflection of feelings, irritability, and anger management, coping with conflicts, social reasoning, role play, and feedback counseling (Westerhof-Evers et al., 2019).

In the SVR-LSM analysis of study 1, the emotional symptom domain was described and categorized by the MADRS items' apparent sadness' and 'reported sadness' and was linked to depressed mood, helplessness, gloom, and despair. Faces displaying 'sadness' in the emotion processing task simulate mood-congruent stimuli, which correspond to the emotion symptoms domain, including the 'sadness' of study 1. In study 1, sadness related to lesions in the anterior-ventral insula, thalamus, and post-central gyrus. In study 3, poorer sadness recognition involved only frontal regions (IFG, MFG, and frontal pole). However, as both studies examine different underlying measures/dependent variables, i.e., emotional symptoms/sadness and recognition accuracy of sad faces, the specific outcomes are not well comparable. Also, in study 3, we could not separate the influence of depressive symptoms on facial recognition accuracy, which should be disentangled in further studies. Nevertheless, both studies contribute to our understanding of a larger emotion processing network in stroke patients. Overall recognition accuracy in study 3 was linked to insular regions, too, suggesting a representation of the underlying emotional state.

6.2 Influence of underlying psychological and neurological mechanisms on post-stroke depression

The development of PSD and the underlying risk factors are still under considerable debate. For predicting PSD, functional impairment, stroke severity, history of depression, psychosocial support, and cognitive impairment have been well-recognized as risk factors (Robinson & Jorge, 2016; Towfighi et al., 2017). Regarding the crucial question of whether PSD is a mere "reactive" psychological adjustment or whether there is a brain-organic contribution, our study findings provide clear evidence of neural involvement. In all three studies, we performed lesion analyses to investigate lesion-symptom relationships of different behaviors of interest, where we observed several significant findings. On the other hand, we could not observe significant associations between increased depression (e.g., MADRS score)

and stroke severity (e.g., NIHSS score) or functional impairment (e.g., JTT score). Thus, contrary to some literature findings (Berg et al., 2003; Kauhanen et al., 1999; Ng et al., 1995; Nys et al., 2005; Robinson & Jorge, 2016; Singh et al., 2000), we found fewer indications for psychological-caused PSD in the sense of an adjustment deficit due to restrictions in patients' everyday life like walking disabilities or language difficulties. We could suggest rather neural causes of PSD, including functional and structural network disruptions, probably causing, for instance, pathophysiological disturbances like monoamine depletion.

Nonetheless, it must be noted that in study 1, we identified a non-significant trend between elevated depression symptoms and stroke severity. Furthermore, as a psychological measure of motivation, we also found that stroke patients with greater motor impairment maximized their monetary outcome by preserving their grip force for high versus low reward trials, thus showing a higher incentive motivation. This seems contrary at first glance because this motivational state may represent an adaptive coping strategy considering that task difficulty of holding one's grip force is increased given restricted physical abilities. Thus, one could argue that increased motor impairment induced a protective feature for motivational symptoms of depression. Interestingly, this initially increased incentive motivation led to less motivational deficits in the MADRS in later stages post-stroke.

Furthermore, our observations regarding fewer psychological correlates of PSD must be handled with caution due to several aspects. First, in study 2, we focused on motivational symptoms of depression only. Other symptom domains, such as those specified in study 1, were not examined and thus neglected in the analyses and discussions. Second, it was not the main scope of our studies to compare several neural and psychological underpinnings or predictive values of PSD. In other words, we did not perform a model to find out whether, e.g., lesion location, lesion disconnection, stroke severity, functional impairment, history of depression, other clinical-demographic variables, psychosocial support, or cognitive impairment do better predict the development of PSD. In studies 2 and 3, we observed rather specific psychological measures via behavioral experiments, i.e., incentive motivation, selective-attentional bias, and emotional processing, and identified significant associations with PSD. Yet, important general demographic or psychosocial factors, such as social networks, living situation, quality of life, personal life values and needs, aspects of resilience, rumination vulnerability, coping strategies, and premorbid personality traits, potentially predicting PSD in our patient sample were not assessed or not specifically the study focus.

