KU LEUVEN



SENSORY SENSITIVITY AFTER ACQUIRED BRAIN INJURY

ADVANCING ASSESSMENT AND UNRAVELLING UNDERLYING MECHANISMS

Hella Thielen

Doctoral thesis offered to obtain the degree of Doctor of Psychology (PhD) · 2023
Supervisor: Prof. Dr. Céline Gillebert · Co-supervisors: Prof. Dr. Christophe Lafosse, Dr. Irene Huenges Wajer
Faculty of Psychology and Educational Sciences · Brain and Cognition

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SUMMARY

Sensory sensitivity after acquired brain injury:
advancing assessment and unravelling underlying mechanisms

Acquired brain injury patients frequently report an increased sensitivity to sensory stimuli following their brain injury compared to their pre-injury state (i.e., post-injury sensory hypersensitivity). Since post-injury sensory hypersensitivity can negatively impact quality of life, it is crucial to have appropriate assessment and treatment methods. However, adequate assessment and treatment is hindered by a lack of appropriate diagnostic tools as well as limited knowledge about the underlying mechanisms of self-reported post-injury sensory hypersensitivity (Chapter 2). To address these issues, we developed the Multi-Modal Evaluation of Sensory Sensitivity (MESSY), a patient-friendly questionnaire that assesses sensory sensitivity across multiple sensory modalities (Chapter 3). Moreover, we demonstrated that the MESSY has adequate psychometric properties in neurotypical adults and is sensitive to sensory hypersensitivity in chronic stroke, traumatic brain injury, and brain tumour patients. After contributing to the improvement of the assessment of self-reported post-injury sensory sensitivity, we were able to start examining its underlying behavioural and neural mechanisms. In Chapter 4 we present evidence supporting a relationship between sensory sensitivity and selective attention. This is supported by Chapter 5 in which we demonstrated a potential relationship between post-stroke visual hypersensitivity and impaired selective attention and lowered sensory thresholds. To explore the neural basis of post-injury sensory hypersensitivity we conducted a systematic literature review (Chapter 6), a multiple case study (Chapter 6), and a lesion-symptom mapping study (Chapter 7). Our studies revealed an involvement of the insula, thalamus, basal ganglia, as well as two white matter tracts (fronto-insular tract 3, uncinate fasciculus) in post-stroke sensory hypersensitivity. The relationship between post-stroke sensory hypersensitivity and these brain structures can be understood through their role in selective attention, sensory appraisal, and auditory processing. Overall, the findings of this thesis provide first-hand evidence for a relationship between self-reported sensory hypersensitivity after acquired brain injury and specific behavioural (selective attention, sensory thresholds) and neural mechanisms (damage to sensory processing regions in the grey or white matter). Moreover, this thesis demonstrates that sensory hypersensitivity is present after different types of brain injury, across different sensory modalities, and in the (sub)acute and chronic stages after injury. By contributing to scientific advancement and providing a patient-friendly diagnostic tool, this thesis has the potential to improve patient care and in turn the quality of life of acquired brain injury patients with post-injury sensory hypersensitivity.

SAMENVATTING

Sensorische sensitiviteit na niet-aangeboren hersenletsel:
faciliteren van assessment en ontrafelen van onderliggende mechanismen

Patiënten met een niet-aangeboren hersenletsel geven regelmatig aan dat zij sinds hun hersenletsel gevoeliger zijn voor zintuigelijke prikkels (i.e., sensorische hypersensitiviteit na hersenletsel). Aangezien sensorische hypersensitiviteit na hersenletsel een negatieve invloed kan hebben op kwaliteit van leven, zijn passende diagnostiek en behandeling cruciaal. Echter, adequate diagnostiek en behandeling worden momenteel belemmerd door een gebrek aan geschikte diagnostische middelen en beperkte kennis over de onderliggende mechanismen van deze subjectieve klachten (Hoofdstuk 2). Om een antwoord te bieden op deze problemen, hebben wij de Multi-Modal Evaluation of Sensory Sensitivity (MESSY) ontwikkeld, een patiëntvriendelijke vragenlijst die de gevoeligheid voor verschillende zintuigelijke modaliteiten bevraagt (Hoofdstuk 3). Wij hebben aangetoond dat de MESSY adequate psychometrische eigenschappen heeft en sensitief is voor sensorische hersensensitiviteit na een beroerte, traumatisch hersenletsel, of hersentumor. Na het verbeteren van de diagnostiek van sensorische sensitiviteit na hersenletsel, waren we in staat om de onderliggende gedragsmatige en neurale mechanismen van deze klachten te onderzoeken. In Hoofdstuk 4 presenteren wij evidentie voor een verband tussen sensorische sensitiviteit en selectieve aandacht. Dit wordt ondersteund door Hoofdstuk 5, waarin we een mogelijk verband aantonen tussen visuele hypersensitiviteit na een beroerte enerzijds, en verminderde selectieve aandacht en verlaagde zintuigelijke drempels anderzijds. Om de neurale basis van sensorische hypersensitiviteit na een hersenletsel na te gaan, voerden we een systematische literatuurstudie (Hoofdstuk 6), een multiple case studie (Hoofdstuk 6), en een letsel-symptoom mapping studie uit (Hoofdstuk 7). Beide studies onthulden een betrokkenheid van de insula, thalamus, basale ganglia, evenals twee witte stofbanen (fronto-insulaire baan 3, uncinate fasciculus) bij sensorische hypersensitiviteit na een beroerte. Het verband tussen deze neurale structuren en sensorische hypersensitiviteit kan begrepen worden door hun betrokkenheid bij selectieve aandacht, de emotionele evaluatie van zintuigelijke prikkels, en auditieve verwerking. Over het geheel genomen levert dit proefschrift evidentie voor een relatie tussen subjectieve sensorische hypersensitiviteit na hersenletsel en specifieke gedragsmatige en neurale mechanismen. Bovendien toonden wij aan dat sensorische hypersensitiviteit aanwezig kan zijn na verschillende soorten hersenletsel, binnen verschillende zintuigelijke modaliteiten, en in de (sub)acute en het chronische stadium na het letsel. Door bij te dragen aan de wetenschappelijke kennis over sensorische hypersensitiviteit na hersenletsel en een patiëntvriendelijk diagnostisch middel te bieden, heeft dit proefschrift het potentieel om patiëntenzorg te verbeteren en de kwaliteit van leven van patiënten met een niet-aangeboren hersenletsel te verhogen.

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Chapter one

General introduction

In 2017, when I was working as a clinical neuropsychologist, I met Ann, a thirty-year-old woman who had just suffered a mild stroke. Ann experienced an increased sensitivity to visual and auditory stimuli after her stroke causing her to feel overwhelmed by bright light, moving visual images (such as moving images on the television or moving traffic), and environmental noise (such as other people talking or music). Before her stroke, Ann was very active: she played group sports multiple times a week and had a high-responsibility job working as a communication manager for a big company. Post-stroke, Ann felt she could no longer handle the responsibilities of her job, had a hard time parenting her young daughter due to her adversity to noise, and experienced helplessness and a depressed mood. To help her cope with her post-stroke sensory hypersensitivity, Ann sought out psychological treatment. To guide my assessment and treatment of Ann's symptoms, I turned to neuropsychological handbooks and scientific literature. To my surprise, literature regarding sensory hypersensitivity after acquired brain injury was scarce and the definitions and terminology used to describe sensory hypersensitivity in the literature were highly diverse. I found myself puzzled regarding the concept of sensory hypersensitivity and its proper definition within populations with acquired brain injuries.

To address these concerns, this introduction starts with a discussion of the terminology and definition of sensory hypersensitivity across different populations followed by a consideration of how applicable these terms and definitions are to the acquired brain injury population. Subsequently, we will formulate a clear definition of sensory hypersensitivity after acquired brain injury, which will provide us with a basis from which we can explore the outstanding questions regarding sensory hypersensitivity after acquired brain injury.

The terminology and definitions used to describe sensory hypersensitivity

When consulting the literature on sensory hypersensitivity, it quickly becomes apparent

that standardized terminology and definitions of sensory hypersensitivity are missing. The heterogeneity in terms and definitions can possibly be attributed to the fact that sensory hypersensitivity is not specific to acquired brain injury but is also reported in individuals with a neurodevelopmental or psychiatric disorder (e.g., autism spectrum disorder, attention deficit hyperactivity disorder, schizophrenia, Tourette syndrome) as well as in the general population (Bijlenga et al., 2017; Dixon et al., 2016; Greven et al., 2019; Isaacs & Riordan, 2020; Kamath et al., 2020; Tavassoli, Miller et al., 2014; Weiland et al., 2020; Zhou et al., 2020). As a result, terms and definitions are emanated from different fields (i.e., psychology, occupational therapy) and are rarely used in a transdiagnostic manner. Moreover, symptoms of sensory hypersensitivity are heterogeneous, as they, for instance, can include uni- (present in one single sensory modality) or multi-modal (present across multiple sensory modalities) sensory hypersensitivity. To illustrate the diversity in the literature, we present a non-exhaustive overview of definitions and terms that are used to describe sensory hypersensitivity across different populations (including the neurotypical population and individuals with obsessive-compulsive disorder, schizophrenia, autism spectrum disorder, or Tourette syndrome) in Table 1.

Table 1. An overview of different terms (uni- and multi-modal) and definitions that are used to describe sensory hypersensitivity across different populations.

Multi-modal terms	Example of a definition	Uni-modal terms
Sensory hypersensitivity	"A constant, heightened awareness of internal (interoceptive) and/or external (exteroceptive) stimuli" (Isaacs & Riordan, 2020, p.627)	Hyperacusis, Hyperaestesis, Hyperosmia, Hypergeusia
	"An over-responsiveness to sensory stimuli" (Ward, 2019, p.139)	Sensitivity to noise, Sensitivity to light, Tactile, olfactory, gustatory sensitivity
Sensory processing sensitivity	"A genetically determined trait involving a deeper cognitive processing of stimuli that is driven by higher emotional reactivity" (Aron et al., 2012, p.262)	

Multi-modal terms	Example of a definition	Uni-modal terms
Sensory over-responsivity	“People with sensory over-responsivity respond to sensation faster, with more intensity, or for a longer duration than those with typical sensory responsivity” (Miller et al., 2007, p. 136)	
Sensory overload	“A perceived increase in the intensity, diversity and/or the pattern of environmental stimuli which exceeds the normally experienced level and are thus experienced as aversive” (Scheydt et al., 2017, p.115)	
Sensory intolerance	“A high level of distress evoked by common environmental stimuli across multiple sensory domains” (Cavanna, 2020, p.42)	Sound or noise intolerance, Light intolerance, Touch intolerance, Smell intolerance, Taste intolerance
Sensory flooding	A breakdown in selective inhibitory function resulting in flooding by an undifferentiated mass of incoming sensory data” (Bunney et al., 1999, p.577-578)	
Sensory defensiveness	“A tendency to react negatively or with alarm to sensory input which is generally considered harmless or non-irritating” (Kinnealey et al., 1995, p.444)	Phonophobia, Photophobia

This list was compiled based on a literature search and is not exhaustive. Three experts within the field of sensory hypersensitivity were consulted to check if a term or definition was missing.

A definition for sensory hypersensitivity after acquired brain injury

Noticeably, a majority of the terms and definitions discussed in Table 1 focus on sensory responsivity (the overt response to sensory stimuli), mention a biological or behavioural mechanism of self-reported sensory sensitivity (e.g., cognitive processing, genetics, impaired inhibition) (Aron et al., 2012; Bunney et al., 1999; Cavanna, 2020; Kinnealey et al., 1995; Miller et al., 2007; Ward, 2019), or refer to increased emotional reactivity (e.g., increased empathy) in addition to sensory sensitivity (Aron et al., 2012). We believe, that in the acquired brain injury population, placing emphasis on sensory or emotional responsivity is not warranted since sensory and emotional behaviours might be exhibited differently by acquired brain injury patients as compared to neurotypical individuals or individuals from other clinical groups. Indeed, sensory responsiveness might be minimized by other common acquired brain injury symptoms such as language or motor impairments (Hankey et al., 2002; Jourdan et al., 2018; Lawrence et al., 2001; Martins et al., 2011; Walker & Pickett, 2007).

These impairments can, for example, make it more difficult to avoid sensory stimuli by walking away, to communicate frustration, or to cover one's ears or eyes with their hands In addition, whether or not sensory hypersensitivity manifests itself in overt behaviour may depend on coping strategies and personality styles. As a result, limiting the definition (and assessment) of sensory hypersensitivity after acquired brain injury to an overt over-responsiveness might underestimate the prevalence and severity of these symptoms. Moreover, in the acquired brain injury population, there is little evidence that brain damage results in higher empathic awareness. Instead acquired brain injury more often seems to result in reduced emotional empathy (De Sousa et al., 2011; Williams & Wood, 2010; Yeh & Tsai, 2014). Since the relationship between emotional reactivity and sensory hypersensitivity after acquired brain injury remains unclear, we propose separating the two concepts when defining sensory hypersensitivity in this population. Furthermore, the focus of some definitions in Table 1 on an underlying biological or behavioural mechanism of subjective sensory sensitivity seems curious, since, to date, the underlying mechanisms of subjective sensory sensitivity remain unknown (Ward, 2019). Until there is more empirical evidence regarding the underlying mechanisms of subjective sensory sensitivity, we believe that a definition (and as a result the assessment) of sensory hypersensitivity should focus on the subjective level: the lived experience of individuals with sensory hypersensitivity.

Another major difference between sensory hypersensitivity after acquired brain injury and sensory hypersensitivity in the general population and other clinical groups is that in the acquired brain injury population sensory hypersensitivity is linked to a specific life event (the acquisition of the brain injury). Therefore, we argue that the definition of sensory hypersensitivity after acquired brain injury should emphasize this change in sensory sensitivity. This corresponds to diagnostic tools, such as the Rivermead Post-Concussion Symptoms Questionnaire, that include this change in sensory sensitivity in their assessment to make a distinction between pre-existing and post-injury sensory hypersensitivity (Ochi et al., 2022; Potter et al., 2006; Shepherd et al., 2019).

Based on the above-mentioned considerations we propose the following definition of sensory hypersensitivity after acquired brain injury: *a self-reported increase in the sensitivity to one or multiple internal or external sensory stimuli after brain injury as compared to before the brain injury. This increased sensitivity can (but does not necessarily have to) be manifested overtly in an altered response towards sensory stimulation (e.g., fatigue, headache, sensory avoidance, anxiety, stress, irritability during or after sensory stimulation).*

When considering all the terms mentioned in Table 1, we believe that the term "sensory hypersensitivity" has the best fit with our definition as it does not refer to sensory responsiveness and has not been previously used to describe the combination of sensory and emotional sensitivity. It is also consistent with previous research that adopted the term "sensory hypersensitivity" in the acquired brain injury population as well as in other clinical groups, hence promoting transdiagnostic research (Baron-Cohen et al., 2009; Dixon et al., 2016; Isaacs & Riordan, 2020; Marzolla et al., 2022; Ochi et al., 2022; Schulz & Stevenson, 2019). Importantly, the hyper in hypersensitivity after acquired brain injury does not refer to an atypically high sensory sensitivity as compared to neurotypical controls, but represents the increase in sensory sensitivity after acquired brain injury (similar to Marzolla et al., 2022; Shepherd et al., 2020). In addition, the term sensory hypersensitivity and its definition in the acquired brain injury population refers to subjective, or self-reported hypersensitivity and not an increased ability to detect or discriminate sensory stimuli (which is operationalized as behavioural sensory sensitivity, see below).

Outstanding questions regarding sensory hypersensitivity after acquired brain injury

We believe that the heterogeneity in the definitions and terminology used to describe sensory hypersensitivity, as well as the subjective nature of the symptoms, have hindered scientific advancement, resulting in a lack of translational knowledge and adequate diagnostic and treatment tools. As a result, healthcare professionals and patients with acquired brain injury are left with many outstanding questions. Why do some patients with acquired brain injury suffer from sensory hypersensitivity while others do not? How prevalent are these symptoms? What is the prognosis of sensory hypersensitivity after acquired brain injury and how should these symptoms be treated?

The lack of scientific attention for post-injury sensory hypersensitivity has significant consequences for acquired brain injury patients such as Ann. Firstly, clinicians often overlook or underestimate the impact of post-injury sensory hypersensitivity, leading to patients feeling stigmatized, misunderstood, or not taken seriously. For instance, there are reports of post-injury sensory hypersensitivity being explained as imaginary by healthcare providers (Landon et al., 2012). As a result, patients with post-injury sensory hypersensitivity have to figure out for themselves how to manage these symptoms which might result in maladaptive illness beliefs and coping strategies (Carlsson et al., 2009; Venkatesan & Ramanathan-Elion, 2022). Secondly, it remains unclear what mechanisms cause and maintain sensory hypersensitivity after acquired brain injury. Recently, Ward (2019) offered a theoretical framework that defined sensory sensitivity across three levels of analysis (i.e., subjective, behavioural, and neural sensory sensitivity). Subjective sensory sensitivity refers to self-reported sensitivity to sensory stimuli, behavioural sensory sensitivity to the ability to detect sensory stimuli and discriminate between different stimuli, and neural sensory sensitivity to the neural basis of sensory sensitivity (e.g., the neural activity in response to sensory stimulation). To date, it is still uncertain if and how these three levels relate to each in acquired brain injury patients but also in other populations. A further investigation of the relationships between subjective, behavioural, and neural sensory sensitivity can identify individuals at risk for developing post-injury sensory hypersensitivity, and can aid in generating an evidence-based treatment protocol for sensory hypersensitivity, which is currently lacking. Developing effective treatments for post-injury sensory hypersensitivity is of high importance since research has shown that these symptoms can negatively impact quality of life (i.e., result in reduced participation in social and vocational activities, economic difficulties, and mental health problems) (Alwawi et al., 2020; Carlsson et al., 2004, 2009; Hallberg et

al., 2005; Shepherd et al., 2020; Trulsson et al., 2003) and are associated with worse functional recovery (i.e., in the presence of post-injury sensory hypersensitivity other symptoms persist longer, recovery time is longer, and hospital reattendance is higher) (Chorney et al., 2017; Mistry & Rainer, 2018; O'Kane et al., 2014; Zuckerman et al., 2016).

In summary, addressing the research gaps in the area of post-injury sensory hypersensitivity is crucial for improving the well-being of individuals experiencing these symptoms, for helping clinicians to better understand and assess post-injury sensory hypersensitivity, and for facilitating the development of effective treatment approaches.

Objectives of the PhD project

This doctoral thesis aims to provide an overview of the available scientific literature on sensory sensitivity after acquired brain injury, to help clinicians adequately recognize and assess these symptoms, to understand what the underlying mechanisms of these symptoms are, and to inspire future research to develop evidence-based treatments[1]. The specific objectives of the PhD project were the following:

1. To provide an overview of existing literature on sensory hypo- and hypersensitivity after acquired brain injury, we performed a systematic literature review (Chapter 2).

2. To assess subjective sensory sensitivity across multiple modalities in acquired brain injury patients, we developed a patient-friendly questionnaire, acquired normative data, evaluated the psychometric qualities of the questionnaire in neurotypical adults, and compared sensory sensitivity between chronic acquired brain injury patients (stroke, traumatic brain injury, brain tumour) and neurotypical adults (Chapter 3).

3. To unravel the behavioural mechanisms of sensory hypersensitivity after acquired brain injury, we provided a commentary on the putative role of selective attention (Chapter 4) and acquired behavioural data in (sub)acute stroke patients that allowed us to study the role of bottom-up sensory processing (sensory threshold, sensory processing speed) and top-down modulation of selective attention in post-stroke visual hypersensitivity (Chapter 5).

4. To identify the neural mechanisms of post-stroke sensory hypersensitivity we conducted a systematic literature review (Chapter 6) and analysed structural brain images in (sub)acute stroke patients (Chapters 6 and 7).

[1] *The terminology of the publications on which the doctoral thesis is based were adapted to establish uniformity.*

While the systematic review in Chapter 2 focuses on both sensory hypo- and hypersensitivity, the remainder of the thesis will focus on sensory hypersensitivity. The definition of sensory hyposensitivity is possibly even more unclear than that of sensory hypersensitivity, partly because in the acquired brain injury population it is hard to differentiate symptoms of sensory hyposensitivity from other common consequences of acquired brain injury such as motor disabilities (hemiparesis), sensory dysfunctions (hemianopia, hemispatial neglect), and apathy. In addition, when deciphering the underlying behavioural and neural mechanisms of sensory hypersensitivity in acquired brain injury patients we decided to focus on stroke patients for two reasons. Firstly, stroke results in focal lesions which makes it the ideal population for studying the lesion neuroanatomy of post-injury sensory hypersensitivity. This is in contrast to traumatic brain injuries, which result in diffuse lesions as well as white matter lesions which are harder to localize on clinical brain scans, and brain tumours which are progressive in nature and where it is difficult to differentiate between the primary influence of the brain injury and secondary influences of cancer treatments such as brain surgery, chemotherapy, and radiotherapy (Abu-Hegazy & El-Hadaad, 2016; Alemany et al., 2020). Secondly, since literature on sensory hypersensitivity after acquired brain injury is biased towards traumatic brain injury patients, we aimed to increase the scientific attention for sensory hypersensitivity after stroke. Increased scientific and clinical attention towards sensory hypersensitivity post-stroke is important, since in stroke patients, these invisible symptoms might be overlooked due to the presence of more obvious motor or language difficulties.

Throughout the research process of this thesis, we met a large number of patients with sensory hypersensitivity after acquired brain injury. To give the reader insight in their experiences and amplify the real-life voices of acquired brain injury patients with post-injury sensory hypersensitivity, we added quotes from participating acquired brain injury patients throughout this thesis.

In conclusion, we are confident that this thesis will have a substantial impact on the scientific field and clinical practice by enhancing our understanding of the behavioural and neural mechanisms of subjective sensory hypersensitivity as well as by providing a patient-friendly sensory sensitivity questionnaire.



“I feel like I am walking around with an invisible illness that is difficult to explain. I am still the same person, but with many invisible disabilities.”

Chapter two

Sensory sensitivity after acquired brain injury: a systematic review

Patients with acquired brain injury frequently report experiencing an in- (sensory hypersensitivity) or decreased sensitivity to sensory stimuli (sensory hyposensitivity) following their brain injury. Although, they can negatively impact daily functioning, these symptoms are poorly understood. To provide an overview of the current evidence on atypical sensory sensitivity after acquired brain injury, we conducted a systematic literature review. The primary aim of the review was to investigate the behavioural and neural mechanisms that are associated with post-injury self-reported sensory sensitivity. Studies were included when they studied sensory sensitivity in acquired brain injury populations and excluded when they were not written in English, consisted of non-empirical research, did not study human subjects, studied pain, related sensory sensitivity to peripheral injury, or studied patients with a neurodegenerative disorder, meningitis, encephalitis, or a brain tumour. The Web Of Science, PubMed, and Scopus databases were searched for appropriate studies. A qualitative synthesis of the results of the 81 studies that were included suggests that abnormal sensory thresholds and a reduced information processing speed are candidate behavioural mechanisms of atypical subjective sensory sensitivity after acquired brain injury. Furthermore, there was evidence for an association between post-injury atypical sensory sensitivity and structural grey or white matter abnormalities, and to functional abnormalities in sensory cortices. However, further research is needed to explore the causation of atypical sensory sensitivity after acquired brain injury. In addition, there is a need for the development of adequate diagnostic tools. This can significantly advance the quantity and quality of research on the prevalence, aetiology, prognosis, and treatment of these symptoms.

Thielen, H., Tuts, N., Welkenhuyzen, L., Huenges Wajer, I.M.C., Lafosse, C., & Gillebert, C.R. (2023). Sensory sensitivity after acquired brain injury: a systematic review. Journal of Neuropsychology, 17(1), 1-31.

Acquired brain injuries have become one of the world's leading cause of disability and reduced quality of life (Feigin et al., 2010; Greenwald et al., 2003). These injuries to the central nervous system are non-congenital, not neurodegenerative, nor induced by birth trauma (World Health Organization, 2006). Acquired brain injuries can be traumatic (i.e., traumatic brain injury (TBI)) or non-traumatic (i.e., stroke, anoxia, brain tumours), and can result in long-term impairments in mobility, speech, cognition, and socio-emotional functioning (Chiavaroli et al., 2016; Kohnen et al., 2019; Takizawa et al., 2016). Less well-known consequences of acquired brain injury are post-injury changes in sensory sensitivity resulting in an increased (i.e., sensory hypersensitivity) or decreased (i.e., sensory hyposensitivity) sensory sensitivity (Alwawi et al., 2020; Chung & Song, 2016; Kumar et al., 2005). These symptoms are subjective by nature and can occur across different sensory modalities (i.e., visual, auditory, gustatory, olfactory, tactile, and vestibular sensitivity), have a significant impact on daily life, and are associated with poor functional recovery (Chorney et al., 2017; Landon et al., 2012; Shepherd et al., 2020).

Self-reported atypical sensory sensitivity is, however, not specific to patients with acquired brain injury. Sensory hypo- and hypersensitivity are also reported in the general population (Greven et al., 2019) and in other clinical populations such as autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), and schizophrenia (Bijlenga et al., 2017; Landon et al., 2016; Tavassoli, Hoekstra, et al., 2014). Importantly, atypical sensory sensitivity after brain injury (i.e., sensory hypo- and hypersensitivity after brain injury) refers to changes in sensory sensitivity that are linked to the brain injury, whereas in other populations atypical sensory sensitivity refers to exceptionally low or high severities of sensory sensitivity that are not linked to a specific life event. Previous research has identified possible behavioural and neural mechanisms associated with atypical sensory sensitivity in neurotypical adults as well as clinical groups (e.g., autism spectrum disorder, chronic pain patients). For instance, atypical sensory sensitivity has been related to abnormal sensory processing (i.e., atypical sensory thresholds or sensory acuity) (Ashwin et al., 2009; Brinkert & Remington, 2020; Brown & Dunn, 2002), attentional impairments (i.e., reduced selective attention, reduced information processing speed) (Liss et al., 2006; Marco et al., 2011; Panagiotidi et al., 2018, see also Thielen & Gillebert, 2019), and abnormal predictive processing (Ward, 2019). At the neural level, atypical sensory sensitivity has been related to functional abnormalities in the sensory cortices (Green et al., 2015; López-Solá et al., 2014), the insula (López-

Solá et al., 2014), thalamus (Acevedo et al., 2018), and limbic structures (Acevedo et al., 2018; Green et al., 2015). Furthermore, several authors (Green et al., 2016; Greven et al., 2019; Ward, 2019) proposed abnormalities within large-scale brain networks (specifically the salience network and the default mode network) as neural mechanisms of sensory sensitivity.

Similar behavioural (i.e., abnormal identification and discrimination of sensory stimuli, attentional impairments, abnormal prediction of subsequent sensory stimulation) and neural mechanisms (i.e., functional abnormalities in regions associated with sensory processing, atypical brain network functioning) may relate to atypical sensory sensitivity after acquired brain injury. The primary aim (1) of this systematic review is to provide an overview of the current evidence for these mechanisms in patients with acquired brain injury. In addition, to get a broader view on potential protective or risk factors associated with post-injury changes in sensory sensitivity as well as on its prevalence and diagnosis, secondary aims of the systematic review were (2) to investigate the association between atypical sensory sensitivity after acquired brain injury and pre-injury demographic factors, injury characteristics, and comorbid symptomatology, (3) to assess the prevalence of post-injury sensory hypo- and hypersensitivity in different types of acquired brain injury as well as across different sensory modalities, and (4) to determine the diagnostic tools that are used to assess sensory hypo- and hypersensitivity after acquired brain injury. Furthermore, to explore the evolution of and treatment possibilities for atypical sensory sensitivity we aimed to (5) summarize results concerning the evolution and (6) treatment of sensory hypo- and hypersensitivity after an acquired brain injury as well as (7) its relationship to injury outcomes.

Methods

Search strategy

We followed the recommendations from the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). The databases Web of Science, PubMed, and Scopus were searched using a search string that included different types of acquired brain injury as well as a variety of terms relating to sensory sensitivity or sensory intensity. The full search string consisted of the following terms: ((“Brain injur*” OR “head injur*” OR stroke OR “subarachnoidal he$morrhage” OR “brain he$morrhage” OR “brain infarction” OR “cerebral infarction” OR “cerebral he$morrhage” OR “intracranial he$morrhage” OR “head trauma” OR “concussion” OR

"craniocerebral trauma" OR "cerebrovascular trauma" OR "transient ischemic attack" OR "lacunar infarct" OR "vascular dementia" OR "brain anoxia" OR "brain hypoxia" OR "cerebral anoxia" OR "cerebral hypoxia" OR encephalop*) AND ("sensory *sens*" OR "sensory processing disorder" OR "sensory processing sensitivity" OR "sensory gating" OR "sensory overload" OR "sensory threshold" OR "sensory filtering" OR phonophobia OR photophobia OR osmophobia OR hyperacusis OR *sensitivit* NEAR/2 (light OR visual OR auditory OR sound OR noise OR touch OR tactile OR smell OR olfactory OR gustatory OR temperature OR taste OR vestibular) OR intensity NEAR/2 (light OR visual OR auditory OR sound OR noise OR touch OR tactile OR smell OR olfactory OR gustatory OR temperature OR taste OR vestibular))). The databases were last consulted in October 2021.

In- and exclusion criteria

Articles were excluded if they were not written in English, if they did not study human subjects (e.g., animal research), or if they did not study self-reported sensory sensitivity in acquired brain injury patients (e.g., research in participants with a neurodegenerative disorder). Articles on vascular dementia were not excluded since stroke can cause vascular dementia (Gorelick et al., 2011). We only included articles that discussed sensory sensitivity after cerebral damage and excluded articles that related atypical sensory sensitivity to peripheral injury (i.e., ocular damage), meningitis, encephalitis (due to the possibility of comorbid peripheral nervous system damage) (Bogovic, 2015), and brain tumours (since we could not specify whether changes in sensory sensitivity are a result of the brain injury or of the cancer treatment) (Huang et al., 2019; Raffa et al., 2006). We also excluded articles on toxic encephalopathy due to long term solvent exposure since solvent exposure (in the absence of encephalopathy) can result in abnormal sensitivity to olfactory stimuli (Zibrowski & Robertson, 2006). Articles on pain were excluded when they described photo- or phonophobia solely during migraine episodes since photo- and phonophobia are known symptoms of migraine (Evans et al., 2008). Articles describing abnormal tactile sensitivity or temperature allodynia limited to a hemiplegic or painful body part were also excluded. Articles that studied military veterans were only included if it was explicitly stated that the veterans suffered from a traumatic brain injury (TBI) and not for example solely blast exposure. Only empirical studies were included, meaning that review articles or book chapters were excluded.

Eligibility assessment

Two reviewers (HT and NT or LW) independently reviewed the abstracts from the various databases for their relevance using the above described in- and exclusion criteria. A third reviewer (CRG) was consulted in case of disagreement (this was the case for four articles, of which three were excluded and one was included (Wehling et al. (2015)).