Third, in studies 1 and 2, we only examined functional impairments of stroke patients in the early-stage post-stroke. Several studies observed associations between functional

impairment and depression in later stages post-stroke, i.e., >4 weeks to months after stroke onset (Amaricai & Poenaru, 2016; Astuti et al., 2020; Herrmann et al., 1998; Singh et al., 2000). Hackett & Pickles (2014) found that PSD symptoms peak at >3 months post-stroke. In the early-stage post-stroke and during hospitalization, the assessment of the relationship between depression or symptom domains and functional impairment may be too blurred in our samples. Many patients participated in early rehabilitation programs and were embedded in frequent multidisciplinary therapies. Functionally impaired patients may develop increased PSD symptoms, for instance, after discharge when confronted with impairments and drawbacks in their everyday lives. Nevertheless, in study 3, we examined stroke patients in the early and chronic stages (>3 months) post-stroke and found no effect of functional impairment on increased depressive symptoms.

Fourth, some evidence suggests that neural correlates of PSD change over time. In a longitudinal study, acute-stage PSD correlated with left anterior lesions (Åström et al., 1993), while longer-term follow-up saw a shift toward right hemisphere involvement. Shimoda & Robinson (1999) reported hospital stay depression linked to left anterior lesions and 1-2-year post-stroke depression associated with right hemisphere lesion volume. A meta-analysis noted an association between PSD and right hemispheric stroke, mainly during subacute stroke (Wei et al., 2015). These findings suggest evolving neuroanatomic underpinnings or diverse PSD mechanisms across stroke stages (Åström et al., 1993; Shimoda & Robinson, 1999).

Fifth, in contrast to the large and more representative patient cohort in study 1, our behavioral studies (studies 2 and 3) focused on a well-defined cohort of stroke patients. Our inclusion criteria dictated the enrollment of subjects exhibiting a substantial impairment, necessitating a minimum hospitalization duration of several days to ensure their participation in the study. We had to balance this requirement by ensuring the patients were not overly impaired, allowing them to effectively engage in the cognitively and physically demanding experiments. This specific patient cohort might be too narrowly selected to allow conclusions about the general stroke population regarding the influence of functional impairment on PSD.

As mentioned earlier, it is important to note that there are no simple mechanisms to explain the development and maintenance of PSD, but several factors interact. Various psychological concepts, for instance, resilience resources, premorbid personality traits, coping strategies, as well as learned schemes and assumptions, influence how patients deal with the burden of a stroke. Supporting a positive dealing with these behavioral patterns is an important component of psychotherapy. A vital concept is the salutogenesis model, developed by Aaron Antonovsky (Antonovsky, 1997). It focuses on factors that promote health and well-being

rather than addressing the disease and impairments. In stroke rehabilitation and PSD treatment, the salutogenesis model can highlight the significance of identifying and reinforcing an individual's strengths, resources, and coping abilities. It underlines the sense of coherence, which consists of three components: comprehensibility, manageability, and meaningfulness. Comprehensibility should enable stroke patients to understand their condition better, including the causes and potential effects of stroke and PSD. Providing clear information about these aspects can motivate patients to actively engage in their rehabilitation. Manageability emphasizes enabling patients to effectively handle recovery challenges by setting achievable goals and involving them in care decisions. Encouraging self-efficacy and self-management may enhance the sense of manageability. Meaningfulness emphasizes finding purpose and significance in life despite health challenges. Finding purpose and significance in one's experiences can enhance overall well-being. For instance, setting personalized life goals, peer mentoring, and counseling can help individuals cope with emotional challenges and regain a sense of meaningfulness in their lives post-stroke, reducing the risk of PSD. Overall, by applying the salutogenesis model, stroke rehabilitation seeks to restore function and improve overall well-being and quality of life during the recovery process.

Another important theoretical framework is the vulnerability-stress model, which suggests that psychological disorders arise from the interaction between individual vulnerabilities and external stressors (Demke, 2022; Zubin & Spring, 1977). Regarding the development and maintenance of PSD, several factors serve as vulnerabilities, such as neural predispositions and dysfunctional coping strategies (Stuller et al., 2012), while life events like the stroke itself are external stressors. Neural vulnerabilities can, for instance, pertain to brain characteristics, which can make individuals susceptible to distress. For instance, a history of mood disorders, neurobiological traits, or psychopathological mechanisms that heighten the experience of negative emotions could increase the risk of PSD. Another set of vulnerabilities involves the individual's cognitive and behavioral coping strategies. Some individuals may have maladaptive ways of coping with stress or adversity, such as rumination (repetitive negative thinking), conditioned avoidance, and social withdrawal (Girard et al., 2014; Leventhal, 2008; Nolen-Hoeksema et al., 2008). In the context of PSD, these dysfunctional coping strategies can contribute to depression and hinder effective adjustment when faced with the stress of stroke-related challenges. A stroke is a traumatic event that disrupts physical and emotional well-being. It causes functional impairments like motor deficits and communication challenges, often resulting in a loss of independence. Moreover, it introduces emotional stressors, including facing mortality, altered self-identity, and the need for rehabilitation. These stressors can trigger