Data extraction

From the included articles, we extracted the characteristics of the article (title, authors, year of publication) as well as demographic characteristics of the studied acquired brain injury population (sample size, age, gender, type of acquired brain injury, time since injury) and, if available, the characteristics of the studied control group (sample size, age, and gender). Based on their mean age we classified the studied samples as adult (mean age ≥ 18 years) or non-adult (mean age < 18 years). Articles on TBI were categorized into two groups based on injury severity: mild traumatic brain injury (mTBI) (including concussions) (Mayer et al., 2017) and moderate to severe TBI. Depending on the mean number of months between brain injury onset and sensory sensitivity assessment we identified time since injury as (sub)acute (less than six months after injury) or chronic (six months or longer after injury) (based on Bernhardt et al. (2017), Bond (1979), Licastro et al. (2016)). Studies that included both acute and chronic patients were classified as 'acute to chronic'. Data extraction also included the sensory modalities that were studied (i.e., auditory, visual, olfactory, gustatory, tactile, or vestibular sensitivity as well as a sensitivity to light), study design aspects (i.e., what diagnostical tools were used to assess sensory sensitivity), whether the study assessed hypo- and/or hypersensitivity, and a summary of the results.

Quality assessment

The methodological quality of the included articles was assessed by two independent reviewers (HT and NT) using the Mixed Methods Appraisal Tool (Hong et al., 2018).

Data analysis

We used qualitative synthesis to summarize results on sensory hypo- and hypersensitivity after an acquired brain injury. In alignment with our research aims, we focused on (1) behavioural and neural mechanisms of post-injury atypical sensory sensitivity, (2) demographic factors, injury mechanisms, and comorbid symptomatology associated with post-injury hypo- or hypersensitivity, (3) the prevalence of post-injury self-reported

sensory hypo- and hypersensitivity across different modalities, (4) the diagnostic tools used to assess post-injury sensory sensitivity, (5) the evolution and (6) treatment of atypical sensory sensitivity after an acquired brain injury, and (7) injury outcomes associated with atypical sensory sensitivity. Conducting a meta-analysis was considered not feasible due to high heterogeneity in the assessment of sensory sensitivity, the study design, and the sample characteristics of the clinical populations in the included studies. Figures were created using Microsoft Excel (2019) and Adobe Illustrator (2020). Details of the included studies (including demographic characteristics of the studied sample, study design aspects) can be found in the supplementary tables as well as in the article extraction file which is available via https://doi.org/10.6084/m9.figshare.14785293.

Results

Search strategy

Figure 1 displays the study flow diagram based on the PRISMA statement (Moher et al., 2009). We identified 998 records through database screening and one additional record through other sources (i.e., library collection). 267 duplicates were removed, leaving 732 articles. Based on the exclusion criteria, we excluded 610 articles. After consulting the full text, an additional 29 articles were excluded (see Figure 1). For 12 articles the full text was not available, leaving 81 studies to be included in the analysis.

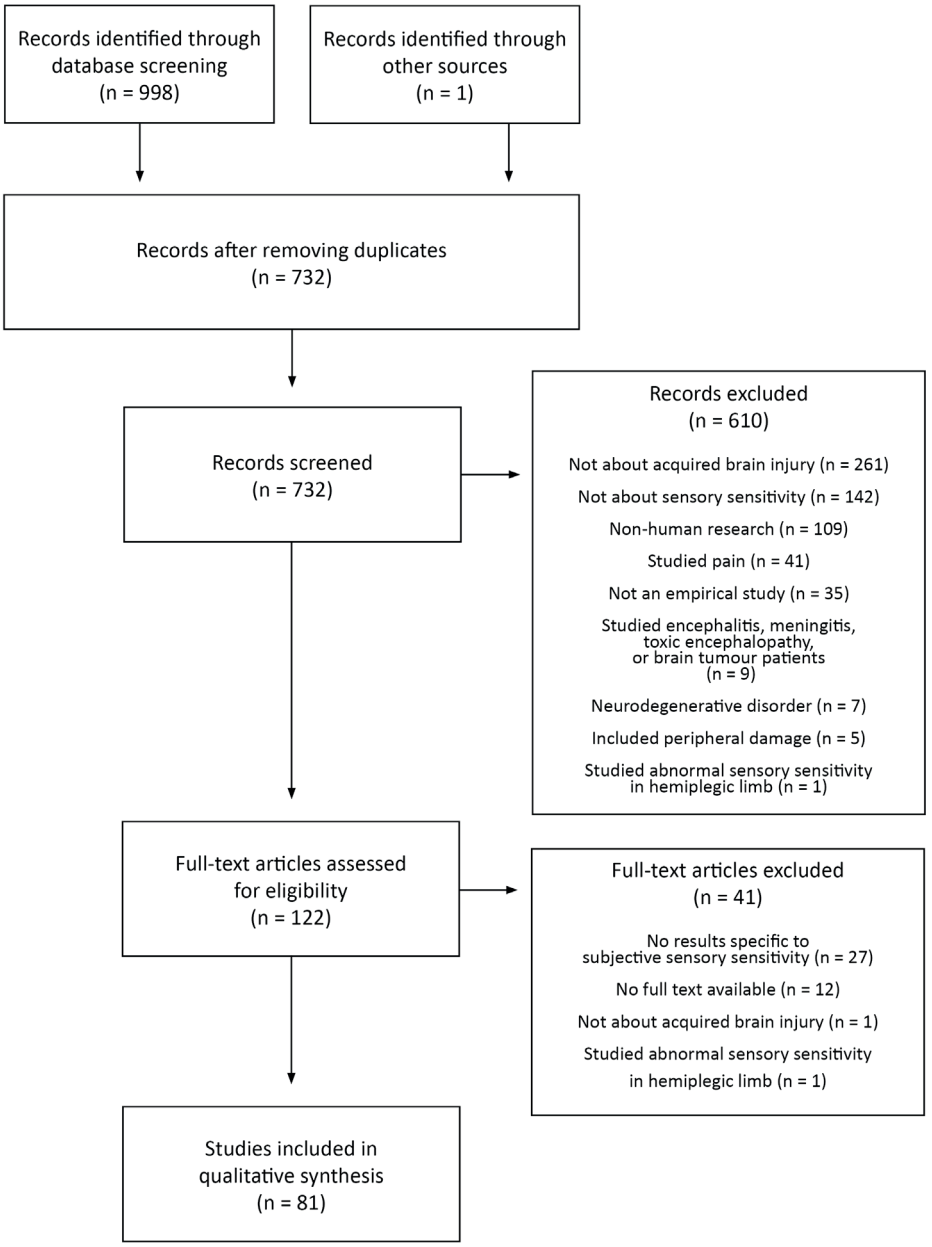


Figure 1. PRISMA flow diagram for the systematic literature review.

Study characteristics

The majority (74%) of the included studies investigated atypical sensory sensitivity in mild TBI (mTBI) patients. One study studied moderate to severe TBI (Colantonio et al., 2010). Other studies about mild to severe TBI did not clearly describe the severity of TBI (n = 6) or included participants across all TBI severities (n = 6). 95% of the included studies assessed post-injury hypersensitivity (see Figures 2 and 3). When considering the different sensory modalities, light sensitivity (73%) and auditory sensitivity (69%) were studied most frequently (see Figure 3). Lastly, more than half of the studies (58%) investigated sensory sensitivity in more than one sensory modality.

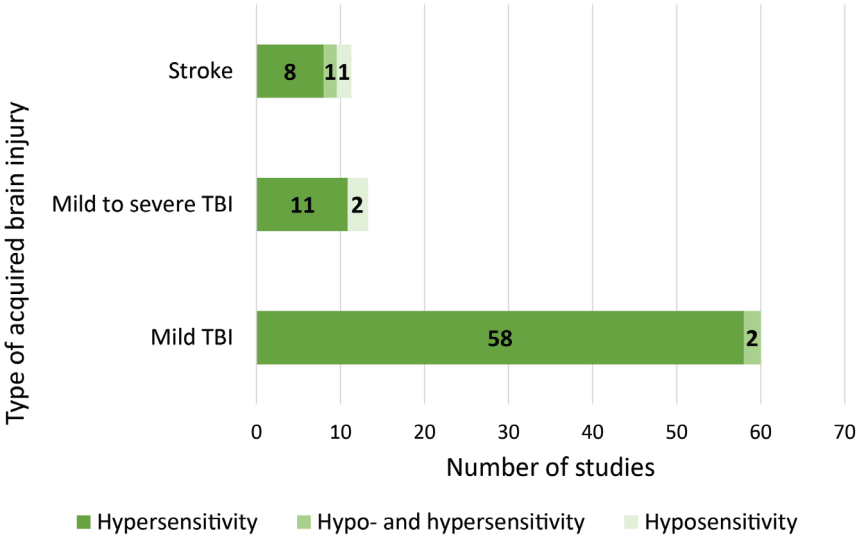


Figure 2. The number of studies that investigated post-injury hypo- and/or hypersensitivity across the different types of acquired brain injury. Note: two studies that studied both TBI and stroke were classified twice.

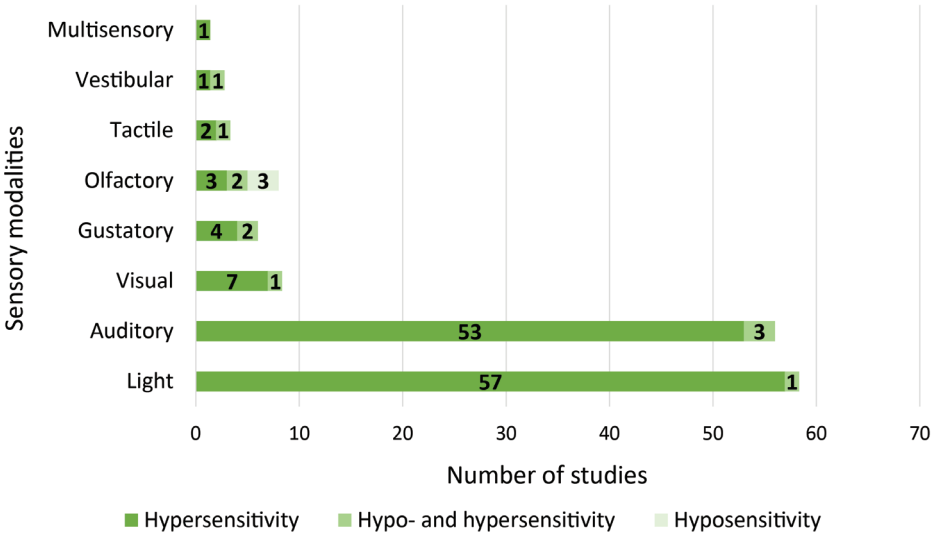


Figure 3. The number of studies that investigated post-injury sensory hypo- and/or hypersensitivity across different sensory modalities. More than half of the studies (58%) investigated sensitivity to multiple sensory modalities and were classified multiple times. Multisensory sensitivity refers to a sensitivity to multiple sensory stimuli that are present simultaneously and belong to different sensory modalities (e.g., experiencing an atypical sensitivity to the combination of visual and auditory stimulation).

Methodological quality of the included studies

The quality of the included studies is presented in Figure 4 (see also Supplementary Table 1). From the 72 studies that were classified as quantitative descriptive research (see Hong et al., 2018), one fulfilled all quality criteria. Importantly, only half of the studies (50%) assessed post-injury sensory hypo- and hypersensitivity using an appropriate method and less than a quarter of the studies (13%) clearly discussed response rate and reasons for non-response (which is needed to assess selection bias). Since there is ongoing debate about the necessity of a correction for multiple comparisons (see for example Frane, 2020), the studies that did not correct for multiple comparisons were marked as 'unclear' regarding the criterium 'appropriate statistical analysis' (if there was no other reason to mark these studies as using an inappropriate statistical analysis).

From the nine studies that were classified as qualitative research, seven fulfilled all quality criteria. Two studies (22%) did not fulfil the quality criteria because the interpretation of the results were not sufficiently supported by the data.

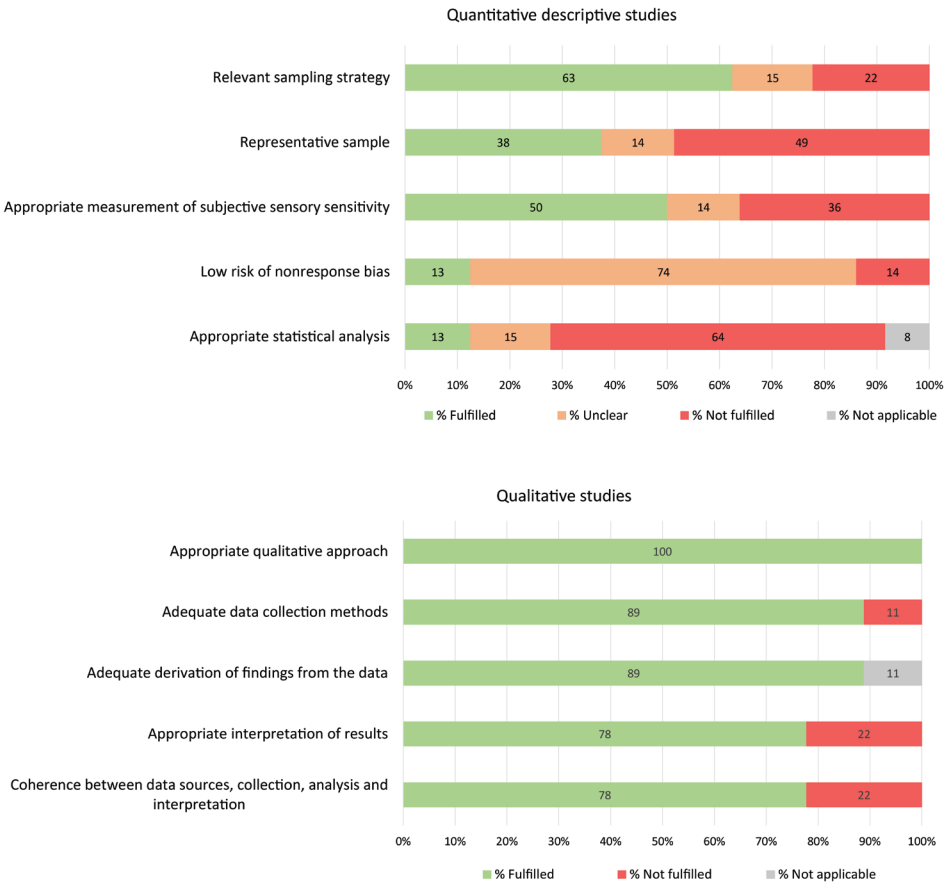


Figure 4. The % of included quantitative descriptive or qualitative studies for which the methodological criteria of the Mixed Methods Appraisal Tool (Hong et al., 2018) are fulfilled, not fulfilled, unclear, or not applicable. The behavioural and neural mechanisms of post-injury atypical sensory sensitivity

The behavioural and neural mechanisms of post-injury atypical sensory sensitivity

Table 1 summarizes the results of the studies (n = 18) that investigated behavioural (n = 7) and/or neural mechanisms (n = 10) of sensory sensitivity after acquired brain injury. One study (Pritchard et al., 1999) studied both the behavioural and neural mechanisms of atypical sensory sensitivity after acquired brain injury.

Behavioural mechanisms of sensory sensitivity

There was no evidence that post-injury sensory sensitivity across different sensory modalities (visual, auditory, tactile, gustatory, and olfactory sensitivity) was related to selective or sustained attention performance (Kumar et al., 2005; Shepherd et al., 2019). However, post-injury sensory sensitivity did correlate with time taken on neuropsychological assessments of attention and cognitive flexibility (Kumar et al., 2005; Shepherd et al., 2019). Noteworthy, in Shepherd et al. (2019), these correlations only reached significance in female participants. No evidence was found for a relationship between post-injury sensory sensitivity and other measures of psychomotor speed, memory, and executive functioning (Kumar et al., 2005; Nelson et al., 2018; Shepherd et al., 2019).

Chang et al. (2007) and Schrupp et al. (2009) studied the relationship between post-injury light and visual motion sensitivity and the critical flicker fusion frequency (i.e., the frequency at which a physically flickering light is no longer perceived to be flickering). Chang et al. (2007) found that the mean critical flicker fusion frequency at the fovea increased according to the severity of light sensitivity in mTBI patients. However, Schrupp et al. (2009) did not find evidence for such a relationship in a similar sample.

Multiple studies reported that patients with olfactory and gustatory hyposensitivity also displayed reduced behavioural sensory awareness (i.e., reduced identification of sensory stimuli or discrimination between stimuli, a higher sensory threshold) (Gudziol et al., 2014; Pritchard et al., 1999). In contrast, Wehling et al. (2015) observed a correspondence between behavioural olfactory hyposensitivity and reduced odour pleasantness, but no relationship with a reduced sense of smell.

Neural mechanisms of sensory sensitivity

Seven studies related post-injury atypical sensory sensitivity to structural brain

abnormalities. Likova and Tyler (2018) reported pontine degeneration in mTBI patients who expressed being hypersensitive to light and Lewis et al. (2020) concluded that biomarkers indicative of cellular and axonal damage (i.e., blood plasma level of ubiquitin C-terminal hydrolase L1 and glial fibrillary acidic protein) correlated with both light and noise sensitivity. Using diffusion tensor imaging, Astafiev et al. (2016) observed higher fractional anisotropy values near the left optic radiation in mTBI patients with versus without light hypersensitivity. Four case studies (Boucher et al., 2015; Cantone et al., 2019; Mak et al., 2005; Pritchard et al., 1999) related atypical post-stroke sensory sensitivity in different modalities (gustatory and olfactory for Mak et al. (2005), auditory for Boucher et al. (2015), visual for Cantone et al. (2019), and gustatory for Pritchard et al. (1999)) to insular lesions. Even though Boucher et al. (2015) focused on post-stroke hyperacusis, their two cases also reported being hypersensitive to other sensory modalities (i.e., comorbid tactile and olfactory hypersensitivity). The case discussed by Mak et al. (2005) reported a post-stroke change in his sensitivity to temperature in addition to gustatory and olfactory hypersensitivity.

Four studies related post-injury atypical sensory sensitivity to functional changes in brain activity. In the study by Astafiev et al. (2016) mTBI patients with light hypersensitivity displayed higher blood-oxygen-level-dependent (BOLD) responses in visual areas. The two stroke cases with auditory hypersensitivity discussed by Boucher et al. (2015) also displayed abnormal auditory event related potentials (i.e., larger P3b amplitude and reduced N1 amplitudes). Furthermore, Yadav and Ciuffreda (2014) and Ciuffreda et al. (2013) reported that wearing binasal occluders (with or without base-in prisms) had a different effect on the P100 amplitude in chronic mTBI patients who were hypersensitive to visual motion as compared to neurotypical adults.

Lastly, two studies related visual and auditory reflexes to post-injury sensory sensitivity. Truong and Ciuffreda (2016) found that mTBI patients who were hypersensitive to light had abnormal pupillary light reflexes which has been linked to autonomic nervous system dysfunction (Wang et al., 2016). Nölle et al. (2004) found that abnormal performance on central auditory pathway testing in mTBI patients was related to atypical auditory sensitivity.

Pre-injury factors, injury mechanisms, and comorbid symptomatology associated with post-injury atypical sensory sensitivity

Details of the studies (n = 28) discussed below can be found in Supplementary Table 2.

Demographic factors

Results on the relationship between gender and post-injury sensory sensitivity were inconsistent. Some studies found that females with a mTBI reported light or auditory hypersensitivity more frequently or with a higher severity as compared to males with a mTBI (Brickell et al., 2017; Bunt et al., 2021, 2022; Frommer et al., 2011; Shepherd et al., 2019) However, no evidence for this gender difference was found by other studies (Elliott et al., 2018; Knoll, Herman et al., 2020; Lumba-Brown et al., 2020).
Some studies reported that the prevalence of post-injury light hypersensitivity decreased with increasing age (Helmich et al., 2019; Hu et al., 2017; Karr et al., 2020). In contrast, Shepherd et al. (2019, 2021) did not find evidence for a relationship between age and post-injury auditory hypersensitivity.

Shepherd et al. (2019) observed an association between sensory sensitivity and place of living with patients from rural areas reporting higher auditory sensitivity after their mTBI than participants from urban areas. However, a more recent study by Shepherd et al. (2021) found no evidence for an association between place of living and post-injury auditory sensitivity. No study found evidence for a statistically significant association between education level and post-injury sensory sensitivity to light or noise (e.g., Elliott et al., 2018; Shepherd et al., 2019).

The severity of post-injury light and auditory hypersensitivity was higher in patients with multiple mTBIs as compared to patients with a single mTBI (Chen et al., 2019; Elliott et al., 2018; Shepherd et al., 2019). Elliott et al. (2018) did not find evidence for an association between medical comorbidities (such as diabetes, hypertension, heart, or lung disease) and post-injury sensory hypersensitivity. Lastly, Han et al. (2008) found that post-injury light hypersensitivity was reported more frequently by TBI patients who took medication (such as antidepressants, antihypertensives, analgesics) than those who did not take medication.

Mechanisms of the brain injury

There was no evidence for a different prevalence or a different severity of post-injury light or auditory hypersensitivity according to the cause of a mTBI (i.e., fall, car accident, assault, sport-related mTBI) (Knoll, Herman et al., 2020; Lumba-Brown et al., 2020; Shepherd et al., 2019). However, Goodrich et al. (2013) found that post-injury light hypersensitivity was reported more frequently by blast exposed TBI patients as

compared to non-blast exposed TBI patients, but this difference was no longer significant when mTBI patients were removed from the analyses. Post-injury auditory hypersensitivity displayed a weak negative association with injury severity (Shepherd et al., 2019).

Comorbid symptomatology

Multiple studies reported that the presence of post-injury self-reported sensory hypersensitivity was associated with an increase in the severity of other post-concussion symptoms, such as difficulties concentrating, dizziness, irritability, and tinnitus (Astafiev et al., 2016; Chandran et al., 2020; Chorney et al., 2017; Elliott et al., 2018; Forrest et al., 2018; Kumar et al., 2005; Shepherd et al., 2019, 2021). However, a reverse relationship (i.e., post-injury auditory sensitivity had a negative association with the presence of comorbid headaches) was reported by Forrest et al. (2018). Furthermore, there is evidence for an association between post-injury light and auditory hypersensitivity (i.e., Chandran et al., 2020; Shepherd et al., 2020).

Evidence for a positive relationship between post-injury atypical auditory and light sensitivity and symptoms of depression, anxiety, or post-traumatic stress disorder (PTSD) was found by multiple studies (Al-Ozairi et al., 2015; Assi et al., 2018; Callahan et al., 2018; Callahan & Storzbach, 2019; Elliott et al., 2018; Goodrich et al., 2014; Shepherd et al., 2019, 2021). One study by Nelson et al. (2018) found no evidence for such a relationship.

Furthermore, post-injury sensory hypersensitivity was associated with other psychological symptoms such as somatization (positive association) (Callahan et al., 2018; Nelson et al., 2018) and perception of recovery (negative association with auditory hypersensitivity, which was stronger for male participants as compared to female participants) (Shepherd et al., 2019). To date, there is no evidence for a relationship between post-injury sensory hypersensitivity and personality traits (e.g., Nelson et al., 2018).

Post-injury sensory hypersensitivity was related to reduced subjective sleep quality (Elliott et al., 2018; Howell et al., 2019) but not to abnormal polysomnographic metrics (Elliott et al., 2018).

The prevalence of post-injury atypical sensory sensitivity

Figure 5 displays the prevalence of post-injury hypo- and hypersensitivity categorized according to the type of acquired brain injury and sensory modality (based on n = 32 studies,

for details see Supplementary Table 3). Most of the studies (91%) investigated the prevalence of light or auditory hypersensitivity after mTBI (see Figure 5, panel A). Two studies reported prevalence rates that were specific to moderate to severe TBI patients (see Figure 5, panel B) and one study considered both mTBI and moderate to severe TBI but did not report prevalences specific to TBI severity (see Figure 5, panel C). No studies mentioned a modality-specific prevalence for atypical sensory sensitivity after non-traumatic acquired brain injury. However, Chung and Song (2016) observed a prevalence of hypo- and hypersensitivity (not specific to a certain sensory modality) in respectively 16% and 18% of stroke patients. Additionally, during semi-structured interviews stroke patients reported being hypersensitive to light, noise, textures, and environmental temperatures (Alwawi et al., 2020; Carlsson et al., 2004, 2009).

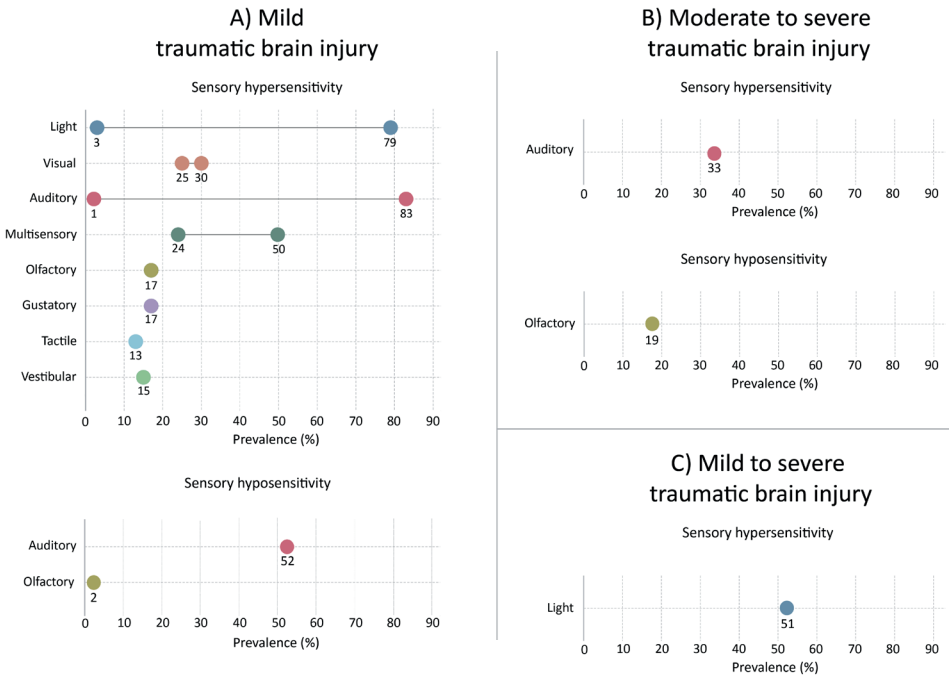


Figure 5. The prevalence of sensory hyper- or hyposensitivity after a mTBI (panel A) or after moderate to severe TBI (panel B) and mild to severe TBI (panel C) (for details of the studies see Supplementary Table 3). A single dot represents a prevalence estimate from a single study. Two dots connected by a line represent the range of estimated prevalences found in different studies with the dots representing the lowest and highest estimates.

The diagnostic tools used to assess post-injury sensory sensitivity

Table 2 outlines the different diagnostic tools that were used to assess sensory sensitivity in acquired brain injury patients. 22% of the included studies did not disclose how they measured sensory sensitivity (e.g., Chandran et al., 2020; Nölle et al., 2004; Truong & Ciuffreda, 2016) and 15% of the studies used a self-developed questionnaire (e.g., Gudziol et al., 2014; Kerr et al., 2018; Zuckerman et al., 2016). Less than half of the studies (36%) used a validated questionnaire such as the Post-Concussion Symptom Scale of the Sport Concussion Assessment Tool (e.g., Bunt et al., 2022; Lumba-Brown et al., 2020), the Rivermead Post-Concussion Symptoms Questionnaire (e.g., King & Kirwilliam, 2013; Lewis et al., 2020), or the Neurobehavioural Symptom Inventory (Brickell et al., 2017; Callahan & Storzbach, 2019). Most of the used questionnaires (85%) assessed post-injury sensory sensitivity using a single item for each modality. Additionally, assessment of post-injury sensory sensitivity mainly (in 79% of the studies) focused on light and/or noise sensitivity

Table 2. The diagnostic tools used to assess sensory sensitivity after an acquired brain injury.

Tool used to assess sensory sensitivity	% of studies (n = 81)
Unclear	22%
Self-developed	15%
Rivermead Post-Concussion Symptoms Questionnaire	15%
Post-Concussion Symptom Scale (from the Sport Concussion Assessment Tool)	10%
Medical file record	9%
Neurobehavioural Symptom Inventory	5%
Post-Concussion Symptom Scale (from the Immediate Post-Concussion Assessment & Cognitive Testing)	5%
Self-reported discomfort	5%
Subjective description (Case)	4%
Self-reported intensity	3%
Concussion Symptom Checklist	1%
Head Injury Symptom Checklist	1%
Structured Interview for Assessing Perceptual Anomalies	1%
Post-Concussion Symptom Inventory	1%
Interview	1%
Problem Checklist from the Head Injury Family Interview	1%
Adult/Adolescent Sensory Profile	1%

Evolution of post-injury atypical sensory sensitivity

Research on the evolution of post-injury atypical sensory sensitivity focused solely on hypersensitivity and was limited to six studies in mTBI patients and one study in stroke patients (see Supplementary Table 4). There is, to date, no research on the evolution of post-injury sensory hyposensitivity.

Barker-Collo et al. (2018) and Shepherd et al. (2021) provided longitudinal measures of sensory hypersensitivity at baseline, 1-, 6-, and 12-months post-injury in mTBI patients (aged 16 years or older). Barker-Collo et al. (2018) found a decreasing trend of the prevalence of post-injury light and auditory hypersensitivity from baseline to 12-months post-injury (see Figure 6, panel A). Similarly, Shepherd et al. (2021) reported that the prevalence of auditory hypersensitivity at baseline (44%) was higher than at 12-months post-injury (27%). Additionally, Shepherd et al. (2021) implied that the severity of post-injury auditory sensitivity decreased after baseline (see Figure 6, panel B). However, it must be noted that it is unclear if these reductions in mean auditory sensitivity severity remained significant after correction for multiple comparisons.

Even though the prevalence and severity of post-injury sensory hypersensitivity seem to decrease at a group level (Barker-Collo et al., 2018; Shepherd et al., 2021), the evolution of post-injury sensory hypersensitivity also varies inter-individually with some patients reporting earlier or greater alleviations of symptoms as compared to others (Alwawi et al., 2020; Truong et al., 2014). Truong et al. (2014), for instance, reported that a reduction of light hypersensitivity was only present in 50% of their sample of 62 mTBI patients and that alleviation of light hypersensitivity was lower in patients who reported other comorbid post-concussion symptoms (such as auditory hypersensitivity). Furthermore, other studies highlight that the severity of the post-injury sensory sensitivity symptoms can wax and wane intra-individually (for instance, the severity can vary according to circadian patterns) (Rabinowitz & Fisher, 2020; Truong et al., 2014).