depressive symptoms, especially when coupled with preexisting vulnerabilities. Thus, the stroke event acts as a catalyst, amplifying these vulnerabilities and heightening susceptibility to depression. As mentioned earlier, psychoeducational training, activation of support networks, and CBT are important applications to address the psychological burden induced by these vulnerabilities and stressors.

Overall, viewing PSD in the framework of a vulnerability-stress model can explain the interplay between functional impairment after stroke, history of depression, (pre-)existing psychosocial support, and cognitive and behavioral coping mechanisms. This model also highlights the importance of considering both individual characteristics and life events in assessing and treating PSD, emphasizing the need for personalized interventions.

6.3 Limitations of studies and applied methods

The presented studies have some methodological limitations. Some aspects have already been discussed in the study-specific empirical section. Here, I resume the most relevant limitations. The first limitation pertains to the relatively small sample size of studies 2 and 3. Especially in study 2, the sample constituted twenty stroke patients, while only twelve patients examined in the follow-up assessment had anatomical MRI scans available. To some extent, this diminishes the generalizability and allows only preliminary interpretation of the findings, as the results may be underpowered. Furthermore, it was not feasible to conduct SVR-LSM analyses with n = 12 patients (n = 14 at early-stage), as the sample size was too small to obtain reliable lesion-symptom associations from multivariate random-permutation testing. Performing a correlational analysis of structural lesion overlaps with the cortico-striatal tracts from the Human Connectome Project database (Yeh et al., 2018) provided a compromise to obtain neural data. Thus, the structural neural analysis level is certainly lower than the multivariate VLSM.

Besides, recruiting acute stroke patients with residual hand motor function for study 2 was quite challenging, as patients were required to be impaired but not overly impaired, as they must engage in a cognitively and physically demanding task. Therefore, the assessment period took a long time, including several drop-outs. This limitation also applies to the recruitment phase of study 3 (n = 26); however, the inclusion criteria of requiring hand motor impairment were not applicable in this case. Furthermore, it must be noted that the enrollment of patients in studies 2 and 3, in the early and later stages, was heavily impacted and restricted by the COVID-19 pandemic and associated safety and health regulations in the hospital. Especially

for study 2, we could not perform a second assessment of the monetary-incentive grip force task or functional deficits due to the current restrictions for in-house patient invitations.

Further, regarding the relevance of sufficient sample sizes, even in the large-scale SVR-LSM analyses of study 1, no lesions, for instance, in the cingulate gyrus and medial PFC were integrated into the model due to insufficient lesion overlap. These regions constitute important correlates in depression research (Ebert & Ebmeier, 1996; Lemogne et al., 2012). Recently, Weaver, Kuijf, et al. (2021) examined a sample of about n = 3000 stroke patients and reached a coverage of 86% of total brain voxels. Thus, our study cannot provide evidence for the association between rare lesions and depression. Nevertheless, very large datasets are needed to exhibit lesion-symptom associations, which requires multicenter cooperation and extensive personal, infrastructural, financial, temporal, and technical resources.

Another important limitation pertains to the assessment of stroke severity or functional impairment. We mainly used the NIHSS to examine stroke-related deficits for our neuropsychological test batteries. The NIHSS score may not represent an ideal scale to depict functional impairment as it is a rather global measure using an ordinal scale, not capturing subtle deficits (Brott et al., 1989). Additionally, the test includes a wide range of potential symptoms and conditions after stroke that are irrelevant to our inclusion criteria and subsequent analyses as, for example, level of consciousness, field of vision, and neglect. Therefore, more relevant and subtle symptoms such as motor impairment or aphasia, which are often found to be related to PSD (Medeiros et al., 2020; Robinson & Jorge, 2016; Singh et al., 2000), may be underrepresented for our study purposes.