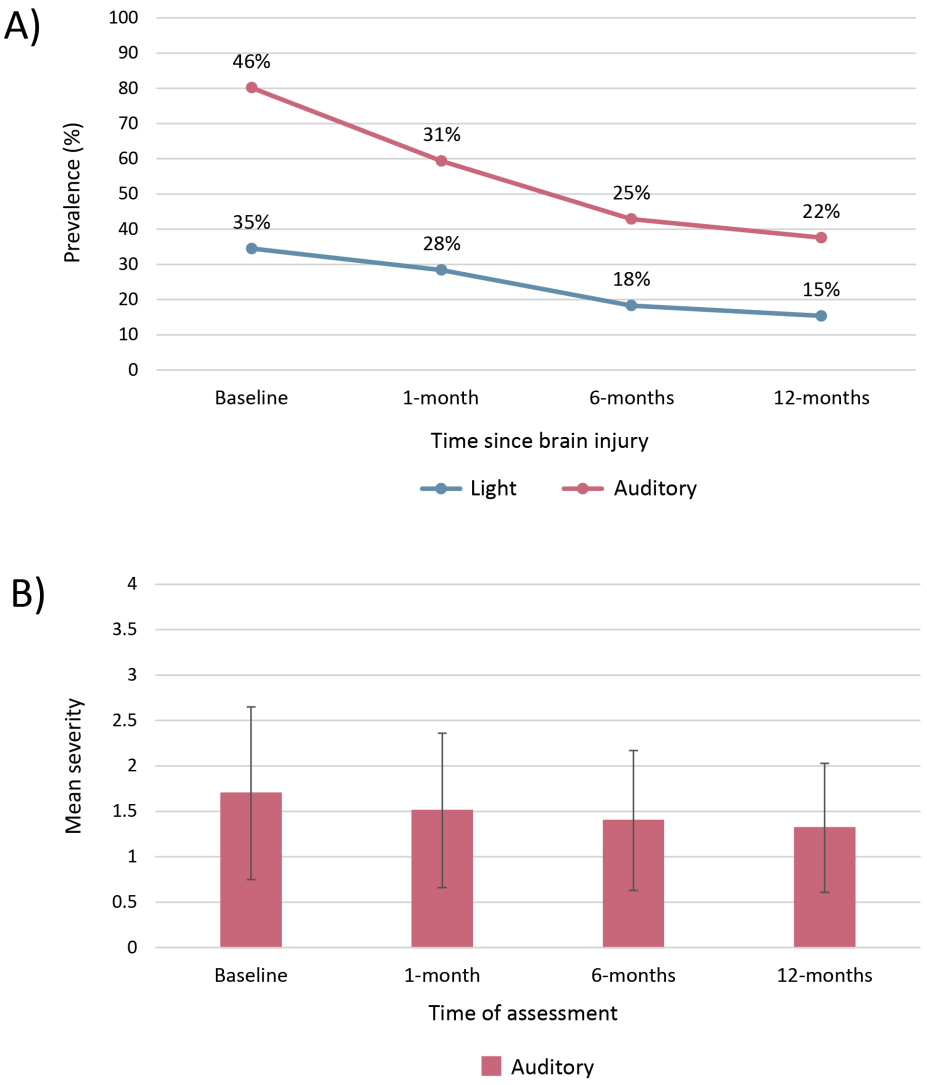


Figure 6. Panel A: The prevalence of light or auditory hypersensitivity after mTBI as reported by Barker-Collo et al. (2018). Panel B: The severity of auditory hypersensitivity after mTBI as reported by Shepherd et al. (2021). The severity scale ranged from 0 indicating no hypersensitivity to 4 indicating severe hypersensitivity. Baseline = maximally 2 weeks post-injury.

Treatment of post-injury atypical sensory sensitivity

Eight studies investigated a possible treatment for hypersensitivity after a TBI (see Supplementary Table 5). Reductions in visual hypersensitivity were reported when wearing binasal occluders (Ciuffreda et al., 2013; Yadav & Ciuffreda, 2014), coloured glasses (Clark et al., 2017), or contact lenses (Truong et al., 2014). Similarly, self-reported discomfort when exposed to a computer screen decreased when using a non-liquid crystal display (non-LCD) screen (Mansur et al., 2018) that refreshed at a lower rate than a standard LCD screen. Lastly, Gunter et al. (2018) and Teare-Ketter et al. (2021) described cases with light hypersensitivity after a mTBI. The cases were both symptom-free after several weeks of physical therapy (no specific treatment for the hypersensitivity symptoms was mentioned).

Considering auditory hypersensitivity, Hallberg et al. (2005) described a treatment program in which chronic TBI patients with post-injury auditory hypersensitivity gradually exposed themselves to an increasing intensity of environmental sounds while participating in daily life. To control this gradual exposure, patients wore individually designed attenuators which were inserted in the external auditory canal to exclude environmental sounds. Throughout the treatment, holes with an increasing diameter (1 mm to 3 mm) were drilled in the attenuators to increasingly expose participants to more external sounds. In addition, the treatment consisted of assisting patients in identifying and challenging maladaptive coping styles (i.e., inflexible avoidance) related to their sensory hypersensitivity. By means of semi-structured interviews participants evaluated the treatment program as positive: patients reported participating in a higher number of social situations as compared to before their treatment as well as being less distracted by environmental sounds.

Injury outcomes related to post-injury atypical sensory sensitivity

Fifteen studies examined the association between functional recovery and post-injury sensory sensitivity (see Supplementary Table 6). Post-injury sensory hypersensitivity was associated with an increased recovery time (Falk et al., 2021; Forrest et al., 2018; O'Kane et al., 2014), increased persistence of other post-concussion symptoms (e.g., Kerr et al., 2018; Zemek et al., 2016; Zuckerman et al., 2016), hospital reattendance (Mistry & Rainer, 2018), and decreased chances of gaining clearance to resume driving (MacDonald et al., 2018). In contrast, Mortera et al. (2018) reported that veterans with a mTBI who returned to productivity were twice as likely to report post-injury light

hypersensitivity as compared to veterans with a mTBI who did not return to productivity. Lau et al. (2011) did not find evidence for a statistically significant association between post-injury light or auditory hypersensitivity and length of recovery.

Nine studies (see Supplementary Table 6) investigated the relationship between quality of life and post-injury sensory hypersensitivity. Multiple studies reported that post-injury sensory hypersensitivity was associated with a self-reported reduction in quality of life in adult samples (e.g., reduced participation in social activities or economic difficulties) (Alwawi et al., 2020; Carlsson et al., 2004, 2009; Shepherd et al., 2020; Trulsson et al., 2003). However, Vassilyadi et al. (2014) found no evidence for a relationship between post-injury hypersensitivity to light or noise and quality of life in a non-adult sample.

Shepherd et al. (2020) found that the association between post-injury hypersensitivity and quality of life remained significant even after controlling for gender, age at injury, education level, and injury severity. Furthermore, this association differed according to sensory modality: post-injury light hypersensitivity was strongly associated with experiencing bodily pain while post-injury noise hypersensitivity was strongly associated with limitations related to emotional problems.

Colantonio et al. (2010) found an effect of gender on the relationship between post-injury auditory hypersensitivity and quality of life: men with a TBI reported a greater reduction in their quality of life due to their hypersensitivity than women with a TBI. There was no evidence for significant gender difference with regard to the reported impact of post-injury light hypersensitivity on quality of life.

Table 1. An overview of studies (n = 18) discussing the behavioural and neural mechanisms of atypical sensory sensitivity after an acquired brain injury.

Study	Type of brain injury Sample size Age of sample [Age Range] Time since injury	Hypo- or hypersensitivity Sensory modality	Measurement of subjective sensory sensitivit	Behavioural or neural mechanisms	Summary of results
				Behavioural mechanisms	
Shepherd et al. (2019)	mTBI n = 151 Adult Acute	Hypersensitivity Auditory	Rivermead Post-Concussion Symptoms Questionnaire	Complex attention (via a composite score that was based on the performance on the Continuous Performance Test, the Stroop Test, and the Shifting Attention Test) Cognitive flexibility (via a composite score that was based on the performance on the Stroop Test and the Shifting Attention Test) Information processing speed (via the reaction time on the Stroop Test) Psychomotor speed (via a composite score that was based on the performance on the Finger Tapping Task and the Symbol Digit Coding Test) Visual and verbal memory (via adaptations of the Rey Auditory Verbal Learning Test and the Rey Visual Design Learning Test)	There was no evidence for a correlation between post-injury auditory sensitivity and the composite scores measuring complex attention, psychomotor speed, visual, or verbal memory. Post-injury auditory sensitivity did correlate with reaction time on the Stroop test which is thought to measure information processing speed and the composite score of cognitive flexibility (which was based on similar tests as the complex attention score). These correlations were only significant in female participants.

Nelson et al. (2018)	mTBI n = 219 Adult Acute	Hypersensitivity Light, Auditory	Post-Concussion Symptom Scale of the Sport Concussion Assessment Tool 3	Immediate Postconcussion and Cognitive Testing	There was no evidence that factor scores containing both light and auditory sensitivity correlated with cognitive performance on the Immediate Postconcussion and Cognitive Testing.
Kumar et al. (2005)	mTBI n = 30 Adult [16-52] Acute	Hypersensitivity Visual, Auditory, Tactile, Gustatory, Olfactory	Structured Interview for Assessing Perceptual Anomalies	Selective and Sustained attention (via the Stroop test and the Digit Vigilance Test) Psychomotor speed (via the Digit Symbol Substitution Test) Executive functioning (via Animal fluency test, Wisconsin Card Sorting Test, Stroop test, and the Tower of London) Visual and verbal memory (via the Auditory Verbal Learning Test, Complex Figure Test)	Sensory sensitivity across several sensory modalities correlated with time taken on a Digit Vigilance Test (test for selective and sustained attention) but there was no evidence for a correlation with performance on the Stroop test (test for selective attention and inhibition) or with performance on other tests measuring psychomotor speed, executive functioning, or visual and verbal memory.
Gudziol et al. (2014)	TBI n = 110 Adult [18-69] Acute to chronic	Hyposensitivity Olfactory	Subjective evaluation of sense of smell (1 item)	The 'Sniffin' Sticks' test for odour threshold, discrimination, and identification Odour threshold, discrimination, and identification performance were combined in a composite score	Five patients (one with mTBI and four with moderate to severe TBI) who reported a reduced olfactory functioning due to their TBI completed the 'Sniffin' Sticks' test. They all displayed deficient performance on the olfactory testing (hyposmic: n = 3, anosmic: n = 2).

Wehling et al. (2015)	Stroke n = 78 Adult Chronic	Hyposensitivity Olfactory	Self-developed questionnaire (1 item)	Olfactory identification via the Scandinavian Odour Identification Test	Self-reported sense of smell (judged as quite poor to excellent) did not differ significantly between normosmic (n = 44) and hypo- / anosmic stroke patients (n = 30) (as identified using the Scandinavian Odour Identification Test). However, the hypo- /anosmic stroke patients reported a significantly lower odour pleasantness than normosmic stroke patients.
Schrupp et al. (2009)	mTBI n = 14 Adult [18-59] Chronic	Hypersensitivity Light, Visual motion sensitivity	Self-developed questionnaire (> 1 item per sensory modality)	Critical flicker fusion frequency at the fovea as well as in the right and left hemifield (10° horizontal retinal eccentricity)	There was no evidence for a correlation between post-injury light or visual motion sensitivity and the mean critical flicker fusion frequency at the fovea, in the right, or in the left hemifield.
Chang et al. (2007)	mTBI n = 18 Adult [19-72] Chronic	Hypersensitivity Light, Visual motion sensitivity	Self-developed questionnaire (> 1 item per sensory modality)	Critical flicker fusion frequency at the fovea	The mean critical flicker fusion frequency threshold at the fovea was significantly higher in mTBI patients who were hypersensitive to light or visual motion (n is not mentioned) as compared to mTBI patients with no light or visual motion hypersensitivity. The mean critical flicker frequency threshold increased according to light sensitivity severity.

				Neural mechanisms	
Truong and Ciuffreda (2016)	mTBI n = 32 Adult [21-60] Not reported	Hypersensitivity Light	Not reported	Pupillary light reflexes	mTBI patients who were photosensitive (n = 21) had a larger baseline pupil diameter, a larger minimum pupil diameter, faster peak dilation velocity (i.e., time between stimulus onset and peak dilation), faster redilation recovery, and larger pupil diameter (6 seconds after stimulus onset) as compared to mTBI patients who were not photosensitive (n =11).
Lewis et al. (2020)	mTBI n = 27 Adult Acute	Hypersensitivity Light, Auditory	Rivermead Post-Concussion Symptoms Questionnaire	Levels of glial fibrillary acidic protein (GFAP), Tau, ubiquitin C-terminal hydrolase L1 (UCH-L1), and cell-free DNA (cfDNA) in blood plasma	Plasma levels of UCL-L1 and GFAP were highly correlated (r > .9) with post-injury sensitivity to light and noise. There was no evidence for a correlation between Tau and cfDNA with post-injury sensitivity to light and noise.
Cantone et al. (2019)	Stroke n = 1 Adult [62] Acute	Hypersensitivity Visual	Subjective description	Lesion location	Subjective description of hypersensitivity to light (facial expression of fear and disgust with a neurovegetative reaction and horripilation in response to visual stimuli) after right temporal-insular lesion.

Study	Type of brain injury Sample size Age of sample [Age Range] Time since injury	Hypo- or hypersensitivity Sensory modality	Measurement of subjective sensory sensitivit	Behavioural or neural mechanisms	Summary of results
Likova and Tyler (2018)	mTBI n = 16 Adult [42-81] Acute to chronic	Hypersensitivity Light	Self-reported light induced discomfort when exposed to a white field stimulus flickering	Tensor-Based Morphometry	mTBI patients with light hypersensitivity (n = 11) showed mid-pontine shrinkage, consistent with degeneration of nuclei of the trigeminal complex. mTBI patients without light hypersensitivity (n = 5) showed bilateral expansion at the pontine / medulla junction.
Astafiev et al. (2016)	mTBI n = 20 Adult [20-57] Chronic	Hypersensitivity Light	Head Injury Symptom Checklist	Task-related and resting-state functional MRI Diffusion Tensor Imaging	mTBI patients with light hypersensitivity (n = 6) had higher BOLD magnitudes in the middle temporal and lateral occipital visual areas during a visual tracking task than mTBI patients without light hypersensitivity (n = 11). Similarly, task-evoked BOLD activity in the middle temporal and lateral occipital visual areas correlated with post-injury light sensitivity. mTBI patients with light hypersensitivity also had higher fractional anisotropy values near the left optic radiation.

Boucher et al. (2015)	Stroke n = 2 Adult [29-40] Chronic	Hypersensitivity Auditory, (Tactile), (Olfactory)	Hearing Sensitivity Questionnaire, loudness discomfort task	Auditory event related potential (ERP) paradigms (mismatch negativity and auditory oddball task) and lesion location	Two chronic stroke cases (both female) reported hyperacusis after insular lesion. Compared to a matched control group (n = 10), these cases showed a significantly larger P3b amplitude at the mid-parietal electrode (Pz) during an auditory oddball task. Case #1 had a reduced N1 amplitude in both the auditory oddball as well as the mismatch negativity paradigms. Case #1 mentioned a comorbid tactile hypersensitivity while Case #2 mentioned a comorbid olfactory hypersensitivity.
Yadav and Ciuffreda (2014)	mTBI n = 15 Adult [25-65] Chronic	Hypersensitivity Visual motion sensitivity	Based on medical file records	Visual evoked potentials during a conventional visual evoked potential (P100) testing while wearing binasal occluders and/or base-in prisms	Wearing binasal occluders with or without a base-in prism when looking at a full-field checkerboard stimulus (vs. not wearing binasal occluders or base-in prisms) decreased the P100 amplitude in control subjects (n = 20). In mTBI patients with visual motion hypersensitivity (n = 15) this amplitude increased as compared to the condition where participants did not wear binasal occluders or base-in prisms, but only when wearing binasal occluders without base-in prisms. Wearing the binasal occluders resulted in a self-reported reduction of symptoms in mTBI patients with visual motion hypersensitivity.

Ciuffreda et al. (2013)	mTBI n = 10 Adult Chronic	Hypersensitivity Visual motion sensitivity	Not reported	Visual evoked potential (P100) during a conventional full-field visual evoked potential testing while wearing binasal occluders	Wearing binasal occluders while looking at a full-field checkerboard stimulus (vs. not wearing binasal occluders) decreased the P100 amplitude in neurotypical adults (n = 10) while in mTBI patients with visual motion sensitivity (n = 10) this amplitude increased. mTBI patients also reported less symptoms of visual hypersensitivity when wearing binasal occluders while they caused discomfort for the neurotypical adults.
Mak et al. (2005)	Stroke n = 1 Adult [70] Chronic	Hypersensitivity Gustatory, Olfactory, (Temperature)	Rating of the intensity of gustatory and olfactory stimuli	Lesion location	A stroke case with an insular lesion reported increased intensity ratings of gustatory and olfactory stimuli especially when stimuli were presented to the contralesional nostril or the contralesional side of the tongue. The stroke patient also mentioned post-stroke alterations in his sensitivity to temperature.
Nölle et al. (2004)	mTBI n = 31 Adult [24-56] Chronic	Hyper- (n=2) and hyposensitivity (transient hearing loss) (n = 16) Auditory	Not reported	Central auditory pathway testing (recording of otoacoustic emissions, stapedial reflexes, and auditory brainstem responses)	A stroke case with an insular lesion reported increased intensity ratings of gustatory and olfactory stimuli especially when stimuli were presented to the contralesional nostril or the contralesional side of the tongue. The stroke patient also mentioned post-stroke alterations in his sensitivity to temperature.

				Behavioural and neural mechanisms	
Pritchard et al. (1999)	Stroke: n = 4 Adult [52-65] Acute TBI: n = 3 Adult [19-72] Not reported	Not reported Gustatory	Self-reported intensities of gustatory stimuli	Behavioural: Gustatory identification test Neural: Lesion location	Three stroke cases with insular lesions reported lower taste intensities on the ipsilesional side as compared to the contralesional side of the tongue. These cases also showed reduced gustatory identification when stimuli were presented to the ipsilesional side of the tongue as compared to neurotypical adults. Another stroke case (who also had an insular lesion) reported no taste intensity differences between the ipsi- and contralesional sides of the tongue. She showed no taste identification impairments. Three TBI patients (with lesions in the frontal and temporal lobes without insular damage) did not report a difference in intensity for taste stimuli applied to the right or left sides of the tongue. They also showed no taste identification impairments.

Discussion

Even though atypical sensory sensitivity after acquired brain injury is a clinically relevant symptom that can have a profound effect on quality of life or functional recovery, it is often overlooked by clinicians and researchers. This systematic review provides an overview of the existing literature on the mechanisms, prevalence, diagnosis, evolution, and treatment of post-injury sensory hypo- and hypersensitivity. Such an overview is beneficial for both clinicians and researchers as it can inform evidence-based practice, decision-making, theory building, and research initiatives. A limitation of this review is that a grey literature search was not conducted. Therefore, the results of the review may be influenced by publication bias since only published manuscripts were included. For future research it could be interesting to include the names of the diagnostic tools mentioned in Table 2 in a search string to investigate if studies that focused on concussion symptoms in general also provided relevant information on sensitivity to light or noise. However, we chose not to include such terms since an overview of diagnostic tools was not yet available prior to the execution of this systematic review, inclusion of the terms was not a priority considering the primary aims of the systematic review, and their inclusion could furthermore bias results towards research on light and noise sensitivity in mTBI as well as limit feasibility. This study has the advantage of reviewing evidence regarding hypo- and hypersensitivity across all sensory modalities and across several types of acquired brain injury. Furthermore, we did not exclude studies based on sample characteristics such as age of the participants or time since injury. This review focuses on subjective symptoms of sensory sensitivity which are often viewed as less reliable, less valid, and more biased than objective, easily quantifiable measures. However, as is mentioned in the context of pain, sensory sensitivity is by definition subjective as it cannot be directly observed. Therefore, in our opinion, focussing on patient-reported sensory sensitivity is, to date, the best available proxy for studying symptoms of sensory sensitivity (similar to what has been described for the assessment of pain by Wideman et al. (2019)). By providing an overview of the available evidence on factors related to subjective sensory sensitivity this review can inspire research on multi-modal approaches to sensory sensitivity (including assessment of the behavioural and neural mechanisms of subjective sensory sensitivity).

The behavioural mechanisms of post-injury atypical sensory sensitivity

In neurotypical adults and other clinical groups, abnormal identification and discrimination of sensory stimuli, attentional impairments, and abnormal prediction of subsequent sensory stimulation are proposed behavioural correlates of atypical sensory sensitivity. However, after acquired brain injury, the literature has only provided empirical evidence for an association between atypical sensory sensitivity on the one hand, and reduced information processing and atypical sensory thresholds on the other hand (Gudziol et al., 2014; Kumar et al., 2005; Shepherd et al., 2019). There is, to date, no evidence for an association between post-injury sensory sensitivity and reduced selective or sustained attention (Kumar et al., 2005; Shepherd et al., 2019). However, post-injury sensory sensitivity did correlate with information processing speed (i.e., time taken on attention-based neuropsychological tests) (Gualtieri & Johnson, 2006) and cognitive flexibility (in female participants) (Shepherd et al., 2019). It must be noted that Shepherd et al. (2019) used identical neuropsychological tests to measure both cognitive flexibility and attention, but the performance on these tests was operationalized in a slightly different manner (Gualtieri & Johnson, 2006). This indicates that the operationalization of performance on an attention-based task (e.g., number of errors, time taken on test) is important when considering its relationship to sensory sensitivity. Lastly, previous studies (Kumar et al., 2005; Shepherd et al., 2019) that investigated the relationship between post-injury sensory sensitivity across different modalities (visual, auditory, tactile, gustatory, and olfactory sensitivity) only used assessments of visual attention. To advance our understanding of the relationship between attention and sensory sensitivity after brain injury, studies should investigate this relationship within and across other sensory modalities. It must further be noted that the possibility remains that the underlying mechanisms that contribute to sensory hypo- and hypersensitivity after brain injury differ from those seen in other clinical groups and neurotypical adults. Further research using similar sensory sensitivity paradigms across different clinical groups as well as in neurotypical children and adults is needed to investigate whether the experienced symptoms of sensory sensitivity as well as its underlying mechanisms are similar, identical, or dissimilar across the different populations.

Studies that investigated the association between subjective sensory sensitivity and objective identification and discrimination of sensory stimuli are sparse. Research on this relationship mainly focused on gustatory and olfactory sensitivity where post-injury subjective hyposensitivity was related to reduced identification or discrimination of

taste and smell stimuli (Gudziol et al., 2014). To date, it remains unclear if post-injury sensory hypersensitivity is associated with a heightened identification or discrimination of sensory stimuli. Chang et al. (2007) reported that post-injury light hypersensitivity was related to a heightened critical flicker fusion frequency (but see Schrupp et al. (2009)). This means that visual stimuli that are normally perceived as constant (such as lights or computer screens), may cause discomfort because they are perceived as flickering (at a higher frequency) by hypersensitive patients. Correspondingly, using a non-LCD screen that does not flicker (but only refreshes when new content is shown) alleviated light hypersensitivity in mTBI patients (Mansur et al., 2018). Further research is needed to examine whether post-injury subjective hypersensitivity to other sensory modalities is related to heightened sensory processing (e.g., increased identification or discrimination of sensory stimuli, reduced sensory thresholds).

Neural mechanisms of post-injury atypical sensory sensitivity

Research on the neural mechanisms of post-injury sensory hypersensitivity yielded variable results. For instance, post-injury hypersensitivity has been related to structural grey or white matter abnormalities in different brain regions (e.g., the insula or the pons) (e.g., Astafiev et al., 2016; Boucher et al., 2015; Cantone et al., 2019; Likova, & Tyler, 2018) and to functional abnormalities in sensory cortices (Astafiev et al., 2016). In addition, post-injury atypical sensory sensitivity has been related to atypical event related potentials (e.g., Boucher et al., 2015; Ciuffreda et al., 2013; Yadav & Ciuffreda, 2014), central pathology (as measured using auditory reflexes) (Nölle et al., 2004), or autonomic nervous dysfunction (as measured using the pupillary light reflex) (Truong & Ciuffreda, 2016). Given the small sample size of the studies discussed above (see Table 1), replication of these results is warranted. It remains unclear how the different results can be unified into a comprehensive framework on the direct and indirect contribution of neural damage to atypical sensory sensitivity after acquired brain injury. In this regard, further research on the neuroanatomy of post-injury atypical sensory (hypo- and hyper) sensitivity at a high spatial resolution is warranted. To distinguish whether injury to a certain region is truly associated with the symptomatology or whether it simply reflects high vulnerability to injury, it is advised that future studies consider the lesions of patients with as well as without atypical sensory sensitivity. In addition, further functional magnetic imaging research could reveal how network abnormalities or abnormal cortical activation might be related to atypical sensory sensitivity.

Potential protective and risk factors associated with post-injury atypical sensory sensitivity

To gain information about potential protective and risk factors, a second aim of the systematic review was to provide an overview of demographic variables, injury mechanisms, and comorbid symptomatology associated with post-injury atypical sensory sensitivity. The results discussed below are based upon research about post-injury sensory hypersensitivity. Firstly, we observed inconsistent results regarding the relationship between post-injury sensory sensitivity and age or gender (Brickell et al., 2017; Bunt et al., 2021, 2022; Frommer et al., 2011; Helmich et al., 2019; Hu et al., 2017; Lumba-Brown et al., 2020; Shepherd et al., 2019). These inconsistencies between studies could be due to differences in sample characteristics (i.e., time since injury), study design (i.e., diagnostic tools used to assess sensory sensitivity, sensory modalities of interest), or other factors. Furthermore, it remains unclear how we should interpret these associations: do they reflect age- and gender-related differences in underlying neural or cognitive mechanisms, in factors related to the maintenance of symptoms (e.g., illness beliefs), or in health behaviour in general? There are, for instance, indications of gender-related differences in the relationship between post-injury sensory sensitivity and cognitive flexibility (Shepherd et al., 2019), perception of recovery (Shepherd et al., 2019), and quality of life (Colantonio et al., 2010).

To date, there is no evidence for a relationship between post-injury sensory sensitivity and education level (Elliott et al., 2018; Shepherd et al., 2019). However, there was inconsistent evidence regarding an association between place of living and post-injury auditory hypersensitivity (Shepherd et al., 2019, 2021). These results may reflect an association between sensory sensitivity and socio-economic status (which is broader than solely education level and additionally includes occupation and income (e.g., Cirino et al., 2002)), a link between sensory sensitivity and pre-injury exposure (and habituation) to sensory stimuli, or other psychosocial factors (e.g., availability of social support, pre-injury depression, and anxiety levels).

When considering medical background, there is evidence for a relationship between atypical sensory sensitivity and the number of mTBIs or medication use (e.g., Chen et al., 2019; Han et al., 2008). This indicates a potential negative relationship between the severity of post-injury atypical sensory sensitivity and medical (i.e., vascular or neural) or cognitive reserve. However, in contrast to this hypothesis, post-injury auditory

hypersensitivity was negatively associated with injury severity (Shepherd et al., 2019) and the severity or prevalence of hypersensitivity did not differ according to the cause of the TBI (e.g., incidental causes such as falls and car accidents or causes that increase the incidence of acquiring multiple TBIs such as sport-related TBI) (e.g., Knoll, Herman et al., 2020; Lumba-Brown et al., 2020).

Noteworthy, multiple studies found an association between post-injury atypical sensory sensitivity on the one hand and symptoms of anxiety, depression, post-traumatic stress, and lower sleep quality on the other hand (e.g., Al-Ozairi et al., 2015; Assi et al., 2018; Callahan et al., 2018; Callahan & Storzbach, 2019; Elliott et al., 2018; Goodrich et al., 2014; Shepherd et al., 2019). Furthermore, there is evidence for a relationship between illness beliefs such as somatization or perception of recovery and post-injury sensory hypersensitivity (Callahan et al., 2018; Nelson et al., 2018; Shepherd et al., 2019). This indicates that coping can influence the incidence or the persistence of atypical sensory sensitivity after acquired brain injury. These results seem to support the 'anxiety hypothesis' as well as the 'negative affect hypothesis' of sensory hypersensitivity (Shepherd et al., 2019). The anxiety hypothesis postulates that sympathetic overarousal (often linked to stress or anxiety) leads to a hypervigilance for environmental stimuli, whereas the negative affect hypothesis postulates that self-reported sensory sensitivity is linked to tendency to negatively appraise situations or the self. However, the causal relationship between atypical sensory sensitivity and maladaptive coping, depression, anxiety, or stress after acquired brain injury remains unclear.

A biopsychosocial model of post-injury atypical sensory sensitivity

The results discussed above suggest that the aetiology of post-injury atypical sensory sensitivity is multifactorial and may include both biological (such as injury severity), social (such as place of living), and psychological factors (such as anxiety, stress, coping). Therefore, we propose that a model of sensory sensitivity after an acquired brain injury should not only consider the behavioural and neural mechanisms of sensory sensitivity but also the influence of other biopsychosocial factors. It remains unclear if the relationship between these biopsychosocial factors and sensory sensitivity differs for sensory hypo- and hypersensitivity. Since previous research mainly focused on post-injury sensory hypersensitivity, more research on the mechanisms of post-injury sensory hyposensitivity is needed. Furthermore, instead of considering an identical stable pathological process that underlies atypical sensory sensitivity in each patient (a

latent disease model) it is possible that the underlying mechanisms of these symptoms vary inter- and intra-individually (Rabinowitz & Fisher, 2020). For instance, in the acute phase after injury atypical sensory sensitivity might be linked to neurogenic injury-related factors, while in the chronic phase after injury the maintenance of these symptoms might be linked to psychosocial factors (e.g., perceived social support, coping, and anxiety). Future research is needed to grasp how inter- and intra-individual differences might covary with the biopsychosocial correlates of post-injury atypical sensory sensitivity. Lastly, it must be noted that the aim of this systematic review was to investigate the underlying mechanisms of abnormal sensory sensitivity in acquired brain injury populations. The results described above provide evidence for certain behavioural, neural, and psychosocial correlates of sensory sensitivity. Whether these relationships are causal remains unclear and necessitates further research in larger samples (for example using lesion studies or randomized experimental designs).

The prevalence and diagnosis of post-injury atypical sensory sensitivity

As illustrated in Figure 5, there was a large variability in the reported prevalence of post-injury sensory hypersensitivity across the different sensory modalities. This variation as well as the focus on mTBI might be due to a lack of appropriate and validated diagnostic tools for sensory sensitivity. Since light and auditory hypersensitivity are known symptoms of a concussion (e.g., Tator et al., 2016), questionnaires on post-concussive symptoms (such as the Rivermead Post-Concussion Symptoms Questionnaire) (e.g., Potter et al., 2006) often assess light and/or noise hypersensitivity. However, as illustrated in Figure 5, post-injury atypical sensory sensitivity is not limited to light or noise sensitivity but can extend across different modalities. Furthermore, the limited number of results regarding sensory sensitivity after stroke (Alwawi et al., 2020; Carlsson et al., 2004, 2009; Chung & Song, 2016; Wehling et al., 2015) or moderate to severe TBI (Goodrich et al., 2014; Knoll, Lubner et al., 2020) indicate that atypical sensory sensitivity is also prevalent after more severe brain injury. To date, there is no validated measure that is adapted to acquired brain injury, that can be used in patients with severe cognitive disabilities, and can assess sensory sensitivity across all modalities (visual, auditory, tactile, gustatory, olfactory, vestibular). Therefore, the prevalence of post-injury atypical sensory sensitivity in other modalities, after moderate to severe brain injury, as well as hyposensitivity in general might be underestimated due to a lack of diagnostic tools. The development of such diagnostic tools would further facilitate the assessment of post-injury sensory hypo- and hypersensitivity across different types of acquired brain

injury. For instance, since the current literature is limited to TBI and stroke, it is uncertain how prevalent atypical sensory sensitivity is after hypoxia or anoxia. Furthermore, it is unclear how prevalent post-injury hypo- or hypersensitivity are across different types of strokes (e.g., stroke due to infarction vs. haemorrhage, lacunar infarction vs. severe stroke), indicating the need for further research. Lastly, research on the prevalence of atypical sensory sensitivity in children with a brain injury was limited to four studies of which the majority investigated sport-related TBI. Further research in children and adolescents with other types of brain injury is advised, especially since these symptoms might have a large impact on the social and academic development of children.

The evolution and treatment of post-injury atypical sensory sensitivity

In contrast to its relatively high prevalence, knowledge on the evolution and treatment of hypo- and hypersensitivity after acquired brain injury is limited. There is evidence that the prevalence and severity of post-injury sensory hypersensitivity decreases within the first year after a mTBI (Barker-Collo et al., 2018; Shepherd et al., 2021) (see Figure 6), nevertheless the symptomatology remained substantial in the chronic stage after brain injury (e.g., Alwawi et al., 2020; Truong et al., 2014). The recovery of atypical sensory sensitivity after brain injury shows inter- and intra-individual variation (Alwawi et al., 2020; Rabinowitz & Fisher, 2020; Truong et al., 2014), which could be due to an influence of other covariates (such as medical background, coping, or comorbid symptomatology). Furthermore, it remains unclear whether hypo- and hypersensitivity symptoms are more prevalent in the acute phase and then recover spontaneously or whether these symptoms become more prevalent when patients leave a hospital context (which is a controlled sensory environment) and return to their sensory rich daily lives. Patients with mild acquired brain injury (such as a mTBI) often return to the sensory rich daily lives quicker than patients with severe acquired brain injury (such as a severe TBI or a stroke) (Prince & Bruhns, 2017). Therefore, mTBI patients might be confronted earlier and to a greater extent with atypical post-injury sensory sensitivity than patients with severe injury. The latter patients can have severe motor, cognitive, or speech impairments which are often the focus of rehabilitation. We hypothesize that this may explain the negative relationship between auditory hypersensitivity and injury severity that was found by Shepherd et al. (2019). Future research is needed to understand if and how individual characteristics and/or underlying mechanisms might influence prognosis. Moreover, more knowledge regarding symptom evolution can guide clinical decisions on whether to offer treatment as well as when to start treatment.

An overview of the research on the treatment of post-injury atypical sensory sensitivity consisted of a small number of studies that focused on hypersensitivity. Some studies reported that patients with visual hypersensitivity benefited from tools such as coloured glasses, contact lenses, or non-LCD screens (e.g., Clark et al., 2017; Mansur et al., 2018; Truong et al., 2014). However, the ecological validity of some of these studies (e.g., Clark et al., 2017; Mansur et al., 2018) is limited since patients did not use these tools in their daily lives but in a controlled, experimental setting in the presence of others, thus increasing the risk of observer bias. Furthermore, although these tools may provide immediate relief, their long-term effects are unclear. These treatments may indeed be detrimental in the long term. Firstly, these tools may result in increased avoidance of sensory stimuli which could impair sensory adaptation as well as might lead to using maladaptive, inflexible coping strategies. Secondly, relying on an external tool to provide symptom relief might decrease patient empowerment. In contrast, Hallberg et al. (2005) found that a treatment program consisting of psychological interventions combined with gradual desensitization to sounds in the daily lives of participants, resulted in less self-reported disabilities in TBI patients. However, since there was no control group it is not certain to what extent these effects can be explained by spontaneous recovery. Furthermore, Hallberg et al. (2005) did not include a quantitative evaluation of their recovery and did not include a follow-up assessment. Similar treatment strategies can be found in graded exposure or desensitization treatments used for chronic pain (e.g., López-De-Uralde-Villanueva et al., 2016), post-traumatic stress, or anxiety disorders (e.g., Forbes et al., 2007; McLay et al., 2011). For these clinical groups evidence-based protocols for graded exposure exist which can act as inspiration for the development of future evidence-based rehabilitation protocols for brain injury patients (e.g., Foa et al., 2009; Simons et al., 2019). Noteworthy, the described treatments do not seem to target behavioural or neural factors that may initiate the symptoms but rather focus on psychological factors related to maintenance of symptoms or providing external tools that provide relief of symptoms.

Conclusion

A better understanding of the underlying behavioural and neural correlates of post-injury atypical sensory sensitivity as well as the biopsychosocial factors that play a role in the incidence and persistence of atypical sensory sensitivity are essential to efficiently treat sensory hypo- and hypersensitivity as well as predict symptom evolution. To achieve this, certain inconsistencies in the existing literature must be resolved. Ideally, similar paradigms are used across different sensory modalities, different types of brain injury, and different phases after injury (e.g., the (sub)acute and chronic phases). To date, most of the research used an unvalidated diagnostic

tool to assess post-injury sensory sensitivity and assessment was often limited to light and auditory hypersensitivity after a mTBI. This again emphasizes the large need for validated diagnostic tools that are adapted to acquired brain injury patients (i.e., can be used after mild and severe brain injury) and assess hypo- and hypersensitivity across multiple modalities. It must be noted that a hyposensitivity to vestibular, visual, or tactile stimuli might be hard to diagnose in patients with motor disabilities (e.g., hemiparesis) (e.g., Lawrence et al., 2001; Wallen et al., 2001) as well as patients with sensory dysfunctions (such as hemianopia or hemispatial neglect) (e.g., Goodwin, 2014) which are highly prevalent after an acquired brain injury. Correspondingly, the studies that assessed hyposensitivity did not indicate whether their included participants had peripheral injuries that could explain their symptoms (e.g., Nölle et al., 2004). Lastly, the terminology that is used to describe atypical sensory sensitivity showed large variation across different studies. For instance, nomenclature used to describe auditory sensitivity included hyperacusis, phonophobia, and noise sensitivity, but the definition of these concepts as well as the distinction between these concepts remain unclear (see also Hallberg et al., 2005). This highlights the need for the development of a golden standard regarding assessment that takes the aforementioned challenges into consideration, as well as a consensus regarding the definition of atypical sensory sensitivity after acquired brain injury.

Further research on effective diagnosis and treatment of post-injury atypical sensory sensitivity is of high importance. Firstly, post-injury sensory hypersensitivity is negatively related to functional recovery time and quality of life (e.g., Alwawi et al., 2020; Carlsson et al., 2004, 2009; Shepherd et al., 2020; Trulsson et al., 2003). Secondly, experiencing post-injury atypical sensory sensitivity was related to increased self-reported severity of other neurological (e.g., tinnitus) or cognitive symptoms (e.g., difficulty concentrating) (e.g., Chandran et al., 2020; Chorney et al., 2017; Elliott et al., 2018; Kumar et al., 2005; Shepherd et al., 2019). Thirdly, acquired brain injury patients report that their sensory sensitivity symptoms are often not addressed by health care providers, increasing patients' feelings of anxiety and stress (Alwawi et al., 2020; Landon et al., 2012). Since an evidence-based treatment protocol is not yet available, early interventions including adequate diagnosis and evidence-based psychoeducation are needed to facilitate recovery and adaptive coping. The development of valid diagnostic tools can advance our understanding of the aetiology of post-injury atypical sensory sensitivity as well as its prevalence, evolution, and treatment and simultaneously increase the methodological quality of future research. These advances in scientific knowledge can lead to better patient care as well as a reduction in the disabilities related to atypical sensory sensitivity after acquired brain injury.



“Sensory hypersensitivity feels like an overload in my brain. I can’t process all the sensory stimuli that surround me, which makes me want to escape.”

Chapter three

The Multi-Modal Evaluation of Sensory Sensitivity (MESSY): assessing a commonly missed symptom of acquired brain injury

Sensory hypersensitivity is common after acquired brain injury. Since appropriate diagnostic tools are lacking, these complaints are overlooked by clinicians and available literature is limited to light and noise hypersensitivity after concussion. This study aimed to investigate the prevalence of sensory hypersensitivity in other modalities and after other types of brain injury. We developed the Multi-Modal Evaluation of Sensory Sensitivity (MESSY), a patient-friendly questionnaire that assesses sensory sensitivity across multiple sensory modalities. 818 neurotypical adults (mean age = 49; 244 male) and 341 chronic acquired brain injury patients (including stroke, traumatic brain injury, and brain tumour patients) (mean age = 56; 126 male) completed the MESSY online. The MESSY had a high validity and reliability in neurotypical adults. Post-injury sensory hypersensitivity (examined using open-ended questions) was reported by 75% of the stroke patients, 89% of the traumatic brain injury patients, and 82% of the brain tumour patients. These complaints occurred across all modalities with multisensory, visual, and auditory hypersensitivity being the most prevalent. Patients with post-injury sensory hypersensitivity reported a higher sensory sensitivity severity on the multiple-choice items of the MESSY as compared to neurotypical adults and acquired brain injury patients without post-injury sensory hypersensitivity (across all sensory modalities) (effect sizes (partial eta squared) ranged from .06 to .22). These results show that sensory hypersensitivity is prevalent after different types of acquired brain injury as well as across several sensory modalities. The MESSY can improve recognition of these symptoms and facilitate further research.

Thielen, H., Huenges Wajer, I.M.C., Tuts, N., Welkenhuyzen, L., Lafosse, C., & Gillebert, C.R. (2023). The Multi-Modal Evaluation of Sensory Sensitivity (MESSY): assessing a commonly missed symptom of acquired brain injury. The Clinical Neuropsychologist, 1-35.

Acquired brain injuries pose a major challenge to the public health system. Every year, about 1.5 million patients with a traumatic brain injury are admitted to a European hospital and by 2030 researchers estimate that there will be 23 million first ever stroke survivors worldwide (Majdan et al., 2016; Strong et al., 2007). Acquired brain injuries are any injuries to the central nervous system that are not congenital, neurodegenerative, or caused by birth trauma (World Health Organization, 2006). These injuries are a leading cause of disability due to their persisting impacts on motor, cognitive, and psychosocial functioning (Lezak et al., 2012; Lv et al., 2021; Marshall et al., 2007; Schneider et al., 2021). A lesser-known consequence of acquired brain injury is sensory hypersensitivity. Sensory hypersensitivity after brain injury can be defined as a self-reported post-injury increase in sensitivity to sensory stimuli, which may manifest itself as an altered response to sensory stimuli (Thielen et al., 2022). Importantly, hypersensitivity after acquired brain injury does not refer to an excessively high sensory sensitivity as compared to neurotypical controls but to an increase in sensory sensitivity post-injury as compared to before the brain injury (similar to Marzolla et al., 2022; Shepherd et al., 2020). Patients with post-injury sensory hypersensitivity can, for instance, experience physical pain, dizziness, fatigue, anxiety, or feel emotionally overwhelmed when surrounded by sensory stimuli (Alwawi et al., 2020; Hallberg et al., 2005; Landon et al., 2012; Thielen, Tuts et al., 2023).

These complaints, which are not limited to acquired brain injury patients but are also seen in the neurotypical population and other clinical conditions (e.g., autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), schizophrenia, Tourette syndrome), are measured along a continuum ranging from a low to a high severity of sensory sensitivity (e.g., Bijlenga et al., 2017; Dixon et al., 2016; Greven et al., 2019; Isaacs & Riordan, 2020; Kamath et al., 2020; Weiland et al., 2020; Zhou et al., 2020). An important distinction between the acquired brain injury population and the other populations in which sensory hypersensitivity is described, is that sensory hypersensitivity after brain injury is linked to a specific life event (the acquisition of a brain injury). Indeed, sensory hypersensitivity can be present within hours or days after brain injury but can also persist up to years after the injury (Alwawi et al., 2020; Landon et al., 2012; Lumba-Brown et al., 2020; Marzolla et al., 2022; Nelson et al., 2018). Since the processing of environmental sensory stimuli is needed for nearly every activity of daily living, sensory hypersensitivity can have an extensive impact on quality of life. In adults with an acquired brain injury, post-injury sensory hypersensitivity is related to mental health difficulties, poorer functional outcomes, and decreased participation in occupational and social

activities (e.g., Carlsson et al., 2009; Forrest et al., 2018; Shepherd et al., 2020; for an overview see Thielen et al., 2022). Due to a lack of scientific attention, the underlying mechanisms of these subjective symptoms are still unclear and there are no evidence-based treatments yet (Thielen et al., 2022).

Scientific research has mostly concentrated on light and noise hypersensitivity after mild traumatic brain injury (Thielen et al., 2022). However, a limited number of studies indicate that sensory hypersensitivity is also prevalent following other (more severe) types of brain injury and can affect all sensory modalities (Alwawi et al., 2020; Kumar et al., 2005; Ochi et al., 2022). Indeed, Chung and Song (2016) reported that 18% of stroke survivors complain of multi-modal sensory hypersensitivity. For adults with a brain tumour this prevalence was estimated at 46% (Ochi et al., 2022) and for adults with a moderate to severe brain injury at 33% (specific to auditory hypersensitivity) (Knoll, Lubner et al., 2020). The focus on light and noise hypersensitivity after mild traumatic brain injury is most likely driven by the diagnostic tools that are currently available (Thielen et al., 2022). After mild traumatic brain injury, post-injury sensory hypersensitivity is routinely assessed using a post-concussion questionnaire (such as the Rivermead Post-Concussion Symptoms Questionnaire), which measures the severity of hypersensitivity to light and noise, among other common post-concussion symptoms (King et al., 1995). This means that assessment of post-injury sensory hypersensitivity is often limited to a questionnaire designed specifically for a particular type of mild brain injury (concussion), using only two items that assess sensitivity in two specific sensory modalities. The limited number of studies that assess multi-modal sensory hypersensitivity after brain injury used non-standardized procedures (e.g., a semi-structured interview by Alwawi et al. (2020)) or measures that have not been validated in acquired brain injury patients (e.g., Kumar et al. (2005) and Ochi et al., (2022)). There is a large need for a questionnaire that can be used after mild and severe brain injury and assesses sensory hypersensitivity across all sensory modalities. The lack of adequate tools has complicated the diagnosis of these symptoms after brain injury. As a possible consequence, the prevalence of these symptoms may be underestimated and symptoms of post-injury sensory hypersensitivity are often overlooked by clinicians prohibiting adequate treatment.

The present study had four objectives. Firstly, we developed the Multi-Modal Evaluation of Sensory Sensitivity (MESSY). The MESSY is a patient-friendly questionnaire that assesses sensory sensitivity across multiple sensory modalities (i.e., visual, auditory,

tactile, olfactory, gustatory, and motion sensitivity as well as sensitivity to environmental temperature). Secondly, we examined the psychometric properties of an online version of the MESSY in a large sample of neurotypical adults and chronic acquired brain injury patients (adults with a stroke, traumatic brain injury, or brain tumour). Specifically, we investigated the internal consistency of the MESSY, its convergent and discriminant validity, and its test-retest reliability in neurotypical adults. In addition, we assessed the factor structure and measurement invariance of the MESSY across neurotypical adults and adults with an acquired brain injury to see if its items measure the same latent constructs in the two groups (Hirschfeld, 2014). Thirdly, we provided normative data for the MESSY and assessed the influence of age, gender, and education level on sensory sensitivity in neurotypical adults. Based on previous studies in neurotypical adults and adults with acquired brain injury we expected females to report higher sensory sensitivity than males (Al-Momani et al., 2020; Benham, 2006; Bunt et al., 2021; Shepherd et al., 2019; Ueno et al., 2019). In neurotypical adults and adults with an acquired brain injury, a relation between age and sensory sensitivity has not been consistently found (Gándara-Gafo et al., 2019; Helmich et al., 2019; Shepherd et al., 2019; Ueno et al., 2019) and, to date, there is no evidence supporting an association between education level and sensory sensitivity (Gándara-Gafo et al., 2019; Shepherd et al., 2019). Thus, we did not expect to find evidence for effects of age and education level on sensory sensitivity. Our fourth and final aim was to examine the severity of sensory hypersensitivity in acquired brain injury patients. To this end, we computed the number of acquired brain injury patients with post-injury sensory hypersensitivity (i.e., patients that reported a post-injury increase in their sensory sensitivity) (per sensory modality) based on open-ended questions. Then we investigated whether patients with post-injury sensory hypersensitivity displayed a higher sensory sensitivity severity (judged using multiple-choice items) as compared to neurotypical adults as well as acquired brain injury patients without post-injury sensory hypersensitivity.

Methods

Respondents

Respondents were recruited through social media, patient newsletters, by contacting participants who had previously participated in research in the department of Brain and Cognition (KU Leuven), by contacting the social networks of the researchers, and by distributing the study link to acquired brain injury patients who received out-patient rehabilitation at Hospital East-Limburg or at the University Medical Center Utrecht using

convenience sampling. In addition, first-year psychology students enrolled at the KU Leuven in November 2022 were invited to complete the survey.

To be included in this study respondents had to complete both the MESSY as well as a structural anamnesis. All respondents had to be adult (aged 18 years or above). Respondents were excluded if they reported having a formal diagnosis of autism spectrum disorder, ADHD, or schizophrenia. Neurotypical adults were additionally excluded if they reported having a neurological condition, if they experienced symptoms of a psychiatric disorder in the month previous to participation, or had a probable history of brain injury (including a concussion with post-concussive symptoms). Adults with an acquired brain injury were assigned to three groups based on the (self-declared) type of brain injury: adults with a traumatic brain injury, a stroke, or a brain tumour. Due to the limited number of respondents with anoxia (n = 1), hydrocephalus (n = 2), meningitis, or encephalitis (n = 5), these respondents were not included. Furthermore, respondents were excluded if: they did not know which type of acquired brain injury they had, they had a history of multiple brain injuries of different types (i.e., respondents who reported having a stroke as well as traumatic brain injury at different time points), or they received in-patient medical care during the month before participation.

Materials

MESSY-NL

The Dutch version of the MESSY (MESSY-NL) consists of two parts. The first part of the MESSY comprises eight open-ended questions which are used to assess whether acquired brain injury patients experienced an increase in their sensitivity from pre- to post-injury for each specific modality (i.e., "Since your brain injury, have you become more sensitive to sounds? How did you notice this or in which situations did you notice this?") (see Panel A of Figure 1 for an illustration of an open-ended question of the MESSY assessing increased olfactory sensitivity). Investigating this increase in the sensory sensitivity after brain injury is needed to make a distinction between sensory hypersensitivity after acquired brain injury and pre-existing complaints (since sensory hypersensitivity is also prevalent in neurotypical adults) (Greven et al., 2019) as seen in previous studies investigating sensory hypersensitivity after acquired brain injury (e.g., Ochi et al., 2022; Shepherd et al., 2019). If acquired brain injury patients reported a heightened sensory sensitivity since their injury, they were asked whether this was still present in the month before their participation. Neurotypical adults filled in eight

similar open-ended questions that focused on a change in the previous month (i.e., "In the previous month, have you become more sensitive to sounds? How did you notice this or in which situations did you notice this?").

The second part of the MESSY consists of multiple-choice items and is used to assess the severity of sensory sensitivity across several modalities (i.e., visual, auditory, tactile, olfactory, gustatory, and motion sensitivity as well as sensitivity to environmental temperature and to multisensory stimulation). Multisensory stimulation refers to stimulation from different sensory modalities that is present simultaneously (for instance, concurrent visual and auditory stimuli). During the development of the MESSY, we generated 30 items based on semi-structured interviews with acquired brain injury patients (n = 10) and clinical neuropsychologists (n = 3) as well as a pilot version of the MESSY (Thielen, Tuts et al., 2023). We also piloted existing sensory sensitivity questionnaires that were developed for neurotypical adults or adults with autism spectrum disorder (the Adult/Adolescent Sensory Profile and Glasgow Sensory Questionnaire) in five acquired brain injury patients and five neurotypical elderly. We found that these questionnaires were not suitable for acquired brain injury patients and neurotypical older adults. Their items, for instance, contain multiple negations (e.g., 'I don't like particular food textures' in the Adult/Adolescent Sensory Profile), and some items cannot be reliably answered by people with motor or cognitive dysfunctions commonly experienced after brain injury (e.g., 'Do you like to run about – perhaps up and down in straight lines or round in circles' in the Glasgow Sensory Questionnaire) (Brown & Dunn, 2002; Robertson & Simmons, 2013). In addition, some items of the Adult/Adolescent Sensory Profile are not applicable to older adults (e.g., I find it hard to concentrate for the whole time when sitting in a class or a meeting') and some items of the Glasgow Sensory Questionnaire seem to specifically target autism-related symptoms (e.g., 'Do you flick your fingers in front of your eyes?'). To adapt the MESSY to acquired brain injury patients as well as older adults, we used pictograms to facilitate comprehension of the items, avoided using multiple negations, kept the items as short as possible (see Panel B of Figure 1 for an illustration of a multiple-choice item of the MESSY assessing visual sensitivity), and strived to make the content of the items well-suited to people with severe motor and cognitive deficits.

Items are answered on a scale from one (never/not at all) to five (very often/extremely) based on respondents' experiences in the previous month. To avoid visual overload

the items of the MESSY are presented one by one. The 30 items are distributed across the different modalities as follows: multisensory sensitivity (seven items), visual and auditory sensitivity (five items each), gustatory sensitivity (one item), tactile, olfactory, environmental temperature, and motion sensitivity (three items each). Per sensory modality, respondents first complete the open-ended questions and then the corresponding multi-choice items. In addition to the online version of the MESSY, suited for an outpatient acquired brain injury population, we have developed a paper version of the MESSY that is adapted to a hospital environment and can be used for bedside testing in acute acquired brain injury patients that receive inpatient care. The items of these two versions are identical but the examples and pictograms that supplement the items differ between the two versions.

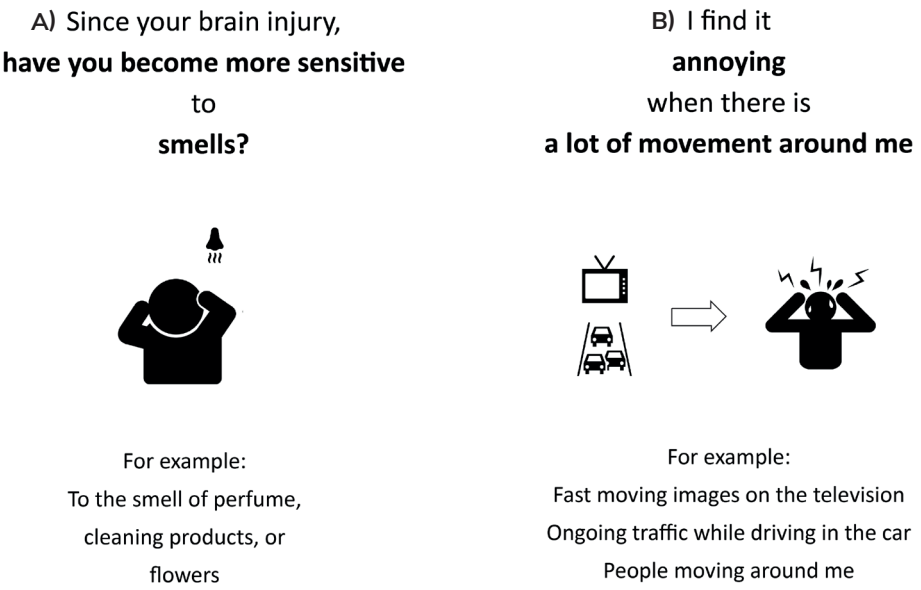


Figure 1. An open-ended (Panel A) and a multiple-choice (Panel B) item of the MESSY.

Structural anamnesis

Respondents were asked to indicate their age, gender, education level, and medical background (e.g., presence of a neurological, neurodevelopmental, or psychiatric disorders, use of psychotropic or -active medication). To examine a previous history of a mild traumatic brain injury, neurotypical adults disclosed if they ever experienced cognitive complaints after a concussion or after losing consciousness for minimally 15 minutes following a fall or blow to the head. Acquired brain injury patients were asked to indicate their type of brain injury/ injuries from a list of different options (including ischemic stroke (blood clot in the brain), brain haemorrhage, stroke, brain injury due to a fall or an accident (a traumatic brain injury), concussion, brain contusion, and brain tumour). Respondents could also indicate that they did not know their specific type of brain injury, could specify any other brain injury type, and, if possible, specified the (approximate) date of their brain injury.

Adult/Adolescent Sensory Profile-NL

To assess the convergent validity of the MESSY, we used the Dutch Adult/Adolescent Sensory Profile which measures the sensitivity to taste, smell, movement, touch, visual, and auditory stimuli (Brown & Dunn, 2002; Rietman, 2007). In addition, the questionnaire includes items about involvement in daily activities which comprises the subscale activity level (e.g., "I work on two or more tasks at the same time"). The questionnaire can be used with participants aged above 11 years old and measures four different patterns of responding to sensory stimuli: (1) sensory sensitivity referring to a heightened responsiveness to sensory stimuli, (2) sensory avoidance referring to actions taken to avoid (unpredictable) sensory stimulation, (3) low registration referring to a underresponsiveness to stimuli, and (4) sensory seeking referring to actively seeking the exposure to sensory stimuli. Each response pattern is measured by 15 items and each item is scored on a scale from 1 to 5. Research on the psychometric properties of the Dutch Adult/Adolescent Sensory Profile is limited. In a sample of 116 Dutch mental health workers the Adult/Adolescent Sensory Profile demonstrated a high internal consistency (Cronbach $\alpha = .84$) (Van den Boogert et al., 2022). In an American standardization sample ($n = 950$), the Cronbach alphas ranged from .64 to .78 for the different response patterns in three age groups (11 - 17 years old, 18 - 64 years old, 65 years or older) (Rietman, 2007).

Social anxiety questionnaires

To assess the discriminant validity of the MESSY, we used the Dutch Social Interaction and Anxiety Scale and the Dutch Inventory of Interpersonal Situations (similar to Kuiper et al., 2019). Both sensory hypersensitivity and social anxiety can result in sensory avoidance

(Alwawi et al., 2020; Landon et al., 2012; Teo et al., 2013), but they require different treatments (i.e., social anxiety treatment specifically targets social behaviours (for instance social skill training)), while the treatment of sensory hypersensitivity focuses on coping with sensory stimuli (Hallberg et al., 2005; Rodebaugh et al., 2004). Clinicians need diagnostic tools that specifically measure social anxiety or sensory hypersensitivity to differentiate between these two causes of social avoidance and offer treatment accordingly. Therefore, as a measure of discriminant validity we assessed whether the total MESSY score was related to measures of social anxiety. The Social Interaction and Anxiety Scale measures distress in social situations using 20 items that are rated on a five-point Likert scale, ranging from 0 to 4 (De Beurs et al., 2014; Mattick & Clarke, 1998). Three items of the Social Interaction and Anxiety Scale require reverse scoring. The Dutch Social Interaction and Anxiety Scale showed an excellent internal consistency (Cronbach $\alpha = .91$) and adequate convergent validity in a social phobia sample ($r = .56 – .69$) (De Beurs et al., 2014).

The Inventory of Interpersonal Situations consists of two parts (Van Dam-Baggen & Kraaimaat, 2000). In the first part respondents indicate how much social anxiety they typically experience during certain social behaviours and in the second part they indicate how frequently they typically engage in these behaviours. Each part consists of 35 statements that are rated using a 5-point Likert scale. The discomfort and frequency scale result in five subscales: (1) giving criticism, (2) expressing opinions, (3) giving compliments, (4) initiating contact, and (5) positive self-evaluation. Both parts of the Inventory of Interpersonal Situations had a high internal consistency (Cronbach $\alpha = .91$ and $\alpha = .93$ respectively) in a Dutch community sample and moderate convergent validity ($r = .76$ and $r = -.59$ respectively) in a sample of psychiatric patients with social anxiety (Van Dam-Baggen & Kraaimaat, 2000). In the current study we only used the second part of the Inventory of Interpersonal Situations (similar to Kuiper et al. (2019).

Procedure

This cross-sectional study was approved by the Social and Societal Ethics Committee of the KU Leuven (application numbers: G-2019031604, G-20202314), the University Medical Centre Utrecht (UMCU) Medical Ethics Committee (application number: 20-835/C), the University of Utrecht's Ethical Review Board (application number: 20-679), and the Medical Ethics Committee of the Hospital of East-Limburg (application number: VT2021-033). Informed consent was obtained in accordance with the World Medical Association Declaration of Helsinki. This study formed part of a larger online study. To keep participation feasible, especially for

acquired brain injury patients, the study was split into two parts. The first part included the questionnaires that were essential (including the MESSY and the structural anamnesis) and lasted approximately 15 minutes. After providing informed consent and before commencing the MESSY respondents indicated whether they had a previous history of a brain injury (yes or no). Based on this answer, respondents viewed the open-ended questions of the MESSY targeted towards neurotypical adults or acquired brain injury patients. After completing the first part, respondents could either stop their participation or continue with the second part of the study that lasted approximately 30 minutes. In this second part, respondents filled in other questionnaires. For the neurotypical adults these questionnaires included the Adult/Adolescent Sensory Profile, the Social Anxiety and Interaction Scale, and the Inventory of Interpersonal Situations (among questionnaires investigating subjective cognitive complaints, negative affect, and coping). Neurotypical adults were asked to complete a second session one week after completion of the first part of the first session. During this second session, that lasted approximately 20 minutes, they completed an identical version of the MESSY a second time (among questionnaires measuring fatigue and pain sensitivity). We distributed the online study using Qualtrics software (https://www.qualtrics.com). Responses were collected between December 2020 and December 2022. The study was automatically closed when respondents indicated that they had an age below 18 years old or when they did not provide informed consent. Respondents were offered the chance to win a noise-cancelling headphone or a gift voucher. The psychology students were offered course credits.

Data analysis

Analyses were conducted in R (version 4.0.3) (RStudio Team, 2020) and IBM SPSS Statistics (Version 28) (IBM Corp, 2021). The Lavaan package was used to conduct the confirmatory factor analysis (Rosseel, 2012). Alpha level was set to .05 and the Holm-Bonferroni method was used to correct for multiple comparisons (Holm, 1979). Graphs were created using R and Adobe Illustrator (2020). The datasets analysed during the current study are available upon request from the corresponding author (CRG) or are openly available at https://doi.org/10.6084/m9.figshare.21840504. This study was not preregistered.