Furthermore, the JTT focuses on motor impairment only and is an interval-scaled measure. Yet, it might be susceptible to not detecting compensation strategies. As the test battery is based on speed measurement and not motor precision, one cannot correct whether a patient uses, e.g., the arm or the shoulder to fulfill a task. Thus, a patient with severe distal hand motor impairment applying proximal compensation strategies may score higher than someone with a similar or less severe impairment.

Moreover, we could not assess the premorbid depressive status of the patients in our studies. Although we excluded clinically diagnosed depression or other psychiatric disorders and specifically asked for symptoms after the stroke during the MADRS interview, we could not examine the patient's affective baseline. This limits the interpretability regarding organic brain causes. However, this is an issue that affects many patient-including hypothesis-testing studies. An alternative would be a prospective study design with high demands and large sample sizes.

Another limitation of the conclusions is that potential cognitive impairments of the patients cannot be fully corrected, which may confound with the cognitive-affective symptoms due to depression. Our studies exclude patients with severe cognitive impairment based on our inclusion criteria. However, mild cognitive decline may still confound our sample which can result from stroke or depression and is difficult to disentangle. Several studies identified that cognitive impairments and depression post-stroke strongly correlate (Kauhanen et al., 1999; Terroni et al., 2012). Some studies reported that cognitive impairment is an important predictor of chronic depressive symptoms post-stroke (Barker-Collo, 2007), while treatment of PSD goes along with the improvement of cognitive deficits (Bueno et al., 2011; Kimura et al., 2000; Simis & Nitrini, 2006). Thus, some authors suggest that PSD might be at least partly a secondary reaction to cognitive deficits after stroke (Kauhanen et al., 1999; Verdelho et al., 2004).

On the other hand, in a randomized, double-blinded trial, improvement of cognitive deficits was independent of effects on depression after escitalopram treatment compared to placebo (Jorge et al., 2010). Thus, whether cognitive deficits are a consequence or a cause of (cognitive-) depressive symptoms after stroke remains controversial. Especially for study 1, mild to moderate cognitive deficits as a symptom of both stroke and depression were difficult to disentangle and may still represent a potential confounder.

6.4 Future prospects

The number of studies on PSD has increased remarkably in the last decade. Our studies further contribute to the understanding of the various mechanisms underlying PSD. The findings provide an interesting outlook for future research in the field. Especially the perspective of analyzing depression as a multi-faceted syndrome in which separate symptoms contribute to PSD has been mostly ignored so far, although it is common knowledge among clinicians (Borsboom & Cramer, 2013; Fried & Cramer, 2017). In future studies regarding predicting, preventing, and treating PSD, these subdomains of depression should be considered important potential markers.

Furthermore, while our used VLSM analyses provide findings regarding the structural lesion locations associated with PSD, looking at a brain network level may be very promising. Especially when considering various PSD symptom subdomains, these may involve disconnection patterns across the brain rather than being confined to single brain regions. For instance, using voxel-based disconnection-symptom mapping, Pan et al. (2022b) recently observed a relationship between increased structural disconnection between bilateral frontal,

parietal, and temporal lobes and PSD at three months post-stroke. Furthermore, while Padmanabhan et al. (2019) found no lesion locations related to depression after stroke, the authors identified a connected brain circuit centered on the left dlPFC, associated with PSD from the same sample. There are several methodological applications to assess neural functional activity or connectivity related to PSD, such as diffusion tensor imaging (DTI) (Oestreich et al., 2020), rs-fMRI (Egorova et al., 2017; Zhang et al., 2018, 2019), structural network topology (Oestreich et al., 2020; Yang et al., 2015), functional disconnection (Padmanabhan et al., 2019), and structural disconnection, which is also termed connectome-based lesion-symptom mapping (Pan et al., 2022b; Yourganov et al., 2016). Diving into the methodological specificities of each of these approaches will be out of the scope of this thesis. Importantly, there's a research gap in exploring the neural network connections to specific subdomains of PSD symptoms. This presents an intriguing opportunity to advance our understanding of the complex interplay between neural networks and distinct facets of PSD. It would be of great interest to promote research in this field and to complement the neural underpinnings of PSD subdomains on functional and network levels.

Related to this, initially, we strived to implement the experimental paradigms of studies 2 and 3 into a task-fMRI design. Unfortunately, we did not continue these projects due to technical, personal, and time constraints, partly related to the COVID-19 pandemic. For study 2, we constructed a fMRI-suitable task design, including an adapted grip-force device. Functional neuroimaging would provide interesting information on the neural correlates of reward processing and incentive motivational behavior in the lesioned brain. For instance, for study 2, a task-fMRI monetary-incentive grip-force task could assess activated brain areas during reward anticipation, motor activation, and reward feedback in high compared to low reward trials (e.g., Cléry-Melin et al., 2011; Knutson et al., 2008; Pessiglione et al., 2007; Rochat et al., 2013; Schmidt et al., 2008, 2012). The activated brain areas may differ among patients with different degrees of motor impairment and PSD symptoms. Similar research questions would have been possible for an fMRI implementation of study 3.

Furthermore, we initially planned to investigate the functional resting-state connectivity and anatomical connectivity of fiber tracts within motor and affective networks in acute-stage stroke patients with PSD. For this, data from stroke patients and healthy control subjects have already been assessed in the MR scanner. Our goal was to compare these connectivity patterns in terms of their predictive value for forecasting the recovery of motor functional deficits (Rehme et al., 2015). It remains unclear whether PSD symptoms exhibit similar alterations in affective resting-state networks as seen in depressed patients or whether specific interactions

exist between motor and affective networks. Thus, one could explore whether functional and anatomical connectivity can offer insights into predicting the individual recovery of depressive and motor symptoms. Unfortunately, we neither continued this project due to infrastructural and personal constraints.

Another prospective outlook is to examine the various behavioral and neural markers measured in our studies in relationship to neurobiological mechanisms, as described in the *Theoretical Background* section. As introduced, several hypotheses are put in to describe the potential mechanisms underlying PSD and MDD. It may be worth looking at how the availability of monoamines, the concentration of BDNF, the glutamate release, or levels of proinflammatory cytokines are responsible for specific behavioral attitudes underlying PSD, such as incentive motivation and emotional processing.

Furthermore, another methodological adaptation could implicate two distinct experimental groups, e.g., comparing patients diagnosed with PSD and those without PSD. Our studies incorporated patients independent of their present depressive symptomatology, specifying no clear-cut depressive score. It would be intriguing to investigate how stroke patients with PSD perform in our motivational and emotional behavioral paradigms compared to non-PSD stroke patients. Importantly, this would provide opportunities for a clearer distinction between neural and psychological causes of PSD.

In future research, exploring the practical applicability of our experimental studies in clinical settings is essential. For example, intervention studies could examine whether enhancing motivation early after a stroke can be a valuable target within physiotherapy training. The primary focus of such studies would be to assess its impact on rehabilitation outcomes and the manifestation of PSD. A recent study by Widmer et al. (2022) examined the effects of providing enhanced feedback and rewards during arm rehabilitative training following a stroke. Interestingly, the authors noted significant improvements in clinical scores, including motor rehabilitation, within the group that received rewards compared to the non-rewarded group.

Moreover, in line with study 2 in our project, prospective investigations may compare residual motor function's influence on incentive motivation and PSD between two distinct patient groups: one receiving antidepressant medication and the other receiving no medication. This inquiry could be further extended by introducing additional interventions, such as repetitive transcranial magnetic stimulation (rTMS), to enhance the neural prerequisites for motivational training. In a broader context, extending the research questions explored in studies 2 and 3 of this project, future intervention studies should consider the combined application of antidepressant treatments and early motor motivation therapy, i.e., social/emotional training.

This approach can potentially offer comprehensive insights into enhancing post-stroke recovery.

Furthermore, in the context of neural and behavioral plasticity and the concept of biological preparedness, there is potential in using our behavioral tasks to prepare patients for subsequent rehabilitative interventions. Biological preparedness suggests humans may have inherent predispositions to learn and respond more readily to specific stimuli (Seligman, 1971). In post-stroke rehabilitation, this concept implies that our brains might naturally be more receptive to certain forms of rehabilitative training. However, it's important to note that these predispositions are modifiable. After a stroke, neural plasticity allows the brain to compensate for damaged areas by rewiring neural connections (Dimyan & Cohen, 2011). Incentive grip force training and emotional processing exercises may help shape neural and behavioral networks, enhancing the overall recovery. This plasticity can be utilized to prepare patients for further individualized training, such as established physiotherapy and emotional skills training, making these interventions more effective in restoring lost functions and treating or preventing PSD.