Internal consistency

Internal consistency was calculated by computing the corrected item-total correlations, Cronbach alpha (including the Cronbach alpha if a certain item was deleted), and McDonald's total and hierarchical omega separately for the neurotypical adults and adults with an acquired brain injury. Mcdonald's omega, in contrast to Cronbach alpha, is robust to violations of the

tau-equivalence assumptions (i.e., the assumption that all items of a scale have the exact same relationship to the underlying construct) which are common in behavioural research (Hayes & Coutts, 2020). Items with a corrected item-total correlation equal to or above .30 were deemed to have a satisfactory association with the other items (Boateng et al., 2018; Field et al., 2012) and a Cronbach alpha or McDonald's omega above .70 were considered appropriate (Streiner, 2003).

Confirmatory factor analysis

Since we had an a priori hypothesis about how the items of the MESSY related to different sensory modalities, we conducted a confirmatory factor analysis to assess the factorial structure of the MESSY. We hypothesized a seven factors model where items loaded on their respective sensory modality (i.e., multisensory, visual, auditory, tactile, environmental temperature, motion, and chemosensory sensitivity). Since there was only one item that assessed gustatory sensitivity, we combined the items assessing gustatory and olfactory sensitivity into one subscale "chemosensory sensitivity" (similar to Mollo et al., 2022; Spielman, 1998). We used the Kaiser-Meyer-Olkin measure of sampling adequacy and the Bartlett test of sphericity to assess if the data were suitable for factor analysis (Beavers et al., 2013). Since our data were ordinal, the confirmatory factor analysis was performed on the polychoric correlation matrix of the items, using the robust diagonally weighted least squares estimator (Li, 2016).

To assess whether the data fit our predetermined measurement model, we compared the seven factors model to a single factor model where all the items loaded directly onto one factor representing general sensory sensitivity as well as a less complex five factor model. The five factor model combined visual and motion sensitivity into one factor (based on their high correlation in Sapey-Triomphe et al. (2018) and Kuiper et al. (2019)) as well as included a somatosensory sensitivity factor that included both tactile sensitivity and sensitivity to environmental temperature (based on previous research on somatosensory sensitivity) (Baad-Hansen et al., 2010; Knazovicky et al., 2016). To determine model fit, the following indices were examined: the comparative fit index (CFI), the Tucker-Lewis index (TLI), the root mean square errors of approximation (RMSEA), and the standardized root mean square residuals (SRMR). We aimed to acquire adequate fit with a CFI and TLI above .95 and RMSE and SRMR below .08 (Hooper et al., 2008; Hu & Bentler, 1999; Schermelleh-Engel et al., 2003; Schreiber et al., 2006; Weiland et al., 2020). This confirmatory factor analysis was conducted based on all available data (neurotypical controls and adults with an acquired brain injury). Items with a standardized factor loading of ≥ .40 were deemed satisfactory (Boateng et al., 2018).

Measurement Invariance

To examine whether the MESSY measured a similar construct across neurotypical adults and acquired brain injury patients we assessed three degrees of invariance which place increasing constraints on the model (Hirschfeld, 2014). Firstly, we tested whether the factor structure (number of latent variables and relationship between manifest and latent variables) of the MESSY is equivalent across the two groups (i.e., configural invariance). Secondly, we tested whether the factor loadings of the items are equivalent across the two groups (i.e., metric invariance), indicating that the items have a similar relationship to the underlying factors in both groups. Lastly, we tested whether the factor loadings and the thresholds of the factor models are equivalent across the two groups (i.e., scalar invariance) to see if the two groups use the response scale in a similar manner. Scalar invariance is needed to quantitatively compare MESSY scores between the two groups. To determine configural invariance we used the same model fit indices as mentioned above with the same criteria. A difference in χ^2 test is traditionally used to test whether a more constrained model results in a substantial decrease in model fit (as compared to a less constrained model). Since this test is sensitive to sample size, authors suggest using a change in CFI larger than -.01 to decide whether an invariance level should be rejected (Cheung & Rensvold, 2002; Hirschfeld, 2014).

Reliability and validity of the MESSY in neurotypical adults

Measures of validity and test-retest reliability were based on data in neurotypical adults. To test convergent validity the correlation between the total score on the MESSY (completed during the first session of the study) and the total score on the sensory sensitivity and sensory avoidance subscales of the Adult/Adolescent Sensory Profile (the scores of these two subscales were summed to form one score) was used. Discriminant validity was assessed using the correlation between the total score on the MESSY (completed during the first session of the study) and the total score on the Social Anxiety and Interaction Scale as well as the total score on the second part of the Inventory of Interpersonal Situations. Test-retest reliability was examined by computing the correlation between the total scores on the MESSY completed during the first session of the study and the MESSY completed during the second part of the study. Since the total score on the MESSY (completed during the first and second session) did not follow a normal distribution, we used spearman rho correlations to assess validity and test-retest reliability. A correlation below .30 was considered weak, a correlation between .30 and .70 was considered moderate, and a correlation above .70 was considered high (Dancey & Reidy, 2007). Respondents were included in these analyses if they completed both questionnaires within 14 days.

The association between demographic variables and MESSY scores in neurotypical adults

To investigate the association between MESSY scores and age, gender, and education level in neurotypical adults, we conducted a multiple regression with the total score on the MESSY (sum of all the items in the second part of the questionnaire) as the dependent variable. Due to a non-normal distribution of the residuals, a heterogeneity of variances, and presence of outliers, we conducted a robust regression (Field & Wilcox, 2017). The variables gender and education level were dummy coded with men and lower education (individuals without at minimum a bachelor degree awarded by a college or university) as reference groups. Age was added to the model as a continuous variable. Since the available literature supports an effect of gender on sensory sensitivity but is inconsistent regarding effects of age or education level (Al-Momani et al., 2020; Benham, 2006; Gándara-Gafo et al., 2019; Ueno et al., 2019), we added gender as the first predictor, and age and education level as subsequent predictors. A quadratic effect of age and interactions between age, gender, and education level were added to the regression model if the corresponding regression coefficients reached statistical significance and if adding the variable significantly increased the model fit.

Normative data

For the total score on the MESSY as well as all the mean item score per modality we determined percentile values stratified according to age and gender. Since the number of items differ per modality, we conducted the mean item score per modality (the total score per modality divided by the number of items) to allow meaningful comparisons across modalities.

Between-group analysis

Based on their answers to the open ended questions of the MESSY, acquired brain injury patients were categorized, per sensory modality, in a group of patients with post-injury sensory hypersensitivity (i.e., patients who reported an increase in their sensory sensitivity from pre- to post-injury, that they still experienced in the month previous to their participation) and a group of patients without post-injury sensory hypersensitivity (i.e., patients who did not report an increase in their sensory sensitivity or did not experience post-injury sensory hypersensitivity in the previous month). An ANCOVA test was used to compare the severity of sensory sensitivity to each sensory modality between neurotypical adults, acquired brain injury patients without post-injury sensory hypersensitivity, and patients with post-injury sensory hypersensitivity (per type of injury[1]) . We used the mean item score per modality as

[1] *To compare the total score across groups we used the acquired brain injury patients who reported an increase in their sensitivity to at least one sensory modality and compared this to acquired brain injury who did not report increased sensory sensitivity across all modalities as well as neurotypical adults.*

the dependent variables as well as the MESSY total score. Since the assumptions of normality and homogeneity of variances were violated and since there were significant differences in the mean age and number of included males between the groups of included stroke, traumatic brain injury, and brain tumour patients (see Supplementary Table 2) we conducted a Quade's non-parametric rank analysis of covariance (ANCOVA) with group and gender as independent variables and age as a covariate (Barrett, 2011; Cangür et al., 2018). Post-hoc Dunn tests (Dunn, 1964) were used to examine whether (1) the severity of sensory sensitivity differed between patients with a stroke, traumatic brain injury, or brain tumour with post-injury sensory hypersensitivity, (2), the acquired brain injury patients with post-injury sensory hypersensitivity scored significantly higher on the MESSY than the patients without post-injury sensory hypersensitivity (in the previous month) as well as (3) neurotypical adults, and (4) whether acquired brain injury patients without post-injury sensory hypersensitivity scored significantly higher or lower than neurotypical adults. As a post-hoc analysis we examined whether there was a difference in sensory sensitivity between patients with sensory hypersensitivity after a mild traumatic brain injury as compared to patients with sensory hypersensitivity after a moderate to severe traumatic brain injury using a non-parametric Wilcoxon rank-sum test (Bridge & Sawilowsky, 1999).

Results

Respondents

Out of the 1559 Dutch-speaking respondents from Belgium and the Netherlands who participated in this online study, 818 neurotypical adults and 341 adults with an acquired brain injury were included in the study (see Figure 2 for the respondent flow chart). Table 1 displays the characteristics of the included respondents and Table 2 the characteristics of the acquired brain injury patients per type of injury. The age of neurotypical adults did not differ significantly from the age of the adults with an acquired brain injury (Wilcoxon rank-sum test, $W = 147744$, $p = .11$). A Kruskal-Wallis Test and corresponding Dunn tests showed that the mean age of stroke survivors was significantly higher than that traumatic brain injury or brain tumour patients ($\chi^2(2) = 40.50$, $p < .01$, adjusted p-value for pairwise contrasts: $p < .01$). Stroke patients also had a significantly lower time since injury than patients with a traumatic brain injury or brain tumour ($\chi^2(2) = 16.95$, $p < .01$, adjusted p-value for pairwise contrasts: $p < .01$). 284 of the included acquired brain injury patients (83%) were first-time brain injury survivors, 28 (8%) patients reported having more than one brain injury (of the same type), and 29 (9%) patients did not specify their number of previous injuries. Both ischemic (50% of included stroke patients) and haemorrhagic stroke patients (43% of included stroke patients) were

included. Two respondents who reported having a transient ischemic attack were classified as ischemic stroke patients. Adults who reported having a concussion or a commotio cerebri were classified as mild traumatic brain injury patients and adults who reported having a cerebral contusion (with intracerebral hematomas) were classified as having a moderate to severe traumatic brain injury. The majority of adults with a traumatic brain injury (65%) had a moderate to severe brain injury.

Table 1. Characteristics of all included respondents.

	Neurotypical adults	Acquired brain injury patients
n	818	341
Age range (in years)	18 - 96	18 - 93
Mean age (sd) (in years)	49 (24)	56 (13)
Number of male respondents (%)[2]	244 (30%)	126 (37%)
Number of respondents who completed higher education (%)[3]	411 (50%)	105 (31%)
Mean time since brain injury (sd) [Range] (in years)[4]		6 (8) [0 - 69]
Number of participants with a single brain injury (%)[5]		284 (83%)

Sd: standard deviation. Higher education: minimally a bachelor degree awarded by a college or university.

[2] *One neurotypical adult and one stroke patient did not specify their gender.*
[3] *40 neurotypical adults and [104] acquired brain injury patients did not specify their education level.*
[4] *33 acquired brain injury patients did not specify the time since injury.*
[5] *29 acquired brain injury patients did not specify the number of brain injuries.*

Table 2. Characteristics of included acquired brain injury patients per type of injury.

	Stroke	Traumatic brain injury	Brain tumour
n	204	80	57
Age range (in years)	23 - 93	18 - 74	28 - 78
Mean age (sd) (in years)	59 (12)	49 (13)	52 (11)
Number of male respondents (%)	81 (40%)	20 (25%)	25 (44%)
Number of respondents who completed higher education (%)[6]	52 (25%)	39 (49%)	14 (25%)
Mean time since brain injury (sd) [Range] (in years)	5 (7) [0 - 69]	8 (10) [0 - 48]	8 (8) [1 - 32]
Number of respondents with a single brain injury (%)[7]	169 (83%)	74 (93%)	41 (72%)
Number of patients with an ischemic / haemorrhagic / unclear stroke type (%)	102 / 88 / 14 (50% / 43% / 7%)		
Mild / moderate to severe traumatic brain injury		28 / 52 (35% / 65%)	

Sd: standard deviation. Higher education: minimally a bachelor degree awarded by a college or university.

[6] *64 stroke patients, 30 traumatic brain injury patients, and 20 brain tumour patients did not specify their education level.*
[7] *11 stroke patients, 2 traumatic brain injury patients, and 16 brain tumour patients did not specify the number of brain injuries.*

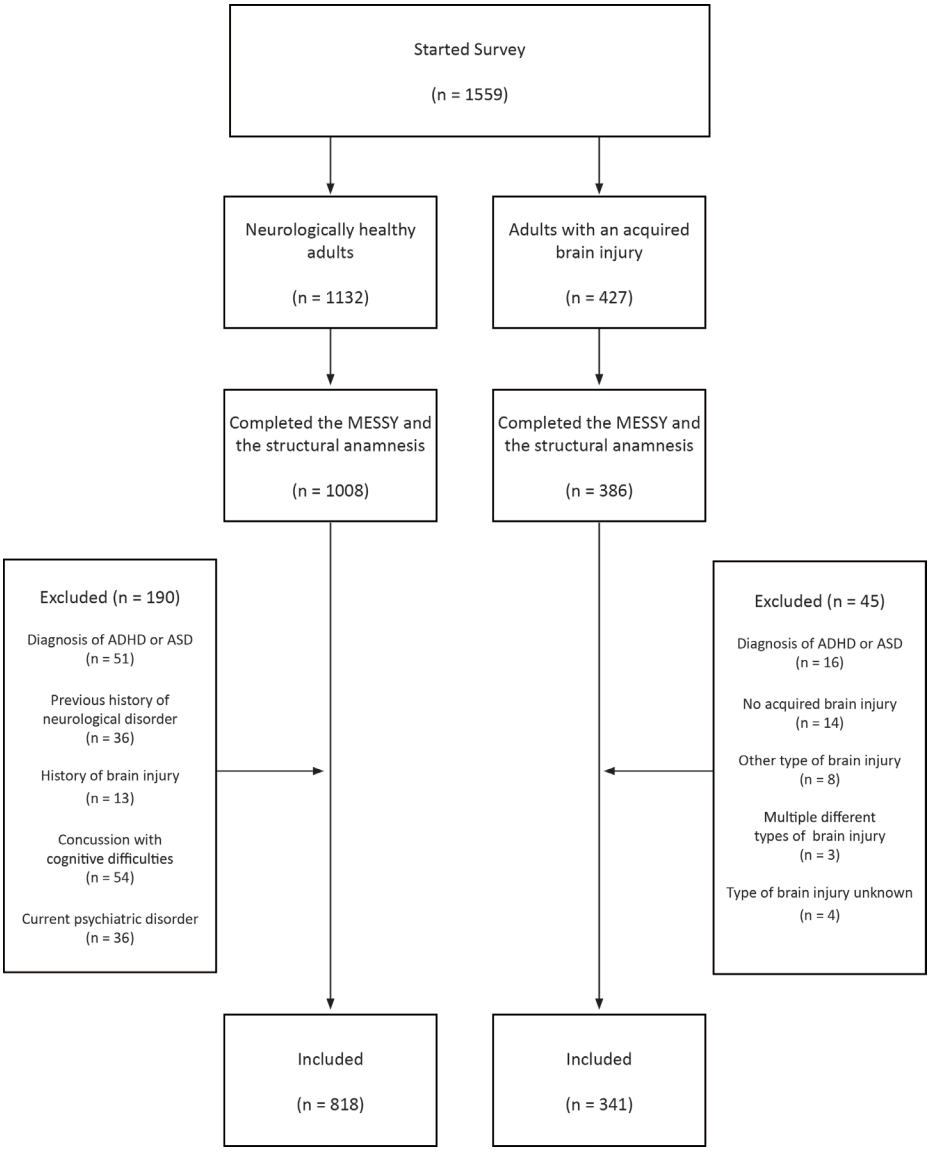


Figure 2. Respondent flow diagram. ADHD = attention deficit hyperactivity disorder. ASD = autism spectrum disorder.

Internal consistency

The measures of internal consistency based on the data of neurotypical adults and acquired brain injury patients are shown in Table 3. For both groups, Cronbach alpha did not increase when an item was dropped. The corrected item-total correlation coefficients for all the items ranged from .42 to .70 in neurotypical adults and from .35 to .81 in adults with an acquired brain injury (see Supplementary Table 1). Some authors suggest that a Cronbach alpha above .90 indicates redundancy in items (Streiner, 2003). Therefore, we computed an inter-item correlation matrix and looked for inter-item correlations above .90 which would suggest that two items measure (almost) the same concept. However, none of the inter-item correlations reached .90 (correlations ranged between .13 and .78 based on the entire sample of neurotypical adults and adults with an acquired brain injury).

Table 3. Internal consistency of the MESSY in neurotypical adults and acquired brain injury patients.

	Neurotypical adults (n = 818)	Acquired brain injury patients (n = 341)
Cronbach alpha	.94	.96
Omega	.96	.98
Hierarchical omega	.79	.82

Confirmatory factor analysis

The Kaiser-Meyer-Olkin measure of sampling adequacy was .95 and the Bartlett test of sphericity was significant ($\chi^2(435) = 21535.11$, $p < .01$). This indicates that the data were appropriate for factor analysis (Beavers et al., 2013). The goodness-of-fit indicators of the different factor models are displayed in Table 4. Only the seven factor model adhered to the a priori set cut-off values for adequate model fit (i.e., a CFI and TLI above .95, and RMSE and SRMR below .08). No standardized factor loadings below .40 were observed (see Table 5).

Table 4. Goodness-of-fit indicators for the different factor models.

Model	χ^2	*df*	*p*	CFI	TLI	RMSEA	95% Confidence interval	SRMR
Seven factors model	2444.49	384	<.01	.95	.95	.07	[.07 - .07]	.05
Five factors model	3482.58	395	<.01	.93	.92	.08	[.08 - .09]	.06
One factor model	10178.53	405	<.01	.78	.76	.14	[.14 - .15]	.11

Df = Degrees of freedom, CFI: Comparative fit index, TLI: Tucker-Lewis index, RMSEA: Root mean square errors of approximation, SRMR: Standardized root mean square residuals. Results are based on the data of 818 neurotypical adults and 341 acquired brain injury patients.

Table 5. Standardized factor loadings of the seven-factor model in neurotypical adults and acquired brain injury patients.

		Standardized factor loadings		
Item	Subscale	Entire Sample (n = 1159)	Neurotypical adults (n= 818)	Acquired brain injury patients (n = 341)
I suffer or feel overwhelmed when there are a lot of people around me	Multisensory	.82	.73	.89
I get a headache when there are many environmental stimuli, such as lights, sounds, or smells, around me	Multisensory	.80	.75	.83
I get tired when there are many environmental stimuli, such as lights, sounds, or smells, around me	Multisensory	.84	.77	.88
When I try to concentrate, I am easily distracted by disturbing environmental stimuli	Multisensory	.76	.68	.86

Item	Subscale	Standardized factor loadings		
		Entire Sample (n = 1159)	Neurotypical adults (n= 818)	Acquired brain injury patients (n = 341)
I have the feeling that my brain has to work too hard or my head feels heavy when I process environmental stimuli, such as lights, sounds, or smells	Multisensory	.87	.84	.89
I have the feeling that my brain does not get calm or quiet	Multisensory	.73	.70	.78
I feel light-headed when there are a lot of environmental stimuli, such as lights, sounds, or smells, around me	Multisensory	.76	.75	.71
I am sensitive to bright light	Visual	.72	.67	.77
I suffer or feel overwhelmed when there is a lot to see around me	Visual	.89	.84	.93
I find it annoying when there is a lot of movement around me	Visual	.87	.81	.92
I suffer from bright colors	Visual	.78	.72	.83
I get annoyed by sounds that are not bothersome for other people	Auditory	.87	.84	.90
I try to block out sound	Auditory	.82	.76	.91
I stay away from noisy environments	Auditory	.72	.58	.88
I am sensitive to sound	Auditory	.90	.86	.95
I find it hard to concentrate on a conversation when there is environmental sound around me	Auditory	.83	.75	.91
Certain fabrics or certain clothing feel uncomfortable	Tactile	.72	.70	.87

Item	Subscale	Standardized factor loadings		
		Entire Sample (n = 1159)	Neurotypical adults (n= 818)	Acquired brain injury patients (n = 341)
It feels unpleasant when my skin gets touched	Tactile	.92	.88	.98
I am sensitive to touch	Tactile	.88	.86	.95
I find strong smells annoying	Chemosensory	.83	.80	.92
I find smells very strong while others do not suffer from them	Chemosensory	.91	.85	.97
When I smell a strong smell I find it hard to concentrate on something else	Chemosensory	.90	.85	.96
Food tastes very strong to me	Chemosensory	.65	.69	.66
Normal environmental temperatures that do not bother other people are too warm or too cold for me	Environmental Temperature	.75	.76	.76
I feel overwhelmed when I feel too hot or too cold	Environmental Temperature	.88	.83	.93
I try to block out sound	Auditory	.82	.76	.91
I stay away from noisy environments	Auditory	.72	.58	.88
I am sensitive to sound	Auditory	.90	.86	.95
I find it hard to concentrate on a conversation when there is environmental sound around me	Auditory	.83	.75	.91
Certain fabrics or certain clothing feel uncomfortable	Tactile	.72	.70	.87
When I feel too hot or too cold, I find it hard to concentrate on something else	Environmental Temperature	.87	.86	.92

Item	Subscale	Standardized factor loadings		
		Entire Sample (n = 1159)	Neurotypical adults (n= 818)	Acquired brain injury patients (n = 341)
When I turn my body or when I stretch or bend, I feel dizzy	Motion	.76	.73	.79
I dislike the feeling of certain movements, like being pushed in a wheelchair, standing or sitting in a moving elevator, or driving in a car	Motion	.92	.84	.99
When I look up, I get dizzy or nauseous	Motion	.79	.79	.77

Measurement Invariance

The seven-factor model was tested for measurement invariance across two groups (neurotypical adults vs. acquired brain injury patients). The results in Table 6 show evidence for scalar invariance of the MESSY across these two groups.

Table 6. Summary of the measurement invariance analysis.

Type of invariance	χ^2	*df*	*p*	CFI	ΔCFI	TLI	RMSEA	95% Confidence interval	SRMR
Configural	2779.46	768	<.01	.960		.954	.067	[.065 - .070]	.055
Metric	2710.04	791	<.01	.962	.002	.958	.065	[.062 - .067]	.061
Scalar	3060.71	874	<.01	.956	-.006	.957	.066	[.063 - .068]	.055

Df = Degrees of freedom, CFI: Comparative fit index, ΔCFI: Difference in Comparative fit index, TLI: Tucker-Lewis index, RMSEA: Root mean square errors of approximation, SRMR: Standardized root mean square residuals. Results are based on the data of 818 neurotypical adults and 341 acquired brain injury patients.

Reliability and validity of the MESSY in neurotypical adults

Table 7 shows the Spearman correlation coefficients among the total score of the MESSY (completed in the first session) and the total scores of the Adult/Adolescent Sensory Profile (limited to the sensory sensitivity and sensory avoidance subscales), the Social Interaction and Anxiety Scale, the Inventory of Interpersonal Situations, and the MESSY completed in the second session.

Table 7. The reliability and validity of the MESSY.

		n	Sample characteristics	Spearman rho correlation coefficient	*p*
MESSY (session 1)	Adult/Adolescent Sensory Profile	326	Mean age (sd): 29 (17) Age range: 18 - 86 16% male	.71	< .01
	Social Anxiety and Interaction Scale	326	Mean age (sd): 29 (17) Age range: 18 - 86 16% male	.39	< .01
	Inventory of Interpersonal Situations	255	Mean age (sd): 25 (15) Age range: 18 - 86 16% male	-.03	.66
	MESSY (session 2)	213	Mean age (sd): 26 (16) Age range: 18 - 86 15% male	.84	<.01

Sd = standard deviation. Age is displayed in years.

The association between demographic variables and MESSY scores in neurotypical adults

A robust multiple regression indicated a significant main effect of gender and age on the total score of the MESSY in neurotypical adults (see Table 8 and Figure 3). This model explained a small proportion of variance in total MESSY scores (adjusted $R^2 = .09$).

Table 8. Multiple regression for the total score on the MESSY in neurotypical adults (n = 818).

	β	95% CI	Standard Error	t	p
Intercept	62.71	[58.95 ; 66.47]	1.91	32.75	< .01
Gender	6.34	[3.82 ; 8.87]	1.29	4.93	< .01
Age	-0.13	[-0.19 ; -0.07]	0.03	-4.19	< .01
Education level	-2.76	[-5.61 ; 0.08]	1.45	-1.91	.06

CI: Confidence interval.

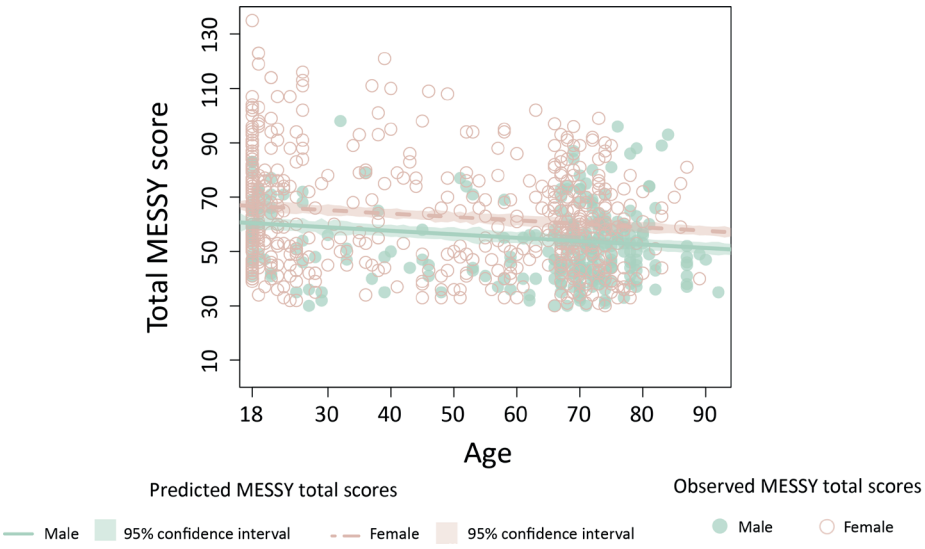


Figure 3. Observed and predicted total MESSY Score based on age (in years) stratified according to gender in 818 neurotypical adults. A higher MESSY score represents a higher severity of sensory hypersensitivity.

Normative data

Normative data for the MESSY are presented in Table 9. An electronic scoring aid that automatically compares the observed score of a patient to age- and gender-adjusted norms is available via www.neuropsychologylab.be/messy.

Table 9. Normative data for the MESSY based on data in neurotypical adults (aged 18-96, n = 818).

	Percentile	Total score		Multisensory		Visual		Auditory		Tactile		Chemosensory		Environmental temperature		Motion	
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
18 - 44 years (n = 54 males, 291 females)	5	35	40	1.3	1.3	1	1	1	1.2	1	1	1	1	1	1	1	1
	10	37	43	1.3	1.4	1.2	1.2	1	1.4	1	1	1	1	1	1.3	1	1
	25	47	51	1.6	1.9	1.4	1.6	1.6	1.6	1	1	1.3	1.3	1.3	1.7	1	1.3
	50	56	64	2	2.4	1.8	2.2	2	2.2	1.3	1.7	1.8	1.8	1.8	2.3	1.3	1.7
	75	68	79	2.4	3.1	2.2	2.8	2.6	3.1	2	2.3	2	2.5	2.7	3.3	1.7	2.3
	90	76	95	3	3.6	2.6	3.2	3	3.8	2.7	3	2.8	3.3	3.2	4	2.2	3
	95	80	106	3.1	4	3.1	3.7	3.8	4.2	3	3.3	3.1	3.8	4.1	4.3	2.3	3.3
	99	90	121	3.6	4.5	3.5	4.4	4.3	4.4	3.3	4	3.6	4.8	4.8	5	2.5	3.7
45 - 69 years (n = 63 males, 166 females)	5	34	34	1.1	1.1	1	1	1	1	1	1	1	1	1	1	1	1
	10	36	39	1.1	1.3	1	1	1.2	1.2	1	1	1	1	1	1	1	1
	25	41	47	1.4	1.6	1.2	1.4	1.5	1.6	1	1	1.1	1.3	1	1.3	1	1
	50	47	57	1.9	2	1.6	1.8	1.8	2.2	1.3	1.3	1.3	1.8	1.3	2	1.3	1.3
	75	58	71	2.3	2.7	2.1	2.4	2.4	3.2	1.5	2	1.8	2.5	2	2.3	1.7	2
	90	73	86	2.6	3	2.4	3.1	3	3.8	2	2.8	2.3	3.3	2.3	3	2	2.3
	95	74	94	3	3.5	2.8	3.4	3.4	4.2	2.3	3.3	2.5	3.3	2.7	3.3	2	2.7
	99	85	104	3.3	3.9	3.1	3.9	4	4.6	4	3.7	3.1	3.5	3	3.8	2.3	3.8

	Percentile	Total score		Multisensory		Visual		Auditory		Tactile		Chemosensory		Environmental temperature		Motion	
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
70 years and older (n = 127 males, 116 females)	5	35	34	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	10	37	37	1.1	1.1	1	1	1.2	1.2	1	1	1	1	1	1	1	1
	25	43	43	1.3	1.4	1.2	1.4	1.4	1.6	1	1	1.3	1.3	1.3	1.3	1	1
	50	50	57	1.7	1.9	1.6	1.8	2	2	1.3	1.3	1.5	1.8	1.7	2	1.3	1.3
	75	59	67	2	2.3	2	2.2	2.7	2.6	1.7	2	2	2.3	2	2.3	2	2
	90	72	78	2.6	2.7	2.6	2.8	3.2	3.4	2.1	2.7	2.5	3	2.7	3.3	2.3	2.3
	95	79	88	2.8	2.9	2.7	3.1	3.4	3.6	2.6	3	2.9	3.1	2.9	3.7	3	2.7
	99	92	92	3.2	3.1	3.5	3.7	4.2	4	3.3	4.2	3.2	3.5	3.6	4	3.6	3.3

M = Male, F = Female.

Between-group analysis

Table 10 displays the percentage of acquired brain injury patients with post-injury sensory hypersensitivity (in the previous month) for each sensory modality. 271 of the acquired brain injury patients (79%) reported an increased sensory sensitivity for at least one modality. This corresponded to 75% of the stroke patients, 89% of the traumatic brain injury patients, and 82% of the brain tumour patients. 81% of the 271 patients with post-injury sensory hypersensitivity reported multi-modal sensory hypersensitivity (i.e., they were hypersensitive to more than one sensory modality) and 4% of the patients with post-injury sensory hypersensitivity reported being hypersensitive to all the measured modalities. The Quade's ANCOVA revealed that for the total score as well as the modality-specific median scores there was a significant difference between the different groups after controlling for age (see Table 11). There was no evidence that these group differences depended on gender after controlling for age.

Table 10. The percentage of acquired brain injury patients with post-injury sensory hypersensitivity per sensory modality and per type of brain injury.