Finally, the *Theoretical Background* section has extensively covered the literature on unipolar depression, providing a robust foundation for our studies. This thesis underscores the importance of revisiting the relationship between PSD and unipolar depression, leveraging prior scientific research as a foundational framework. Notably, during the recruitment and assessment of stroke patients and healthy control subjects in studies 2 and 3, we conducted concurrent investigations on age-matched individuals with unipolar depression. This cohort served as an additional control group, allowing a comparative analysis of the influence of depressive symptoms in the presence or absence of stroke on incentive motivation and emotional processing parameters. The research questions and the incorporation of this second control group carry substantial significance, as they hold the potential to unveil fundamental insights into the mechanisms underlying PSD. For instance, the exclusive manifestation of specific behaviors in depressed stroke patients but not in those with unipolar depression could suggest a distinct neural basis for PSD. Of note, our results showed large similarities to the data of healthy controls regarding the behavioral parameters of interest in the task paradigms.

Research is scarce when it comes to the comparison of pathophysiological underpinnings between PSD patients and unipolar depressed patients. For our behavioral paradigms, we recruited unipolar depressed patients from the Department of Psychiatry of the University Hospital Cologne. Unfortunately, this control group's recruitment, examination, and data analysis were quite challenging as we observed a heterogeneous group sample (Lynch et

al., 2020). At the time of assessment, patients were either in hospitalized or ambulant settings. Thus, the patients varied in their experience of an acute depressive episode or a chronic depression. Furthermore, they varied in time-onset of their depressive disorder, past and current medication, psychotherapeutic experiences, and potential causes of depression, e.g., endogenous and exogenous depression. Besides, these slightly outdated terms refer to whether the depression stems from internal factors like genetics or neurochemical imbalances (endogenous depression), while exogenous depression arises from external events or stressors such as traumatic experiences (Kahn, 1954; Malki et al., 2014). Furthermore, some depressed patients participated in many previous studies examining depression. This suggests that they must have reflected on their mental states and dealt with their disorder, thus showing illness insight about a disorder, which is still taboo in some parts of society. They chose to come to the hospital on their own because of their suffering. On the other hand, stroke patients must come to the hospital because they are experiencing an acute life-threatening event. Accordingly, we experienced, to some extent, that stroke patients showed less illness insight (anosognosia) in view of their affective and physical state compared to depressive patients.

It has to be further noticed that depression in older adults (late-life depression) differs in their clinical phenotype compared to depression in younger ages, especially when first diagnosed. Sad moods are less common, as the current cohort of older people is not used to complaining about depressed mood, whereas somatic, psychotic symptoms and anxiety are more likely (Hegeman et al., 2012; Sekhon et al., 2023). The long-term prognosis is poorer, and relapse and suicidal rates are higher (Mitchell & Subramaniam, 2005; Sekhon et al., 2023). An fMRI study using a risk-taking task that induces feelings of regret found that healthy participants showed reduced neural responsiveness to regretful events compared to late-life depressed adults (Brassen et al., 2012). These findings may suggest that depression in older ages might exhibit behavioral, clinical, and neural differences compared to similarly aged PSD patients.

Moreover, another important aspect describing the difficulty in assessing and evaluating the depressive sample group was that those who were acutely hospitalized (i.e., similar external circumstances to the stroke patients) mostly refused to participate in the studies due to the severity of depressive symptoms. These patients regularly suffer, for instance, from pronounced motivational deficits that were of special interest in study 2. This may have biased the sample selection. Ultimately, the heterogeneity of unipolar depressed patients was not interpretable, and the data, therefore, was excluded from the final analyses. Nonetheless, comparing PSD patients and unipolar depressed patients concerning the pathophysiological underpinnings

remains crucial to investigate and ultimately unravel the underlying mechanisms of PSD. Future research should aim to possibly study and identify more homogeneous patients and reliable endophenotypes (Fried, 2017).