	Number of acquired brain injury patients with post-injury sensory hypersensitivity			
Modality	Stroke	TBI	Brain tumour	Total (%)
Multisensory	122	68	45	235 (69%)
Auditory	97	63	31	191 (56%)
Visual	97	54	30	181 (53%)
Motion	35	29	14	78 (23%)
Environmental temperature	32	23	15	70 (21%)
Chemosensory	30	18	11	59 (17%)
Tactile	19	12	6	37 (11%)

Sensory modalities were ordered from most to least prevalent. TBI: Traumatic brain injury.

Table 11. Results of the Quade's ANCOVA (n = 1159).

		Total Score			Multisensory			Visual			Auditory		
	df	*F*	*p*	η^2_{par}	*F*	*p*	η^2_{par}	*F*	*p*	η^2_{par}	*F*	*p*	η^2_{par}
Group	4	50.49	<.01	.15	83.00	<.01	.22	59.88	<.01	.17	67.34	<.01	.19
Gender	1	20.05	<.01	.02	20.89	<.01	.02	13.49	<.01	.01	4.32	.49	.004
Group *Gender	4	1.06	1	.004	1.10	1	.004	1.20	1	.004	.32	1	.001
		Tactile			Chemosensory			Environmental Temperature			Motion		
	df	*F*	*p*	η^2_{par}	*F*	*p*	η^2_{par}	*F*	*p*	η^2_{par}	*F*	*p*	η^2_{par}
Group	4	23.59	<.01	.08	32.24	<.01	.10	32.24	<.01	.10	17.89	<.01	.06
Gender	1	.88	1	.001	3.34	.81	.003	2.92	.96	.003	1.27	1	.001
Group *Gender	4	1.45	1	.004	.38	1	.001	.03	1	0	.89	1	.003

Df = degrees of freedom. F = Quade's F. p = adjusted p value. η^2_{par} = partial eta squared. The sample sizes of the different groups and the number of male respondents per group can be found in Supplementary Table 2.

The Dunn tests revealed three patterns (see Table 12 and Figures 4 and 5). Firstly, regarding the total score of the MESSY, traumatic brain injury patients with post-injury sensory hypersensitivity scored significantly higher than the stroke and brain tumour patients with post-injury hypersensitivity. When looking at the different sensory modalities specifically, there was no evidence for a difference in the mean item score across brain injury type (traumatic brain injury, stroke, brain tumour) and there was no evidence for a difference in modality-specific sensory sensitivity severity between patients with sensory hypersensitivity after a mild traumatic brain injury and patients with sensory hypersensitivity after a moderate to severe traumatic brain injury (see Table 13).

Secondly, within each modality and for the total score of the MESSY, respondents with post-injury sensory hypersensitivity after a stroke, traumatic brain injury, or brain tumour scored significantly higher as compared to acquired brain injury patients without post-injury sensory hypersensitivity as well as compared to neurotypical adults.

Thirdly, acquired brain injury patients without post-injury sensory hypersensitivity had a significantly lower total and modality-specific scores (for auditory, tactile, and chemosensory sensitivity as well as sensitivity to environmental temperature) as compared to neurotypical adults. However, there was no evidence for a statistically significant differences in multisensory, visual, and motion sensitivity between patients without post-injury sensory hypersensitivity and neurotypical adults.

Table 12. The adjusted p values of the pairwise Dunn tests per sensory modality.

	ABI patients with post-injury sensory hypersensitivity (per type of injury)			ABI patients with post-injury sensory hypersensitivity (per type of injury) compared to ABI patients without post-injury sensory hypersensitivity			ABI patients with post-injury sensory hypersensitivity (per type of injury) compared to neurotypical adults			ABI patients without post-injury sensory hypersensitivity compared to neurotypical adults
	Stroke TBI	Stroke Brain tumour	TBI Brain tumour	Stroke ABI (SH-)	TBI ABI (SH-)	Braintumour ABI (SH-)	Stroke NT	TBI NT	Braintumour NT	ABI (SH-) NT
Total score	< .01	**.59**	.01	< .01	< .01	< .01	< .01	< .01	< .01	< .01
Multisensory	**.13**	**.39**	**.08**	< .01	< .01	< .01	< .01	< .01	< .01	**.05**
Visual	**.25**	**.33**	**.13**	< .01	< .01	< .01	< .01	< .01	< .01	**.14**
Auditory	**.34**	**.69**	**.85**	< .01	< .01	< .01	< .01	< .01	< .01	< .01
Tactile	**1**	**1**	**.96**	< .01	< .01	< .01	< .01	< .01	< .01	< .01
Chemosensory	**.43**	**.63**	**.48**	< .01	< .01	< .01	< .01	< .01	.03	< .01
Environmental Temperature	**1**	**1**	**.80**	< .01	< .01	< .01	< .01	< .01	< .01	< .01
Motion	**.98**	**.97**	**.94**	< .01	< .01	< .01	< .01	< .01	< .01	**.52**

Non-significant p values ($\alpha \geq .05$) are displayed in bold. ABI (SH-): acquired brain injury patients without post-injury sensory hypersensitivity (in the month previous to participation). ABI: acquired brain injury. TBI: traumatic brain injury. NT: neurotypical adults. The sample sizes of the different groups and the number of male respondents per group can be found in Supplementary Table 2.

Table 13. Results of the Wilcoxon rank-sum test comparing the sensory sensitivity between patients with sensory hypersensitivity after a mild traumatic brain injury and patients with sensory hypersensitivity after a moderate to severe traumatic brain injury.

	Number of patients with sensory hypersensitivity after mild traumatic brain injury	Number of patients with sensory hypersensitivity after moderate to severe traumatic brain injury	W	p
Total Score	25	46	635.5	.47
Multisensory	25	43	591	.50
Visual	22	32	316	.53
Auditory	24	39	471	.97
Tactile	8	4	13.5	.73
Chemosensory	6	12	27.5	.44
Environmental temperature	10	13	65.5	1
Motion	11	18	92	.77

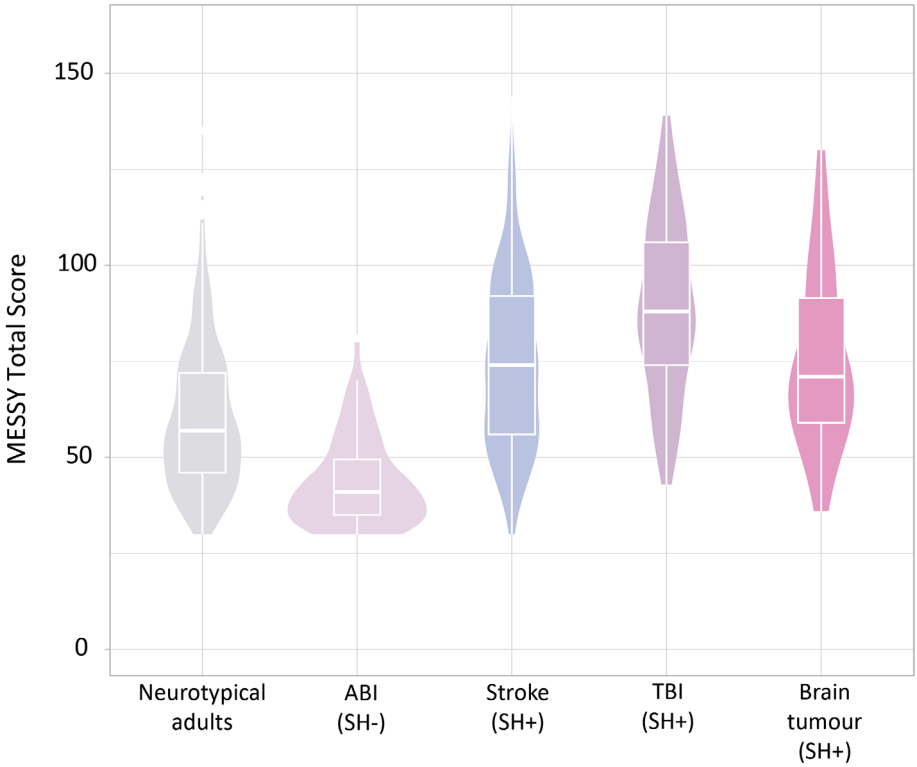


Figure 4. The distribution of the total score on the MESSY for neurotypical adults, for acquired brain injury patients without post-injury sensory hypersensitivity (ABI SH-), and stroke, traumatic brain injury (TBI), and brain tumour patients with post-injury sensory hypersensitivity (SH+).

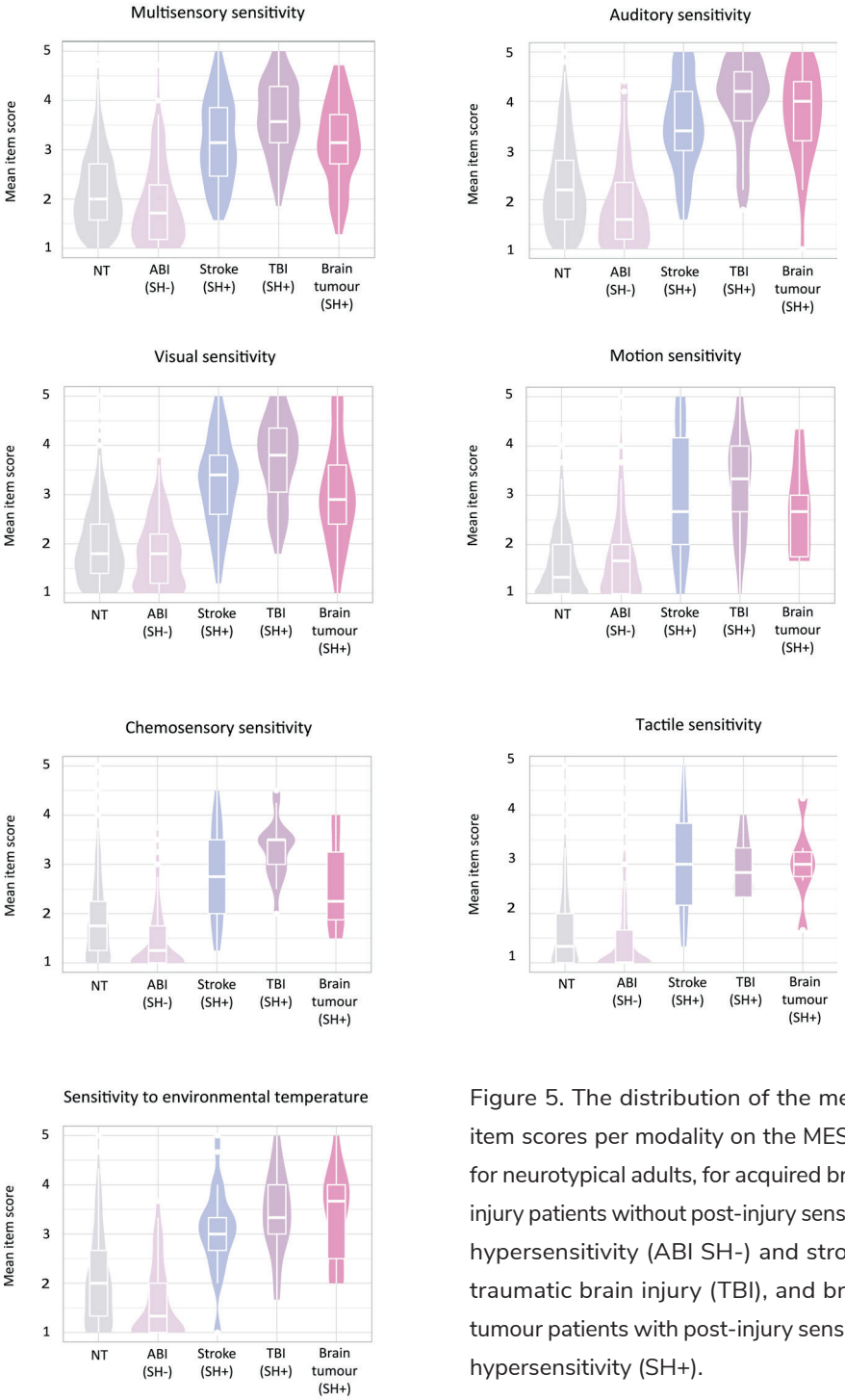


Figure 5. The distribution of the mean item scores per modality on the MESSY for neurotypical adults, for acquired brain injury patients without post-injury sensory hypersensitivity (ABI SH-) and stroke, traumatic brain injury (TBI), and brain tumour patients with post-injury sensory hypersensitivity (SH+).

Discussion

The primary aims of this study were to study the psychometric properties of the MESSY, provide normative data, as well as compare sensory sensitivity between neurotypical controls and acquired brain injury patients. Overall, the results show that the MESSY was reliable, valid, and sensitive to post-injury sensory hypersensitivity after brain injury in a heterogeneous sample. This is important because a systematic review of available literature revealed that a limited number of studies (36%) used a validated questionnaire to assess sensory hypersensitivity after acquired brain injury (Thielen et al., 2022) meaning that adequate diagnostic tools are currently lacking in research and (as a result) in clinical practice. Therefore, the development of the MESSY as a reliable and valid questionnaire that is sensitive to sensory hypersensitivity after brain injury could greatly improve clinical practice as well as the quality of future research.

Another notable strength of this study is that we studied modality-specific sensory hypersensitivity in a large sample of stroke patients, traumatic brain injury patients (including many patients with moderate to severe traumatic brain injury), and brain tumour patients. Since previous research on post-injury sensory hypersensitivity mainly focused on mild traumatic brain injury and on sensitivity to light and noise (for an overview see Thielen et al., 2022), this study provides first-hand evidence that post-injury sensory hypersensitivity is prevalent across all sensory modalities, across different brain injury types, and across different injury severities.

Limitations and future research

However, some caveats of this study should be mentioned. Firstly, we used a convenience sample where the respondents of the study might not reflect the entire population. For instance, the generalizability of our results to the entire population might be limited to the gender imbalance (i.e., more females participated in the study than males). Furthermore, no data was gathered regarding relevant demographic characteristics such as race/ethnicity and socio-economic status which limits our understanding of the generalizability of our sample to the general population. When targeting respondents via social media we mentioned that the aim of the study was to investigate sensory processing. Therefore, neurotypical adults and patients with an acquired brain injury with higher sensory sensitivity might be more inclined to partake in the study. In addition, we recruited patients through outpatient rehabilitation clinics which might increase the risk of including patients with more post-injury deficits (who have a higher need for

outpatient rehabilitation). This could explain why the prevalence of post-injury sensory hypersensitivity found in our sample (75% for stroke patients, 89% for traumatic brain injury patients, and 82% for brain tumour patients) was considerably higher than what was found in previous studies who recruited a less-biased inpatient sample (18% for stroke patients, and 46% for brain tumour patients) (Chung & Song, 2016; Ochi et al., 2022). On the other hand, it must be noted that previous studies used questionnaires that were ill-suited (i.e., the Adult/Adolescent Sensory Profile) or were not validated in an acquired brain injury population. For future research a more representative sample could be targeted by contacting patients through primary care facilities (i.e., general practitioners) and acute hospitals. Targeting a more acute sample of acquired brain injury patients is of additional interest since only two of the included patients acquired their brain injury within a year of participating in this study. In future studies we plan to investigate if the MESSY is also sensitive to acute changes in sensory sensitivity after brain injury in an inpatient population.

Another limitation of the study is that patients reported retrospectively on their experienced change in sensory sensitivity after their brain injury which could be influenced by a good old day bias (Iverson et al., 2010; Silverberg et al., 2016). In addition, answering these questions online without being able to consult a clinician could limit the reliability of these responses. Further research is needed to investigate how reliable the answers to these open questions are, for instance, by assessing their reliability across different time points. As an alternative to the retrospective analysis future investigations could track the sensory sensitivity in participants that are at risk for a brain injury (such as athletes at risk for a sport-related concussion or individuals with a high risk of stroke due to the presence of vascular risk factors). However, it should be noted that this would also result in a biased sample since, for instance, the acquisition of a brain injury due to collision-based trauma is hard to predict on an individual level. A third limitation is that we classified acquired brain injury patients into three groups (stroke, traumatic brain injury, and brain tumour patients) based on a self-reported type of brain injury. For future research we would suggest classifying these groups based on medical file data or a clinical evaluation. This would also allow us to gather data on injury severity and location which can then be used to investigate how these variables might impact post-injury sensory hypersensitivity. Since we included patients with different types of injuries and varying severities (i.e., we included patients with concussion and lacunar strokes as well as patients with severe traumatic brain injury and different brain

tumour grades) a heterogeneity regarding injury severity and lesion characteristics (i.e., location, volume, diffuse vs. focal lesions) can be expected. In addition, although the majority of the included patients acquired their brain injury more than one year before participation (a chronic sample), there was a large variation in the time since injury (ranging from within one year to 69 years since injury). In future studies it would be interesting to investigate how these injury related variables (time since injury, injury location, injury severity) might impact post-injury sensory hypersensitivity. For instance, we recommend examining how the prevalence and severity of sensory hypersensitivity after brain injury evolve from the acute to the chronic stage and if the prognosis of post-injury sensory hypersensitivity differs according to brain injury type. Especially since, to date, data on the longitudinal progression of sensory hypersensitivity after brain injury is limited to light and noise sensitivity in mild traumatic brain injury patients during the first year after brain injury (Barker-Collo et al., 2018; Marzolla et al., 2022; Shepherd et al., 2021, see also Thielen et al., 2022). Lastly, we excluded respondents with certain types of brain injury (e.g., anoxia, encephalitis, hydrocephalus, meningitis). Since sensory hypersensitivity after these types of brain injury receives little scientific attention, future research on sensory hypersensitivity after other types of acquired brain injury (not limited to stroke, traumatic brain injury, and brain tumours) is encouraged.

The psychometric properties of the MESSY

The multiple-choice items of the MESSY had a high convergent validity and test-retest reliability in neurotypical adults. To assess the discriminant validity of the multiple-choice items of the MESSY we used two questionnaires that are thought to measure social anxiety (similar to Kuiper et al., 2018). The total score of the MESSY correlated moderately with the total score on the Social Anxiety and Interaction Scale but there was no evidence for a significant correlation with the total score on the Inventory of Interpersonal Situations. The relationship between the MESSY with one social anxiety scale and not with the other might be explained by a mediating influence of general trait anxiety and depression. The Social Anxiety and Interaction Scale is known to correlate moderately with state and trait anxiety as well as depression (Mattick & Clarke, 1998). Since previous research showed that sensory sensitivity also correlates moderately with state anxiety and depression (Brindle et al., 2015; Engel-Yeger & Dunn, 2011; Liss et al., 2008), the relationship between the MESSY and the Social Anxiety and Interaction Scale might merely be a reflection of their associations with negative affect. This is supported by the fact that the Social Anxiety and Interaction Scale and the second part of the Inventory of Interpersonal Situations use different outcome measures

to measure social anxiety. The Inventory of Interpersonal Situations looks at the frequency in which participants engage in certain social behaviours which might be more specific to social anxiety and less influenced by general trait anxiety or depression as compared to the distress that is experienced in social situations which is measured by the Social Anxiety and Interaction Scale. Furthermore, the amount of distress experienced in social situations might be a result of individuals' sensory hypersensitivity (regardless of social anxiety) since social situations often take place in sensory rich environments. Further research is needed to examine these hypotheses and acquire further data regarding the discriminant validity of the MESSY.

We found evidence for measurement invariance across groups (neurotypical adults vs. acquired brain injury patients) at a scalar invariance level. This means that the same latent construct is thought to underlie MESSY scores in neurotypical adults and patients with an acquired brain injury, and, therefore, that differences in observed MESSY scores between the two groups reflect differences in the theoretical construct that is being measured (sensory sensitivity) (Borsboom, 2006; Wicherts, 2016). Even though the MESSY measures sensory sensitivity in a similar manner in both groups, it remains unclear if the underlying mechanisms of sensory hypersensitivity are equivalent in neurotypical adults and adults with an acquired brain injury. For instance, research on sensory hypersensitivity in neurotypical adults often points to atypical sensory thresholds as the underlying mechanisms of sensory hypersensitivity (Brown & Dunn, 2002; Dixon et al., 2016; Trå et al., 2022). However, to date, research on the relationship between sensory thresholds and sensory hypersensitivity after acquired brain injury is limited and results remain inconsistent (see Thielen et al., 2022). Further research is needed to investigate whether the underlying mechanisms of sensory hypersensitivity differ across different populations (including neurotypical adults and acquired brain injury patients but also other clinical groups such as individuals with autism spectrum disorder, ADHD, schizophrenia, or Tourette syndrome). In this regard, we believe that adapting the MESSY to the cognitive profile of acquired brain injury patients and older neurotypical adults does not necessarily mean that the MESSY is ill-suited for other clinical groups (as they may also benefit from the removal of multiple negations and the use of short items supported by examples and pictograms). Future investigations could confirm whether the multiple-choice items of the MESSY measure a similar construct across different clinical groups. This, in addition to research on the underlying mechanisms of sensory hypersensitivity, will allow us to examine whether these seemingly similar subjective symptoms can be assessed and treated uniformly across different groups.

In neurotypical adults, MESSY total scores slightly decreased with increasing age and were significantly higher in females (as compared to males). Possible explanations for the higher sensory sensitivity in neurotypical females (as compared to neurotypical males) could be endocrine differences, gender-related differences in the cognitive appraisal of sensory stimuli, as well as gender stereotypes in self-reporting on health status (Boerma et al., 2016; Ohla & Lundström, 2013; Shuster et al., 2019). The discussed age-related decline in sensory sensitivity in neurotypical adults could be explained by decreased sensory functioning in older adults (Schumm et al., 2009) as well as differences in the sensory richness of the (social) environments of older vs. younger adults. However, it must be noted that Gándara-Gafo et al. (2019) found a higher sensory sensitivity in adults aged above 65 as compared to adults which an age below 65 years old. Therefore, further research is needed to investigate the existence and direction of the relationship between age and sensory sensitivity.

Sensory hypersensitivity after acquired brain injury

A large proportion of included acquired brain injury patients (79%) reported experiencing an increase in their sensitivity to at least one sensory modality after their brain injury that was still present in the month previous to participation. For most of these patients (81%) these hypersensitivity complaints could be considered multi-modal (i.e., were present in more than one modality) while 4% of these patients reported a post-injury hypersensitivity to all seven measured sensory modalities.

When comparing the different sensory modalities, an increase in sensitivity to multisensory, visual, or auditory stimuli was reported by more than half of the acquired brain injury patients (see Table 10). An increase in sensitivity to motion, taste, smell, touch, or environmental temperature was less common. This pattern was similar across different brain injury types (stroke, traumatic brain injury, brain tumour) (see Table 10). For future research it would be interesting to investigate if this difference in prevalence across different modalities is related to certain underlying neural mechanisms (such as lesion location) or, for instance, could be explained by how difficult it is to control or avoid certain sensory modalities (i.e., some stimuli (e.g., certain types of fabrics, certain flavours, whether the furnace is on or not) might be easier to avoid or control than other stimuli (i.e., light, the voices of other people)).

Even though post-injury visual and auditory hypersensitivity were most common, a focus on just these two modalities (as is common in previous research, see Thielen et al., 2022) would offer an underestimation of the prevalence of sensory hypersensitivity after acquired brain injury. In

our sample of acquired brain injury patients a relatively large number of patients reported a post-injury hypersensitivity to motion (23%), environmental temperature (21%), taste or smell (17%), or tactile stimulation (11%). Since the modalities in which post-injury sensory hypersensitivity are experienced can vary inter-individually and since post-injury sensory hypersensitivity can occur in one single modality, it is important to consider modality-specific normative data instead of solely relying on the total score of the MESSY. A confirmatory factor analysis revealed that the MESSY consists of seven modality-specific subscales measuring visual, auditory, tactile, gustatory, and olfactory sensitivity[8] as well as sensitivity to environmental temperature and motion. We comprised gender- and age-dependent normative data which can be used by clinicians to assess the severity of an individual's sensory sensitivity per modality. This allows for the development of rehabilitation protocols to specifically target the modalities to which an individual patient is hypersensitive.

The sensory sensitivity of patients who reported an increase in their sensitivity after a stroke, traumatic brain injury, or brain tumour measured using the MESSY was significantly higher than that of neurotypical adults and acquired brain injury patients without post-injury sensory hypersensitivity. This implies that the MESSY is sensitive to post-injury sensory hypersensitivity and that patients with post-injury sensory hypersensitivity, on average, report a higher sensory sensitivity severity as compared to neurotypical adults and acquired brain injury patients without post-injury sensory hypersensitivity. Interestingly, the acquired brain injury patients without post-injury sensory hypersensitivity scored slightly lower on the MESSY than neurotypical adults. The neurotypical adults that were included in our study were mainly recruited through social media posts that communicated the focus of the study as 'investigating sensory processing'. Therefore, it is possible that neurotypical adults with sensory hypersensitivity (not related to brain injury) had a higher chance of participating in this study than neurotypical adults without these complaints. In addition, the group of acquired brain injury patients without post-injury sensory hypersensitivity might include patients with post-injury sensory hyposensitivity (a decrease in their sensory sensitivity after brain injury) (Gudziol et al., 2014; Nölle et al., 2004; Wehling et al., 2015). However, it must be mentioned that there was no evidence for a difference in sensory sensitivity between neurotypical adults and acquired brain injury patients without post-injury sensory hypersensitivity for some modalities (e.g., multisensory, visual, and motion sensitivity). These inconsistent findings across different modalities might be explained by modality-specific differences in the prevalence of sensory hyposensitivity after acquired brain injury. For instance, post-injury sensory hyposensitivity for environmental temperature, taste, smell, and touch might be more common than post-injury sensory hyposensitivity for visual or motion stimuli. Further

[8] *Gustatory and olfactory sensitivity are combined within one subscale.*

research is needed to investigate these findings.

Results showed that there was no evidence for a statistically significant difference in modality-specific sensory sensitivity between stroke, traumatic brain injury, and brain tumour patients with post-injury sensory hypersensitivity (after controlling for age). Interestingly, there also was no evidence for statistically significant differences in modality-specific sensory sensitivity between patients with sensory hypersensitivity after mild traumatic brain injury and patients with sensory hypersensitivity after moderate to severe traumatic brain injury. This provides evidence that the focus of the scientific literature on sensory hypersensitivity after mild traumatic brain injury is not necessarily due to an elevated severity of symptoms in this group (as compared to other types of brain injury) but could be attributed to a lack of adequate diagnostic tools. The MESSY can facilitate research on post-injury sensory hypersensitivity after moderate to severe brain injury which, in turn, can decrease the bias of scientific literature towards a certain type of brain injury. It must be noted that results showed slightly higher MESSY total scores in traumatic brain injury patients as compared to stroke patients. Since the included acquired brain injury sample can be considered heterogenous, it would be interesting to study if this group difference remains significant after controlling for injury-related factors (such as lesion location, lesion volume, and time since injury). Future studies could, for instance, investigate whether the diffuse brain damage that is related with traumatic brain injury increases the risk of higher sensory sensitivity severity as compared to the focal damage related to stroke. Lastly, it must be noted that there were inter-individual differences in sensory sensitivity severity in the group of acquired brain injury patients with post-injury sensory hypersensitivity. For future research it would be interesting to investigate whether symptom severity is related to the previously mentioned injury-related factors (such as lesion location, lesion volume, and time since injury), the contribution of different underlying mechanisms, or psychosocial factors (such as coping and experienced social support).

In conclusion, this study introduced a reliable, valid, and patient-friendly assessment of sensory sensitivity (the MESSY) which was able to differentiate between neurotypical controls and acquired brain injury patients with post-injury sensory hypersensitivity. Since sensory hypersensitivity after acquired brain injury is often missed by healthcare providers, the MESSY can aid clinicians in adequately diagnosing these symptoms as well as stimulate research on treatment and the underlying mechanisms of post-injury sensory hypersensitivity. These scientific and clinical advances are of vital importance since post-injury sensory hypersensitivity is known to negatively affect quality of life in acquired brain injury patients (Alwawi et al., 2020; Carlsson et al., 2004, 2009; Shepherd et al., 2020; Trulsson et al., 2003).



“When I am overloaded by sensory stimuli
I literally become physically ill:
I feel nauseous, I start vomiting, and I have severe headaches.
I can’t walk properly anymore,
can’t control my mouth – so I can’t speak.
When there is background noise, I can’t think properly.
I’ve even fainted when a situation got too busy”

Chapter four

Sensory sensitivity: should we consider attention in addition to prediction?

Ward (2019) proposes a signal detection framework to explore sensory sensitivity across different conditions, and links it to the predictive coding theory. More generally, however, perception is determined not only by sensory input and by prediction or prior knowledge, but also by behavioural relevance. We argue that selective attention, the process that allows us to prioritise the processing of behaviourally relevant over irrelevant information, should be taken into account when considering individual differences in sensory sensitivity.

Thielen, H., & Gillebert, C.R. (2019). Sensory sensitivity: should we consider attention in addition to prediction? Cognitive Neuroscience, 10(3), 158-173.

Why are some people more likely than others to have an abnormally intense or adverse reaction to simple sensory stimuli? In his Discussion paper, Ward (2019) offers a comprehensive framework to unify evidence on sensory sensitivity at different levels and across several conditions. According to Ward, individual differences in sensory sensitivity can be understood by considering the perceptual processing of neural signal and neural noise.

$$O = K(S) \cdot (1+Nm) + Na$$

Ward links the signal detection framework to several theoretical models including the predictive coding theory. According to this theory, sensory sensitivity is related to differences in perceptual processing of the neural signal (i.e., K(S)). More specifically, predictable sensory stimuli are postulated to have a sparser neural representation, which is supported by studies reporting attenuated sensory neural activity for predicted relative to unfamiliar or unexpected information (Kok et al., 2012; Summerfield et al., 2008). Differences in neural sensory sensitivity are then thought be related to differences in the balance between priors and sensory input. Inadequate prediction models have indeed been found in several conditions linked to atypical sensory sensitivity, such as autism spectrum disorder (e.g., Pellicano & Burr, 2012; Van de Cruys et al., 2014).

Perception, however, is not only influenced by sensory input and priors, but also by the relevance of the sensory input for our current goals. Predictive coding models that include this effect of attention (Friston, 2009; Rao, 2005), suggest that it can boost the precision of predictions, resulting in increased weighting of sensory signals that are behaviourally relevant ('endogenous' attention) or sensory salient ('exogeneous' attention). While predicted stimuli evoke reduced neural activity, activity in sensory regions is higher for attended relative to unattended information (e.g., Corbetta et al., 1990; Reynolds & Heeger, 2009). In an elegant fMRI study, Kok et al. (2012) independently manipulated attention and prediction, showing that attention can silence the sensory attenuating effect of prediction. Their results suggest that attention (i.e., whether a signal is behaviourally relevant) and prediction (i.e., whether a signal is likely to be presented) act together synergistically to improve the precision of sensory signals. Translating this into individual differences, sensory sensitivity may not only result from the inability to predict the sensory experience, but also from the inability to prioritise the processing of information that is sensory salient or behaviourally relevant.

There is evidence across multiple conditions and methodologies that inadequate attentional priority maps can be related to sensory (hyper)sensitivity. For instance, atypical attention processes seem to be among the earliest symptoms of autism (Elison et al., 2013; Zwaigenbaum et al., 2005) (see also Van de Cruys et al., 2014) and have been found in children with attention deficit hyperactivity disorder (ADHD) who also frequently report sensory hypersensitivity (i.e., Bijlenga et al., 2017). Furthermore, patients with mild traumatic brain injury report selective attention impairments as well as sensory hypersensitivity (Lundin et al., 2006). Also, ADHD traits such as distractibility correlate with self-reported subjective sensitivity in the general population (Panagiotidi et al., 2018). These studies suggest that the inability to prioritise the processing of relevant over irrelevant information may be related to atypical subjective sensory sensitivity.

The suggested relationship between attentional priority maps and sensory hypersensitivity is supported by neuroimaging research of the salience network. This large-scale brain network is involved in the detection of relevant sensory input as well as attentional filtering of distractors (Menon, 2015). In line with the behavioural research, we propose that abnormalities within this network could lead to inadequate attentional templates and therefore also to sensory hypersensitivity. Indeed, across conditions salience network abnormalities were linked to reduced attentional control (Bonnelle et al., 2012; Qian et al., 2018) and sensory hypersensitivity (Green et al., 2016).

In summary, several studies point to a relationship between selective attention and sensory sensitivity in the neurotypical population as well as in individuals with developmental disorders and in patients with acquired brain injury. Attention and prediction likely join forces to support the adequate processing of sensory input. It, therefore, seems important that a comprehensive account on sensory sensitivity considers the influence of attention.



“Since my brain injury I am more aware of environmental stimuli. I am no longer able to shut myself off from my surroundings and concentrate on the things I’m working on.”

Chapter five

Why am I overwhelmed by bright lights? The behavioural mechanisms of post-stroke visual hypersensitivity

After stroke, patients can experience visual hypersensitivity, an increase in their sensitivity for visual stimuli as compared to their state prior to the stroke. Candidate behavioural mechanisms for these subjective symptoms are atypical bottom-up sensory processing and impaired selective attention, but empirical evidence is currently lacking. In the current study, we aimed to investigate the relationship between post-stroke visual hypersensitivity and sensory thresholds, sensory processing speed, and selective attention using computational modelling of behavioural data. During a whole/partial report task, participants (51 stroke patients, 76 orthopedic patients, and 77 neurotypical adults) had to correctly identify a single target letter that was presented alone (for 17 to 100 ms) or along a distractor (for 83ms). Performance on this task was used to estimate the sensory threshold, sensory processing speed, and selective attention abilities of each participant. In the stroke population, both on a group and individual level, there was evidence for impaired selective attention and lower sensory thresholds in patients with post-stroke visual hypersensitivity as compared to neurotypical adults, orthopedic patients, or stroke patients without post-stroke sensory hypersensitivity. These results provide a significant advancement in our comprehension of post-stroke visual hypersensitivity and can serve as a catalyst for further investigations into the underlying mechanisms of sensory hypersensitivity after other types of acquired brain injury as well as post-injury hypersensitivity for other sensory modalities.

Thielen, H., Welkenhuyzen, L., Tuts, N., Vangkilde, S., Lemmens, R., Wibail, A., Lafosse, C., Huenges Wajer, I.M.C., & Gillebert, C.R. (2023). Why am I overwhelmed by bright lights? The behavioural mechanisms of post-stroke visual hypersensitivity. Submitted to Neuropsychologia.

Humans are surrounded by a limitless number of sensory stimuli. At any given moment this external sensory information is processed by our brain to guide functional behaviour. For example, when our smartphone beeps, we respond by looking at an incoming text; when we feel hot, we open a window; and through the processing of fast-moving visual images, we can follow the plot of a movie. There are large inter-individual differences in how sensitive humans are to these sensory contexts, ranging from a low to a high sensory sensitivity (Ward, 2019). Stroke can impact this individual level of sensory sensitivity resulting in post-stroke subjective sensory hypersensitivity, referring to a self-reported increased sensitivity to sensory stimuli post-stroke as compared to pre-stroke (Thielen et al., 2022; Thielen, Huenges Wajer et al., 2023). Sensory hypersensitivity can manifest itself as feelings of nausea, anxiety, pain, or irritability when exposed to one or multiple sensory modalities. Even though post-stroke sensory hypersensitivity is prevalent both in the subacute and chronic stages after stroke (Alwawi et al., 2020; Thielen, Tuts et al., 2023), to date, its behavioural mechanisms remain unclear. As a result, it also remains uncertain how these symptoms should best be treated. Since post-stroke sensory hypersensitivity is known to have a negative effect on quality of life (Alwawi et al., 2020; Carlsson et al., 2009; Thielen, Tuts et al., 2023), elucidating the mechanisms of these subjective symptoms is of high importance in order to guide the development of evidence-based treatment protocols.

Sensory hypersensitivity is not specific to stroke but is also seen in other neurological or neurodevelopmental disorders such as Tourette syndrome, autism spectrum disorder, attention deficit hyperactivity disorder (ADHD) (e.g., Bijlenga et al., 2017; Isaacs & Riordan, 2020; Kamath et al., 2020; Weiland et al., 2020), in the neurotypical population (Dixon et al., 2016; Greven et al., 2019), and after other types of acquired brain injury (traumatic brain injury and brain tumours) (Knoll, Lubner et al., 2020; Ochi et al., 2022; Shepherd et al., 2020). Similar to the stroke population, it remains unclear if and how subjective sensory sensitivity (an individual's self-reported sensitivity to sensory stimuli) relates to behavioural sensory sensitivity (the processing of sensory stimuli) within these populations (see Ward, 2019). Previous studies across different populations have proposed three different behavioural mechanisms underlying subjective sensory hypersensitivity: (1) low sensory thresholds, (2) atypical sensory processing speed, and (3) impaired selective attention.

A relationship between sensory sensitivity and sensory thresholds is suggested by the Four Quadrant Model of Sensory Processing (Brown & Dunn, 2002; Dunn, 2001). In this model, an individual's response to sensory stimulation is based upon their sensory threshold (the lowest intensity at which a stimulus is detected) in combination with either an active or a passive coping style (whether or not individuals actively try to control their sensory environment by seeking out or avoiding sensory stimuli). This idea is consistent with the name of the "low sensory threshold" subscale of the Highly Sensitive Person Scale (a scale commonly used to assess sensory processing sensitivity in neurotypical adults) which assesses the extent to which individuals are easily overwhelmed or aroused by sensory stimuli (Smolewska et al., 2006; Trå et al., 2022). Despite the hypotheses of these models, there is little empirical evidence for a relationship between sensory sensitivity and sensory thresholds in the scientific literature. In neurotypical individuals, one study reported that adults with sensory hypersensitivity display higher visual detection abilities than adults without sensory hypersensitivity (Gerstenberg, 2012), while another study did not find evidence for a relationship between visual detection thresholds and visual sensory sensitivity (Schulz & Stevenson, 2019). In adults with a mild traumatic brain injury, a relationship was found between self-reported light sensitivity and the critical flicker fusion frequency (the frequency at which a flickering stimulus is no longer perceived to be flickering but is perceived as constant) (Chang et al., 2007). However, this finding was not replicated by Schrupp et al. (2009) in a similar sample. After stroke, a decrease in an individual's sensory threshold could induce higher processing demands by increasing the number of stimuli that require simultaneous processing, which could manifest itself as post-stroke sensory hypersensitivity. However, to our knowledge, there is no study investigating the relationship between sensory thresholds and post-stroke sensory hypersensitivity specifically.

A second candidate mechanism is sensory processing speed. Sensory processing speed is defined as the speed at which the sensory system can process information which is often operationalized as the time it takes to respond to a single stimulus or the number of stimuli that can be processed in a certain amount of time (e.g., Costa et al., 2017). A link between sensory processing speed and sensory sensitivity is supported by findings of reduced processing speed in clinical populations with sensory hypersensitivity (autism spectrum disorder, ADHD, Tourette syndrome, stroke, traumatic brain injury) (Draper & Ponsford, 2008; Khalifa et al., 2010; Kibby et al., 2019; Su et al.,

2015; Zapparrata et al., 2022). Similarly, evidence was found for a negative relationship between sensory sensitivity and reaction time on a visual detection task in neurotypical adults (Gerstenberg, 2012). In contrast, in patients with a mild traumatic brain injury, hypersensitive individuals displayed slower responses on different neuropsychological tests (Kumar et al., 2005; Shepherd et al., 2019). Hence, the direction between sensory processing and sensory hypersensitivity can be hypothesized in two directions. On the one hand, a reduced processing speed can cause sensory input to build up and in turn cause feelings of overwhelm and sensory hypersensitivity. On the other hand, a faster processing speed could cause individuals to be more aware of subtle stimuli because their sensory system is able to process more stimuli. However, since the results of the small number of studies investigating the relationship between sensory sensitivity and sensory processing speed are inconsistent, future research is needed to determine the existence and directionality of this relationship.

A last hypothesis is the filter hypothesis which describes a relationship between selective attention impairments and sensory hypersensitivity (Thielen & Gillebert, 2019). Selective attention represents the ability to attend to stimuli that are relevant for our current goals while filtering out irrelevant stimuli. This filtering mechanism prevents the sensory system from being overflooded with irrelevant information. A relationship between selective attention and sensory hypersensitivity is supported by the relatively high prevalence of sensory hypersensitivity in individuals with ADHD (Bijlenga et al., 2017) and by an association between self-reported distractibility and sensory hypersensitivity in neurotypical adults (Panagiotidi et al., 2018). Furthermore, adding tactile distraction to an attentional task caused more interference in performance in neurotypical adults with high sensory sensitivity than in neurotypical adults with low sensory sensitivity (Panagopoulos et al., 2013). Research on this relationship in acquired brain injury patients is limited to two studies that found no evidence for a relationship between sensory hypersensitivity and selective attention performance in mild traumatic brain injury patients (Kumar et al., 2005; Shepherd et al., 2019).

In summary, to date, the behavioural mechanisms of post-stroke sensory hypersensitivity remain unclear. The primary aim of the current study was to examine the impact of these mechanisms on post-stroke subjective sensory sensitivity using computational modelling of behavioural data in subacute hospitalized stroke patients. To this end, we adapted a patient-friendly sensory sensitivity questionnaire (the Multi-Modal Evaluation

of Sensory Sensitivity, MESSY) (Thielen, Huenges Wajer et al., 2023) and paradigms developed within the framework of the Theory of Visual Attention (TVA) (Bundesen, 1990) to be used at the bedside of subacute stroke patients. More specifically, we investigated, on a group- and individual level, whether visual thresholds, visual processing speed, and selective visual attention differed between stroke patients with post-stroke visual hypersensitivity and stroke patients without post-stroke sensory hypersensitivity, neurotypical controls, and hospitalized orthopedic patients (without neurologic injury). By including orthopedic patients, we could control for the potential influence of hospitalization and recovery from a medical event on sensory sensitivity and its underlying mechanisms. Based on previous studies, we expected lower sensory thresholds and impaired selective attention in patients with post-stroke visual hypersensitivity as compared to the other three groups. Previous results regarding the hypothesized relationship between sensory processing speed and sensory sensitivity are contradictory. Due to the considerable evidence for processing speed impairments in clinical groups with heightened sensory sensitivity (including acquired brain injury patients) (Draper & Ponsford, 2008; Khalifa et al., 2010; Kibby et al., 2019; Kumar et al., 2005; Shepherd et al., 2019; Su et al., 2015; Zapparrata et al., 2022), we hypothesized lower visual processing speed in patients with post-stroke visual hypersensitivity as compared to stroke patients without post-stroke sensory hypersensitivity, orthopedic patients, and neurotypical adults.

Methods

Participants

Non-hospitalized neurotypical adults were recruited through social media, by contacting participants who had previously participated in research in the department of Brain and Cognition (KU Leuven), and by utilizing the social networks of the researchers. Hospitalized stroke patients were recruited at three different clinical settings (the acute stroke unit of University Hospitals Leuven and the rehabilitation units of RevArte Rehabilitation Hospital and Hospital East-Limburg). Hospitalized orthopedic patients were recruited at RevArte Rehabilitation Hospital. Recruitment took place between December 2019 and January 2023. Because of the COVID-19 pandemic, recruitment was halted during several periods such as between March 2020 until June 2020 for stroke patients and between March 2020 until July 2020 and between October 2020 and March 2022 for the neurotypical adults.

To be included in this study participants had to: be able to give informed consent, be adult (aged 18 years or above), complete the MESSY, a structural anamnesis, and the TVA-based assessment, and have normal or corrected-to-normal vision and hearing. Participants were excluded if they had a formal diagnosis of autism spectrum disorder, ADHD, or schizophrenia. Additional exclusion criteria for neurotypical adults and orthopedic patients were having a neurological disorder (including a brain injury) or an invalidating psychiatric disorder (i.e., a disorder that required inpatient care or limited their vocational activities in the month before participation). In addition, we excluded neurotypical adults and orthopedic patients with a suspicion of mild cognitive impairment (based on their performance on the Montreal Cognitive Assessment, see below). Additional exclusion criteria for stroke patients were not being able to complete the TVA-based assessment, having a psychiatric disorder that could impact their sensory sensitivity, and clinical imaging (Computed Tomography (CT) scan, Diffusion-weighted imaging (DWI), Magnetic Resonance Imaging (MRI)) or radiology notes not confirming the presence of a stroke.

Materials

MESSY-NL

The Dutch version of the MESSY (MESSY-NL) measures subjective sensory sensitivity across several modalities (i.e., visual, auditory, tactile, olfactory, gustatory, and motion sensitivity as well as sensitivity to environmental temperature and to multisensory stimulation) (Thielen, Huenges Wajer et al., 2023). Multisensory stimulation refers to stimulation from different sensory modalities that is present simultaneously (for instance, concurrent visual and auditory stimuli). The questionnaire consists of two types of questions. The first type comprises eight open-ended questions where patients are asked, for each modality separately, if they experience an increase in their sensitivity from pre- to post-injury (i.e., “Since your brain injury, have you become more sensitive to sounds? How did you notice this or in which situations did you notice this?”). These questions were used to differentiate between patients who did or did not experience a post-stroke increase in their sensory sensitivity (i.e., patients with or without post-stroke sensory hypersensitivity). Orthopedic patients and neurotypical adults answered similar open-ended questions (i.e., “Since hospitalisation, have you become more sensitive to sounds?” and “In the previous month, have you become more sensitive to sounds?” respectively). The second type of questions consists of 30 multiple-choice items which assess the severity of sensory sensitivity across the different sensory modalities. These

items are answered on a Likert-scale which ranges from one (never/not at all) to five (very often/extremely). Per sensory modality, participants first answer the open-ended questions and then the multiple-choice items. To avoid visual overload the items of the MESSY are presented one by one and pictograms and examples are used to facilitate the comprehension of the items. In addition, the content of the items is adapted to acquired brain injury patients and older adults (see Thielen, Huenges Wajer et al., 2023). The 30 items are distributed across the different modalities as follows: multisensory sensitivity (seven items), visual and auditory sensitivity (five items each), gustatory sensitivity (one item), tactile, olfactory, environmental temperature, and motion sensitivity (three items each).

The MESSY can be used online or offline (using pen and paper) as well as in outpatient and inpatient populations. Since inpatient facilities offer a different sensory environment (i.e., more structure, less irrelevant sensory input) than sensory rich daily life, the items of the MESSY were developed so that they can apply to both out- and inpatient environments. The two versions of the MESSY are nearly identical, except for nine items where the examples and pictograms that supplement the items are adapted to the respective sensory environment (see Figure 1). The orthopedic patients and hospitalized (sub)acute stroke patients completed the inpatient version of the MESSY and the neurotypical adults the outpatient version of the MESSY. We have previously described and validated the online outpatient version of the MESSY in neurotypical adults and chronic acquired brain injury patients and found that it had a high convergent validity (spearman rho = .71) and test-retest reliability (spearman rho = .84) in neurotypical adults (Thielen, Huenges Wajer et al., 2023). Unpublished data of 77 neurotypical adults (age range: 18-90 years old, mean age: 59 years old, 43% male) showed a very high equivalence between the online and paper-and-pencil versions of the outpatient version of the MESSY (spearman rho = .95).

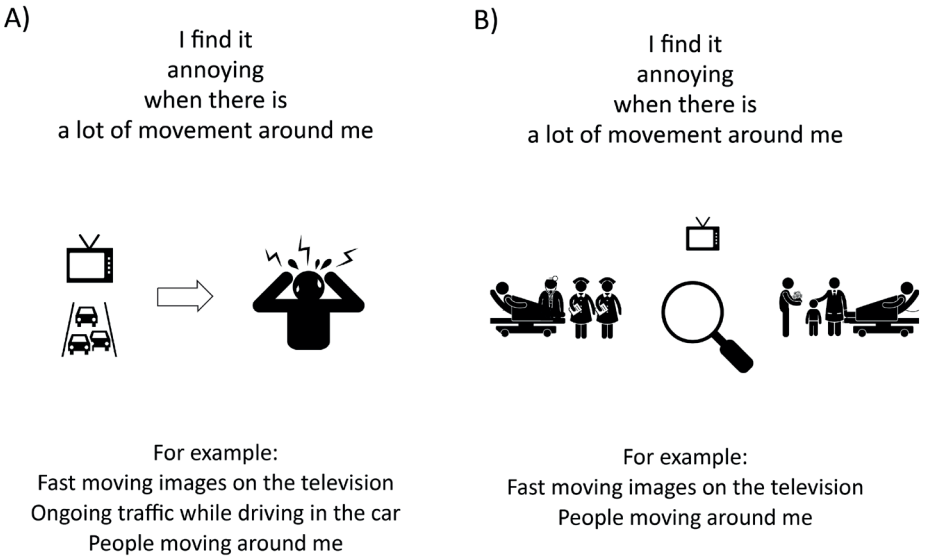


Figure 1: An item of the MESSY of the out- (panel A) and inpatient (panel B) versions of the MESSY.

Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is a cognitive screening tool that is used to detect mild cognitive impairment (Nasreddine et al., 2005). The MoCA can be administered in approximately 15 minutes and consists of 13 subtests that assess language, orientation, visuoconstruction, attention, verbal memory, and executive functioning. The test is scored using a single total score (where a higher score represents better cognitive abilities) with a maximum score of 30. In this study we used the Dutch MoCA version 7.1 (www.mocatest.org). Using the weighted mean of 20 different studies, De Roeck et al. (2019) found that the MoCA has an adequate internal consistency (.78), as well as a high inter-rater reliability (.97) and test-retest reliability (.88). Originally, a cut-off score of 26 was determined to detect cognitive impairment (Nasreddine et al., 2005). However, since the total score on the MoCA is influenced by age, gender, and education level (Borland et al., 2017; Bruijnen et al., 2020), we used the gender, age, and education level dependent norms for the Dutch version of the MoCA as published by Kessels et al. (2022). The 24th percentile, which corresponds to a below average performance (Guilmette et al., 2020; Hendriks et al., 2020) was used as a cut-off point for mild cognitive impairment.

The Oxford Cognitive Screen-NL

To screen post-stroke cognition, included stroke patients completed the Dutch version of the Oxford Cognitive Screen (OCS) (version A) (Huygelier et al., 2019). The OCS can be administered in approximately 20 minutes and consists of 11 subtests that assess the presence of visual field deficits, attention, memory, language, praxis, and numeracy (for details see Demeyere et al., 2015; Huygelier et al., 2019). The OCS was developed to overcome limitations of the MoCA by offering domain-specific test scores instead of one total score thought to measure general cognitive functioning and by minimizing the confounding effects of common stroke symptoms such as aphasia and hemispatial neglect on test performance. Previous studies determined that the OCS had adequate parallel-form reliability (intraclass correlation coefficient ranged from .47 to .96) (Huygelier et al., 2022) and convergent validity (correlation coefficients ranged from .32 to .72) in subacute stroke patients (Demeyere et al., 2015). In subacute stroke patients, the sensitivity of the OCS relative to the MoCA ranged from 68% to 92% (according to the age of the stroke patients) (Huygelier et al., 2022).

TVA-based assessment

The TVA-based assessment consisted of a combination of whole and partial report tasks. In the whole report task, a single red letter was presented for a variable amount of time (17-100 ms). The target was displayed on four positions: below, above, or besides the fixation cross on either the left or right side (with 2 visual degrees between the centre of the letter and the centre of the screen) (see Figure 2, Panel A). In the partial report task, the single red letter was presented along a distractor (a blue letter presented opposite to the target). During each trial, participants had to identify the target, while ignoring the distractor (during partial report trials) (see Figure 2, Panel B). Participants were seated in a dimly lit room approximately 50 cm from a 16 inch laptop monitor (resolution 1920 x 1080, refresh rate 60 Hz[1]). The centre of the screen was positioned at the eye level of the participant. The letters had a height of two visual degrees. The TVA-based assessment consisted of one practice block of 24 trials and six experimental blocks of 52 trials (20 masked whole report trials, eight unmasked whole report trials, 24 masked partial report trials). During each trial, participants had to, firstly, maintain central fixation while looking at a red fixation cross presented on a black background for 1000ms. Then according to the trial type, the red target letter was shown in absence (during whole report) or presence (during partial report) of a distractor. The stimulus display was followed by a multi-coloured pattern mask for

[1] *Two participants completed the TVA task on a 14 inch laptop monitor. The size of the presented stimuli and the distance between the target letters and the center of the screen were identical to those on the 16 inch laptop monitor.*

500ms. The masks, which completely covered the stimulus locations (size: 2.4 x 2.4 visual degrees), controlled the amount of time the target and distractor were available for sensory processing. Lastly, participants had to indicate which letter they saw using a multiple-choice display either by naming the target letter or by pointing to the target letter. Participants were instructed to focus on the fixation cross throughout the task. The display of a single target was shown for a variable duration (17, 33, 50, 83, or 100 ms), while the partial report displays were shown for 83 ms (based on Vangkilde et al., 2011). Unmasked trials with two possible durations (17 and 100 ms) were added to increase the motivation of the participants by decreasing the difficulty of the task. During these unmasked trials the stimulus display was followed by a blank screen instead of a mask. All trial types were intermixed within each block. The target and distractor letters were randomly chosen without replacement from a set of 10 capital letters (A, B, C, D, E, H, J, K, L, M). Participants were told to report the red target letters that they were 'fairly certain' of having seen without a time limit. After each block the participants were given feedback based on their accuracy of their responses (the number of correctly reported letters divided by the number of reported letters) and were offered the chance to take a break or to complete the test in multiple sessions. The test took approximately 25 minutes to complete. The TVA task was run using the PsychoPy software (v3.2.4) (Peirce et al., 2019). To investigate whether the ability to keep central fixation during target presentation predicted TVA performance, we recorded eye movements during the TVA task at 250 Hz using a screen-based Tobii pro fusion eyetracker in a subsample of our participants (n = 41 neurotypical adults, n = 55 orthopedic patients, n = 12 stroke patients). The eyetracker was calibrated to each individual participant using a calibration and validation interface designed by the Titta package (Niehorster et al., 2020). To exclude participants who had difficulties identifying letters and discriminating between letters as well as difficulties with differentiating between the blue and red colours, participants were asked during the instructions to name the ten different letters as well as differentiate between blue and red letters.

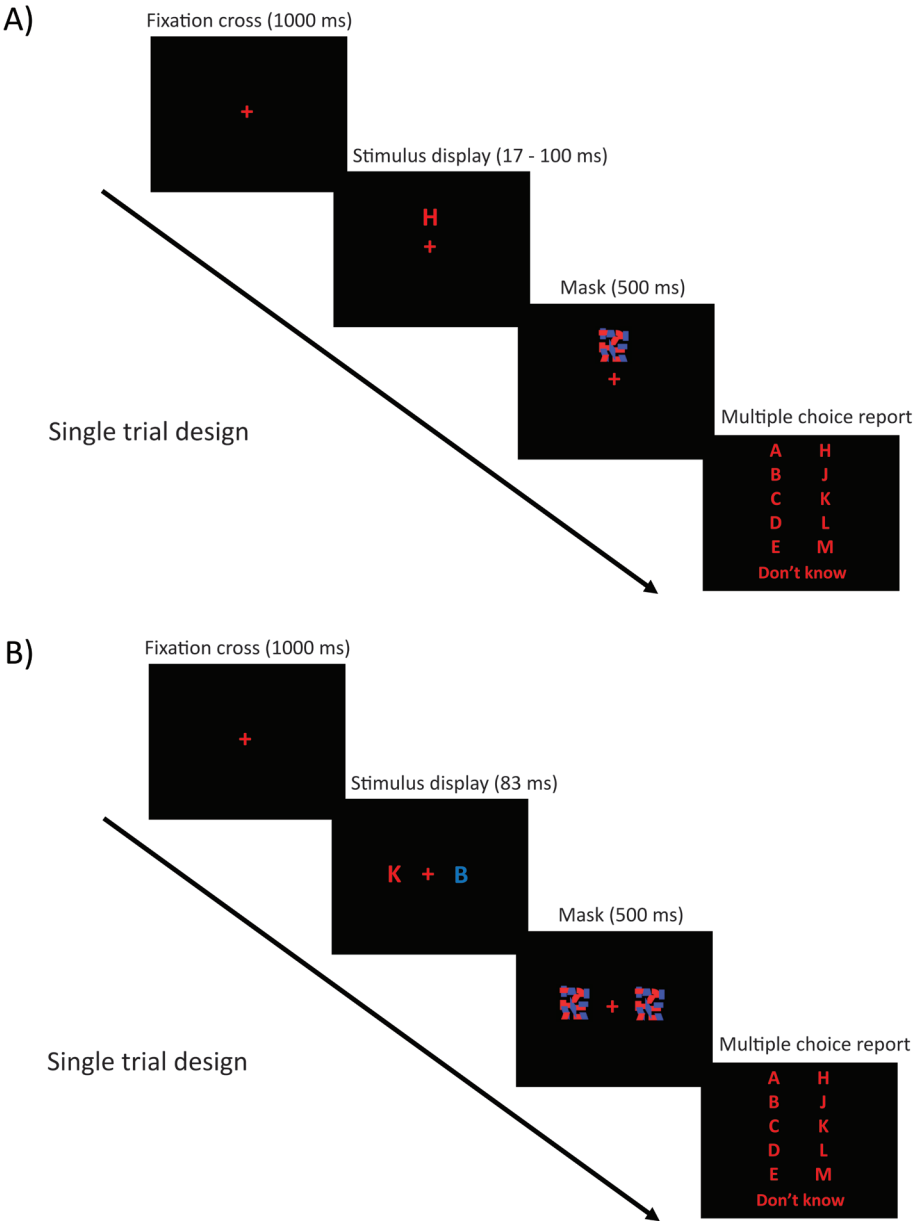


Figure 2. A single trial during whole (Panel A) or partial report (Panel B).

Structural anamnesis

During a structural anamnesis participants were asked about their age, gender, education level, and medical background (e.g., presence of a neurological, neurodevelopmental, or psychiatric disorder). The type of injury, time since injury, number of injuries, and the lesioned hemisphere (for stroke patients) were gathered from the medical files of the stroke and orthopedic patients.

Procedure

Ethical approval for this cross-sectional study was granted by the Social and Societal Ethics Committee of the KU Leuven (application number: G-2019031604), the Medical Ethics Committee of the Hospital of East-Limburg (application number: CTU2019055), the Ethics Committee Research UZ/KU Leuven (application number: S63063), and Medical Ethics Committee of the GasthuisZusters Hospital Antwerp (application numbers: 190904ACADEM, 200605ACADEM). Behavioural data were collected by individuals trained in neuropsychological assessment (HT, NT, LW) in a distraction-free room. This study was a part of a larger study about sensory sensitivity in which neurotypical controls and orthopedic patients were asked to complete two test sessions and stroke patients were asked to complete three sessions. During the first session, informed consent was acquired in accordance with the World Medical Association Declaration of Helsinki. Afterwards, participants completed the MESSY, a cognitive screen (the Montreal Cognitive Assessment for neurotypical controls and orthopedic patients and the Oxford Cognitive Screen for stroke patients), and the structural anamnesis. During the second session, all participants completed the TVA-based assessment. Both sessions lasted approximately 60 minutes. The second session was planned maximally 15 days after the first session. If needed, the sessions could be split up to keep participation feasible for stroke patients. All participants were asked to complete additional neuropsychological tasks and questionnaires that are not of interest in this current study.

Data analysis

Analyses were conducted in R (version 4.2.2) (RStudio Team, 2020) and IBM SPSS Statistics (Version 28) (IBM Corp, 2021). Alpha level was set to .05 and the Holm method was used to correct for multiple comparisons (Holm, 1979). Graphs were created using R and Adobe Illustrator (2020). Datasets analysed during the current study are available at https://doi.org/10.6084/m9.figshare.23905560 (private link that can be used during review process: https://figshare.com/s/c3835cf972827c1a1af5).

Post-stroke visual hypersensitivity

Stroke patients were categorized as patients with post-stroke visual hypersensitivity if they reported an increased sensitivity to visual stimuli during the open-ended questions of the MESSY (similar to Thielen, Huenges Wajer et al., 2023). Stroke patients that did not report a post-injury increase in their sensory sensitivity (across all sensory modalities) were categorized in the group without post-stroke sensory hypersensitivity. Three subacute patients reported an increase in their visual sensitivity that had normalized at the moment of testing and were excluded from these analyses. We calculated the self-reported severity of visual sensitivity by summing the multiple-choice items of the visual sensitivity subscale of the MESSY.

TVA-based estimation of sensory threshold, processing speed, and selective attention

Using a maximum likelihood fitting procedure that is implemented in the Matlab toolbox libtva (Dyrholm et al., 2011; Kyllingsbæk, 2006) three parameters were estimated based on the participants TVA performance: sensory threshold (t0, in milliseconds), sensory processing speed (C, in elements/second), and selective attention (alpha). During this fitting procedure an exponential curve is fitted that models the number of correctly reported letters as a function of exposure duration (Habekost, 2015; Vangkilde et al., 2011). t0 is the lowest exposure duration at which a target letter can be detected correctly, C represents the slope of the curve at t0, and alpha reflects the difference in performance at 83 ms when a target is presented alone or alongside a distractor (i.e., the ratio between the attentional weight that is given to a distractor and the attentional weight that is given to a target). Higher alpha values represent lower selective attention abilities with 0 representing perfect selective attention abilities. Negative t0 values were fixed to 0 after which the model was refitted to the data (Gillebert et al., 2016; Wang et al., 2021; Wang & Gillebert, 2018). There was no evidence for a difference in the proportion correctly reported letters (i.e., number of correctly reported letters divided by the number of trials) across the four target locations for the different exposure durations in the neurotypical adults, orthopedic, and stroke patients (see Supplementary Table 1). Therefore, we averaged the performance across the four target positions to increase the number of trials available for each exposure duration. As a measure of goodness of fit of the TVA model, we computed the mean correlation coefficient between the observed performance and the predicted performance across different exposure durations. We included the data of nine stroke patients who only completed five out of six experimental blocks to increase the power of our analyses

as including these participants did not decrease the goodness of fit of the TVA model (see below). 17 stroke patients and two orthopedic patients completed the TVA task in multiple sessions. The number of sessions it took to complete the TVA task (one or multiple) did not significantly affect the TVA parameters in the stroke and orthopedic patients (after controlling for sensory sensitivity (total MESSY score) and demographic variables). Analyses that examined whether the presence of eye movements outside of a region of central fixation during target presentation predicted the estimated TVA parameters are described in Supplementary Analysis 1.