6.6 Conclusion

The present dissertation aimed at improving the understanding of different mechanisms and properties in post-stroke depression. Furthermore, we intended to disentangle the neural and psychological influences after a stroke on developing and maintaining depressive symptoms on different pathological levels. For this purpose, we executed three separate studies. The first one identified the structural neuroanatomy of specific PSD sub-symptoms using a multivariate lesion-symptom mapping approach, deepening the importance of viewing PSD as a multi-faceted syndrome. The second study used a monetary incentive grip-force task design to reveal the relationship between motor impairment after stroke, incentive motivation, and PSD symptoms, specifically motivational deficits. In the third study, by applying an emotion-processing task, it was investigated how PSD affects emotion-processing capacities in social contexts, more specifically, how it promotes biased attention toward negative emotions. In behavioral studies 2 and 3, analyses of lesion locations were performed to inspect the neural correlates of the underlying behavioral parameters.

Our studies further provide relevance and suggestions for clinical applications during early hospitalization, in rehabilitation centers, in the patient's everyday life, and to relieve caregivers' burden. Integrating specific psychological treatment components may become essential to alleviate potential symptoms of PSD. These can include psychoeducation on sleep hygiene, day structuring, validation of negative feelings, behavior regulation, cognitive training, and psychotherapy. Also, strengthening the social network and social support can be achieved via emotional and social compensatory training such as discussing and reflecting on one's feelings, practicing perspective-taking, listening, and coping effectively with conflicts. Moreover, pharmacological medications such as SNRIs, SSRIs, and sedatives targeting specific neurotransmitter systems are crucial and efficient in treating PSD and motor impairment.

Our studies detected important characteristics regarding PSD's neural and psychological pathophysiology. More precisely, our findings strongly indicated a neural involvement, as suggested by lesion-symptom analyses in our studies. In contrast to some existing literature suggesting causes of PSD due to, e.g., bodily restrictions in everyday life, we did not find significant links between increased depression and stroke severity or functional impairment.

Nevertheless, it remains important to notice that there are possibly no simple mechanisms to explain the development and maintenance of PSD. The underlying pathophysiology includes many aspects that influence each other, flowing into specific behavioral characteristics of PSD. Future research should focus on further disentangling these factors, potentially taking the comparison with unipolar depressed patients without stroke into account. These efforts should aim at further developing personalized interventions to enhance the effectiveness of rehabilitation outcomes.

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8. Personal contributions

Study 1 was a shared first-authorship project with Sebastian Krick from our lab. He was a student assistant, a bachelor's student in neuroscience, and a medical student in human medicine. We performed the data extraction from the patient's medical records, the lesion drawings, preprocessing of MR images, data evaluation, and computing SVR-LSM analyses with guidance and support from PD Dr. Anne Rehme and Prof. Dr. Christian Grefkes. Together with Sebastian Krick, I drafted the first version of the introduction, methods, results, and discussion section. Under the supervision of PD. Dr. Anne Rehme and Prof. Dr. Christian Grefkes we integrated feedback from all co-authors and revised the manuscript during the review process from *Brain Communications.*

In study 2, I contributed to the recruitment and assessment of study participants and the preprocessing, evaluation, and analyses of the acquired data. I drafted the first and revised versions of the manuscript under the supervision of PD Dr. Anne Rehme and Prof. Dr. Christian Grefkes. The psychology master's student Maike Mustin wrote her thesis using part of the data acquired in this study.

For study 3, I contributed to the experimental conception, design, and structure. I acquired all participant's data, completed lesion drawings and preprocessing of MR images and behavioral data, and performed all data analyses. I drafted the current version of the manuscript and integrated feedback until now from the co-authors. PD. Dr. Anne Rehme and Prof. Dr. Christian Grefkes served as supervisors for this study, too. A psychology master's student, Maximilian Gorski, wrote his thesis using part of this data. I supervised him during his thesis, guided him during data acquisition and preliminary analyses, and was the first contact person.

Data collection, which was not part of this thesis but is described in the *Future Prospect* section, was as follows: I recruited acute stroke patients and healthy control subjects for functional and structural MRI acquisitions. These included sequences of rs-fMRI, T1, T2, DWI, FLAIR, DTI, diffusion spectrum imaging, and quantitative magnetization transfer. Furthermore, concerning studies 2 and 3, I recruited and examined unipolar depressed patients from the Department of Psychiatry, University Hospital Cologne.