Group analyses based on subjective sensory sensitivity

We compared the severity of visual sensitivity and the estimated TVA parameters (t0, C, alpha) between the four groups (neurotypical adults, orthopedic patients, stroke patients with post-stroke visual hypersensitivity, and stroke patients without post-stroke sensory hypersensitivity). To control for the effect of age and to check whether group effects interacted with effects of gender or education level we conducted an analysis of covariance (ANCOVA). Since the normality assumption was violated, we used a non-parametric Quade's ANCOVA (with partial Eta-squared as a measure of effect size) (Barrett, 2011; Cangür et al., 2018) with post-hoc Dunn tests (Dunn, 1964).

Single case-control analyses

To investigate if differences in TVA performance were significant on an individual level, we compared the TVA parameters between individual cases with post-stroke visual hypersensitivity to the stroke patients without post-stroke sensory hypersensitivity, orthopedic patients, and neurotypical adults using the t test described by Crawford and Howell (1998). This method is suitable even in small samples and is robust to violations of the normality assumption (Crawford et al., 2006; Crawford & Garthwaite, 2006). To conduct these analyses we used the software package Singlims_ES (Crawford et al., 2010).

The relationship between the TVA parameters and visual sensitivity

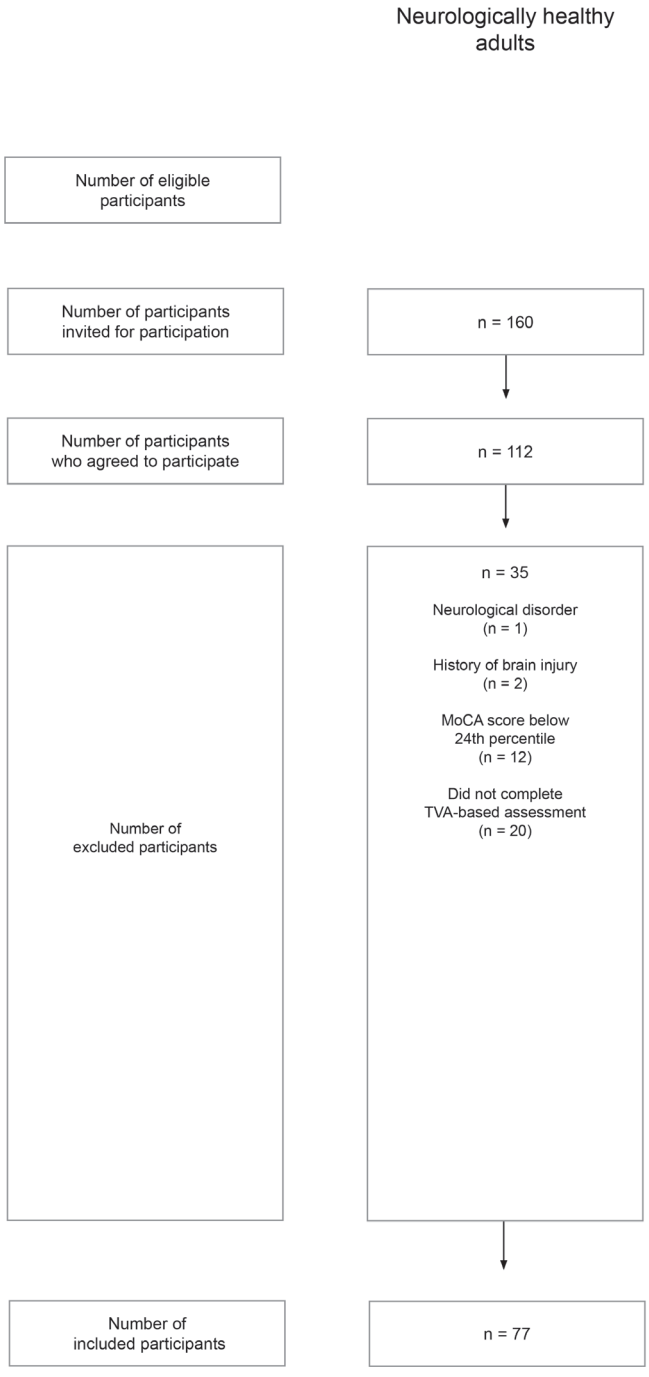
As a supplementary analysis, we investigated whether sensory thresholds (t0), sensory processing efficiency (C), and selective attention (alpha) predicted the severity of subjective visual sensitivity (i.e., the score for the multiple-choice items of the visual subscale of the MESSY) by conducting multiple regressions in all stroke patients (pooled across patients with and without post-stroke sensory hypersensitivity), orthopedic patients, and neurotypical adults. This analysis is described in Supplementary Analysis 2.

Results

Participants

Of the 122 neurotypical adults, 105 orthopedic patients, and 208 stroke patients that participated in the study, 77 neurotypical adults, 76 orthopedic patients, and 51 stroke patients were included in the analyses (see Figure 3 for the participant flow chart). Reasons for not completing the TVA-based assessment included fatigue, finding the task too monotonous or too difficult, dropout (due to hospital dismissal), COVID-19 related isolation, technical errors, language impairments, and difficulties discriminating between the red and blue letters used in the TVA-based assessment (for an overview see Supplementary Table 2). Being overwhelmed by the sensory demands of the task was not mentioned as a reason to quit the TVA-based assessment. The characteristics of the included participants are displayed in Table 1. There was evidence for a significant difference in the mean age of the four groups (Kruskal-Wallis Test: $\chi^2(2) = 12.57$, $p = .01$). The mean age of the orthopedic patients was significantly higher than the mean age of the neurotypical adults and the stroke patients with post-stroke visual hypersensitivity (Holm adjusted p values Dunn tests: $p = .02$ and $p = .04$ respectively). There was no evidence for a difference in mean age between stroke patients with and without post-stroke sensory hypersensitivity, between the two groups of stroke patients and the neurotypical adults, and between the orthopedic patients and the stroke patients without post-stroke sensory hypersensitivity. Moreover, there was no evidence for differences in lesion volume (Wilcoxon rank sum test: $W = 260$, $p = .53$) (see Table 1) or cognitive profile (see Table 2) between patients with post-stroke visual hypersensitivity and patients without post-stroke sensory hypersensitivity.

70% of the stroke patients were hospitalized after an ischemic stroke and 30% after a haemorrhagic stroke. Most of the stroke patients (70%) were first-time stroke survivors. 11% of the stroke patients were tested in the acute phase after stroke (i.e., within the first seven days after stroke) and 89% in the subacute phase after stroke (i.e., within the first six months after stroke excluding the first seven days) (Bernhardt et al., 2017). The stroke sample was heterogenous in lesion side: 28% of the patients had a left-hemispheric lesion, 55% a right-hemispheric lesion, and 17% a bilateral lesion. Figure 4 displays an overlay of the lesion distribution of all included stroke patients. The majority of the orthopedic patients (82%) received inpatient care after a joint replacement surgery.


Neurologically healthy adults
Number of eligible participants
Number of participants invited for participation
n = 160
Number of participants who agreed to participate
n = 112
Number of excluded participants
n = 35
Neurological disorder (n = 1)
History of brain injury (n = 2)
MoCA score below 24th percentile (n = 12)
Did not complete TVA-based assessment (n = 20)
Number of included participants
n = 77

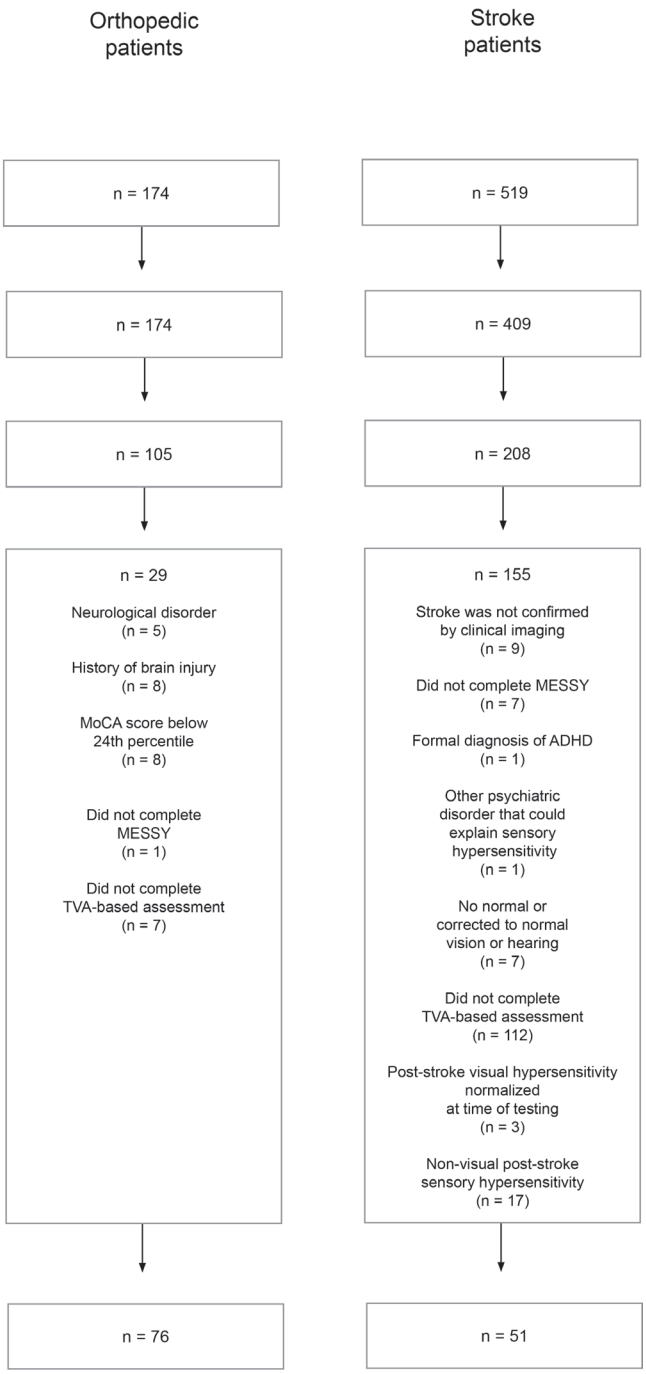


Figure 3. Participant flow diagram.

Table 1. Characteristics of included participants.

	Neurotypical adults	Orthopedic patients	Patients without post-stroke sensory hypersensitivity	Patients with post-stroke visual hypersensitivity
n	77	76	35	16
Age range (in years)	18-90	46-84	29-88	26-76
Mean age (sd) (in years)	60 (18)	68 (8)	66 (12)	56 (16)
Number of male participants (%)	34 (44%)	30 (39%)	18 (51%)	9 (56%)
Number of participants who completed higher education (%)	60 (79%)	27 (36%)	6 (17%)	4 (25%)
Number of participants with joint replacement surgery / bone fracture (%)		62 (82%) / 14 (18%)		
Mean time since orthopedic injury / stroke (sd) [Range] (in days)		26 (16) [12-113]	31 (16) [2 – 60]	53 (49) [7 – 175]
Number of patients with a ischemic / haemorrhagic stroke (%)			28 (80%) / 7 (20%)	7 (44%) / 9 (56%)
Number of acute / subacute stroke patients (%)			5 (14%) / 30 (86%)	1 (6%) / 15 (94%)
Number of participants with a single brain injury (%)			23 (66%)	11 (69%)
Lesion lateralization (Bilateral/Left/Right)			5 (14%) / 10 (29%) / 20 (57%)	4 (25%) / 4 (25%) / 8 (50%)
Lesion volume: mean (sd), in cc			5811 (7886)	4129 (5276)

Sd: standard deviation. Higher education: minimally a bachelor degree awarded by a college or university. Patients with a transient ischemic attack were classified as ischemic stroke patients. Left: left-hemispheric lesion. Right: right-hemispheric lesion. Cc: cubic centimetre.

Table 2. The cognitive profile of the stroke patients with post-stroke visual sensory hypersensitivity and stroke patients without post-stroke sensory hypersensitivity assessed using the OCS-NL.

OCS subtest per cognitive domain	Range of possible scores	Incidence of impairment per group: (%)		Median score		Results of the Mann Whitney U Test		
		Without sensory hypersensitivity (n = 35)	With visual hypersensitivity (n = 16)	Without sensory hypersensitivity (n = 35)	With visual hypersensitivity (n = 16)	W	Adjusted p	Effect size
Visual Field test	0 - 4	6%	0%	4	4	264	1	.14
Language								
Picture naming	0 - 4	3%	13%	4	4	267.5	1	.04
Semantics	0 - 3	3%	0%	3	3	272	1	.09
Sentence reading	0 - 15	6%	0%	15	15	249	1	.15
Numeracy								
Number writing	0 - 3	3%	0%	3	3	289.5	1	.08
Calculations	0 - 4	3%	6%	4	4	327.5	1	.20
Praxis								
Meaningless gesture imitation	0 - 12	6%	0%	11	12	188	.67	.28

OCS subtest per cognitive domain	Range of possible scores	Incidence of impairment per group: (%)		Median score		Results of the Mann Whitney U Test		
		Without sensory hypersensitivity (n = 35)	With visual hypersensitivity (n = 16)	Without sensory hypersensitivity (n = 35)	With visual hypersensitivity (n = 16)	W	Adjusted p	Effect size
Memory								
Orientation	0 - 4	6%	6%	4	4	281.5	1	.01
Verbal memory: free recall and recognition	0 - 4	17%	25%	3	4	250	1	.09
Episodic memory: recognition	0 - 4	6%	6%	4	4	239	1	.16
Attention								
Broken hearts cancellation:								
Top score	0 - 50	26%	31%	46	47	276.5	1	.01
Object asymmetry	-50 - 50	14%	13%	0	0	295	1	.06
Spatial asymmetry	-20 - 20	29%	31%	0	-1	367.5	.97	.25
Trail making task	-12 - 12	23%	19%	0	0	304.5	1	.07

We determined the number of stroke patients with a deficient performance on a certain subtest using the cut-off values specified by Huygelier et al. (2019). *P* values were adjusted for multiple comparisons with a Holm correction.

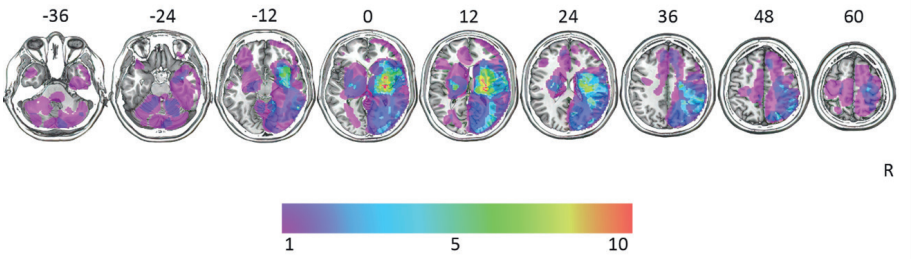


Figure 4. Lesion overlay plot of the individual lesions of 46 stroke patients (clinical imaging was missing for five stroke patients). Lesions were manually delineated on DWI (n = 9), Fluid-attenuated inversion recovery (FLAIR) (n = 23), or CT (n = 14) scans following the procedures described by Biesbroek et al. (2019). Normalization of the brain scans were performed using the OldSeg toolbox under SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Montreal Neurological Institute (MNI) coordinates of each transverse section (z-axis) are given. Lesion maps were overlaid on the Ch2 template available in the MRICron software using the neurological convention. The colour scale indicates the number of cases having a lesion in this voxel (with 10 as the maximum number of cases with a lesion in the same voxel).

TVA-based estimation of sensory threshold, processing speed, and selective attention

The TVA model had a high goodness-of-fit (correlation between observed and predicted scores across all participants, spearman rho = .87)[2] . Panel A of Figure 5 shows the observed and the predicted TVA performance for the whole report trials averaged across the participants of each group. In panel B the averaged number of correctly reported letters on the partial report trials as compared to the 83 ms whole report trials are displayed.

[2] *Deleting the data of the 8 stroke patients that completed five instead of six experimental blocks did not change the goodness of fit of the TVA model (spearman rho = .87), thus these participants were included in our analyses.*

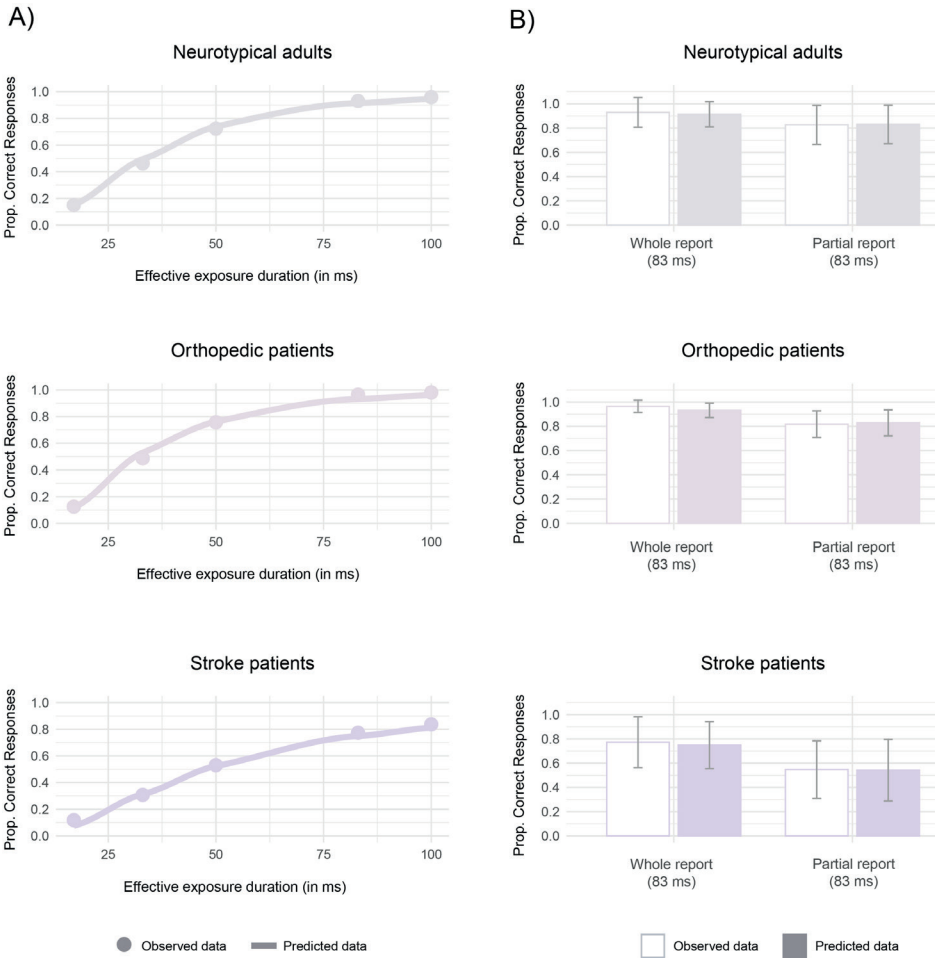


Figure 5. Panel A: Whole report performance averaged across participants for neurotypical adults, orthopedic, and stroke patients as a function of effective exposure duration (in ms). The circles display the observed correct responses and the solid lines display the predicted correct responses. Panel B: Whole and partial report performance (at 83 ms) averaged across participants for neurotypical adults, orthopedic patients, and stroke patients. The white bars displayed the observed correct responses and the solid bars displayed the predicted correct responses.

Group analyses based on subjective sensory sensitivity

16 stroke patients reported an increased visual sensitivity after their stroke on the open-ended questions of the MESSY and 37 stroke patients reported no increase in their sensory sensitivity across all sensory modalities (see Table 1). None of the included orthopedic patients reported an increased sensitivity to any of the studied sensory modalities since hospitalization and none of the included neurotypical adults reported an increased sensitivity to any of the studied sensory modalities in the previous month. The answers patients with post-stroke visual hypersensitivity gave on the open-ended questions of the MESSY to describe their symptoms are reported in Table 3.

Table 3. The descriptions patients gave of their visual hypersensitivity on the open-ended questions of the MESSY.

Case	Description of visual hypersensitivity
#1	Light is very disturbing. It was absolute hell when they moved me from the hospital to the rehabilitation centre in an ambulance. I was so overwhelmed by all the traffic that was flashing by and by all the different coloured lights in the ambulance. I also notice that I'm often distracted by what is happening around me. I didn't have this before my stroke. When I get physical therapy or when I'm eating the therapists or nurses put a screen around me so I can't see what's happening around me. This helps me feel less overwhelmed. When there are a lot of visual stimuli around me, I feel sick and my head starts to hurt.
#2	I have to wear sunglasses during the day to be able to stand the fluorescent lights in the rehabilitation centre. I also detest moving images on the television or on a computer. When I had to do a cognitive exercise with a lot of fast-moving images on the computer I started yelling "Stop! Stop!". It made me feel miserable. When I am overwhelmed I feel a sort of pressure in my head, and I can't do anything anymore. I just have to rest.
#3	I can't watch television for longer than 10 minutes. When I watch too much television, I get a headache and I get really tired. It's not that I can't concentrate on what's happening, I get overloaded by the images that I see.
#4	I can't stand lights. I get really annoyed and nauseous when there's a lot to see around me.
#5	I'm easily overwhelmed. I feel like there are too many stimuli around me. There is too much information coming at me. I feel like I have a different body since my stroke. I am a new person. Moving and flashing images on the television make me feel anxious. I can't watch television anymore.

Case	Description of visual hypersensitivity
#6	Light bothers me the most. To avoid lights, I close my eyes or cover my eyes with my hands. Before my stroke I loved watching television. Now I don't like to watch television. I feel there is too much movement and it gives me a headache.
#7	I hate when there is a lot to see around me. For example, when my family comes to visit me and they move around in my room.
#8	My eyes seem more sensitive to sunlight, and I feel overwhelmed when the nurses move around me during morning care.
#9	I'd rather be in the dark. I never really liked bright lights but after my stroke this has become worse. I turn off the lights and close all the blinds.
#10	I get a headache when there are a lot of visual stimuli around me such as lights.
#11	I don't like to see things move around me such as people or images on the television. It makes me very tired.
#12	I dislike lights and visual stimuli. I prefer calm and quiet settings now.
#13	I don't feel comfortable when I'm surrounded by many or strong visual stimuli. For example, the strong light of the lamp in our room, I really don't like it. I'm also easily distracted when many people pass by my room. I need to rest.
#14	I tend to close my eyes when there's a lot of sunlight, more than I used to before my stroke.
#15	I really dislike watching television because of the quickly changing and fast-moving images.
#16	I feel headaches, neck pain, and I feel a building pressure building behind my eyes when I am confronted with brights lights or when they shine in my eyes with a light during a neurological exam. During the day I wear eye patches or I put a blanket over my face to shield myself from the bright lights. I also close the blinds and I've asked my family to bring my sunglasses to the hospital.

The Quade's ANCOVA analyses revealed significant group differences in visual sensitivity, sensory thresholds (t0), processing speed (C), and selective attention (alpha) after controlling for age (see Table 4 and Figure 6). There was no evidence for a significant interaction between group, gender, and education on the age-corrected scores.

Regarding the severity of visual sensitivity, the Dunn tests showed that patients with post-stroke visual hypersensitivity (i.e., patients who reported an increase in their visual

sensitivity on the open-ended items of the MESSY) scored significantly higher on the multiple-choice items of the visual subscale of the MESSY as compared to patients without post-stroke sensory hypersensitivity (i.e., patients who reported no increase in their sensory sensitivity across all open-ended items of the MESSY), orthopedic patients, and neurotypical adults (Holm adjusted $p < .01$). Stroke patients without post-stroke sensory hypersensitivity and orthopedic patients scored significantly lower than neurotypical controls (Holm adjusted $p < .05$) but there was no evidence for a significant difference in visual sensitivity between the patients without post-stroke sensory hypersensitivity and the orthopedic patients (Holm adjusted $p = .94$).

Regarding t0, the Dunn tests showed that patients with post-stroke visual hypersensitivity had a significantly lower t0 as compared to patients without post-stroke sensory hypersensitivity (Holm adjusted $p = .03$). There was no evidence for a difference in t0 between the stroke patients with and without post-stroke hypersensitivity and neurotypical adults (Holm adjusted p values: .38 and.17 respectively) or the orthopedic patients (Holm adjusted p values = .30 and .25 respectively). There was no evidence for a difference in t0 between the neurotypical adults and the orthopedic patients (Holm adjusted $p = .99$).

Regarding C, the Dunn tests showed that both patients with and without post-stroke sensory hypersensitivity had a significantly lower C as compared to the neurotypical adults and the orthopedic patients (Holm adjusted p values < .01). There was no evidence for a difference in C between the stroke patients with and without post-stroke sensory hypersensitivity (Holm adjusted $p = .20$) or between the neurotypical adults and the orthopedic patients (Holm adjusted $p = .58$).

Regarding alpha, the Dunn tests showed that patients with post-stroke visual hypersensitivity had a significantly higher alpha value than patients without post-stroke sensory hypersensitivity (Holm adjusted $p = .02$). In addition, both patients with and without post-stroke sensory hypersensitivity had a significantly higher alpha as compared to the neurotypical adults and the orthopedic patients (Holm adjusted $p < .05$). Lastly, there was no evidence for a difference in alpha between the neurotypical adults and the orthopedic patients (Holm adjusted $p = .42$).

Table 4. Results of the Quade's ANCOVA analyses.

		Visual sensitivity			t0		
	Df	*F*	p	η^2_{par}	*F*	p	η^2_{par}
Group	3	14.72	< .01	.19	5.33	.03	.08
Gender	1	.02	1	0	.02	1	0
Education	1	.22	1	.001	3.52	1	.02
Group*Gender	3	.83	1	.01	.92	1	.01
Group*Education	3	2.95	.68	.05	2.07	1	.03
Group*Gender* Education	4	.72	1	.02	2.27	1	.05
		C			Alpha		
	Df	*F*	p	η^2_{par}	*F*	p	η^2_{par}
Group	3	18.15	< .01	.23	12.87	< .01	.17
Gender	1	.23	1	.001	.52	1	.003
Education	1	1.09	1	.01	.03	1	0
Group*Gender	3	.58	1	.01	1.83	1	.03
Group*Education	3	.21	1	.003	.26	1	.004
Group*Gender* Education	4	.67	1	.01	1.46	1	.03

Df = degrees of freedom. *F* = Quade's *F*. p = adjusted p value. η^2_{par} = partial eta squared.

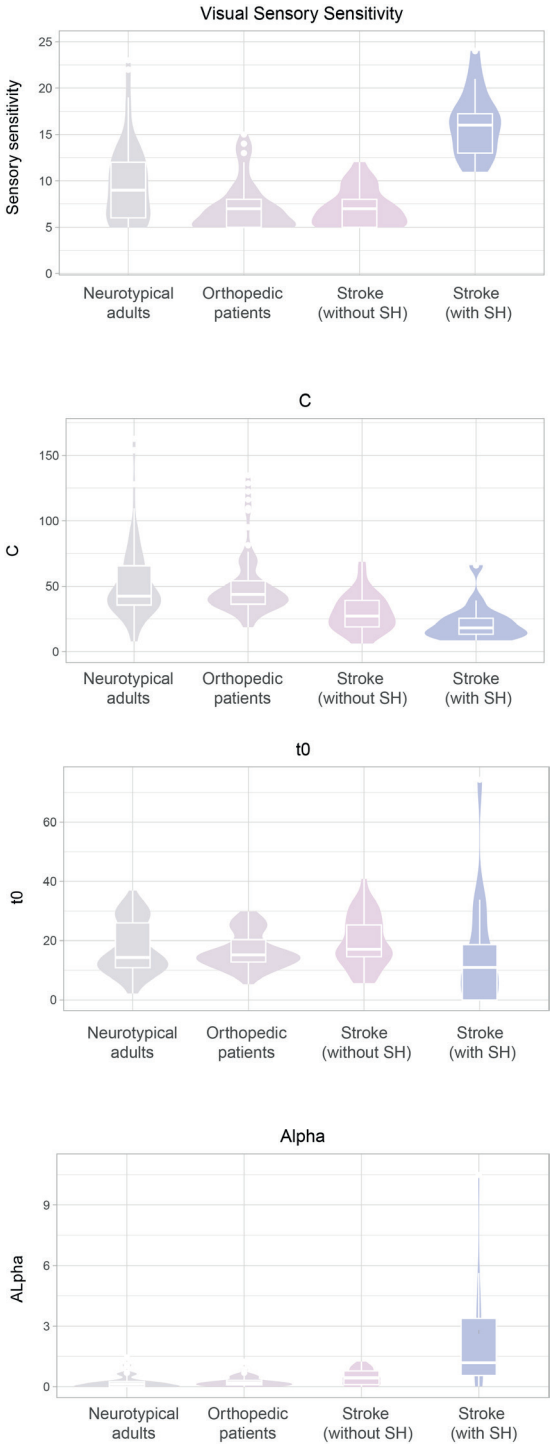


Figure 6. The distribution of the scores on the visual subscale of the MESSY and the estimated TVA parameters for neurotypical adults, orthopedic patients, stroke patients without post-stroke sensory hypersensitivity (Stroke without SH), and stroke patients with post-stroke visual hypersensitivity (Stroke with SH).

Single case-control analyses

The results of the case-control comparisons are found in Table 5. Eight of the 16 cases with post-stroke visual hypersensitivity (cases #1, #2, #3, #4, #5, #7, #11, #16) showed significantly higher alpha values as compared to all three comparison groups (patients without post-stroke sensory hypersensitivity, neurotypical adults, orthopedic patients). For two other cases (cases #6 and #10), there was evidence for a statistically significant difference in alpha when compared to the neurotypical adults and the orthopedic patients, but not when compared to the stroke patients without post-stroke sensory hypersensitivity. Cases #2, #3, #4, #5, #7, and #16 both had heightened alpha values as compared to all three comparison groups and statistically significantly lower t0 values when compared to orthopedic patients or patients without post-stroke sensory hypersensitivity. The significantly higher alpha value and significantly lower t0 value was complemented with significantly lower C values when compared to the orthopedic patients for two cases (cases #4, #5). In contrast, three cases (#6, #11, #12) had a significantly higher t0 as compared to the orthopedic patients and one case (#1) a significantly higher C as compared to the stroke patients without sensory hypersensitivity. Case #11 also had a significantly higher t0 when compared to the neurotypical adults and patients without post-stroke sensory hypersensitivity.

Table 5. Results of the case-control comparisons where the estimated TVA parameters of single cases with post-stroke visual hypersensitivity were compared to the estimated TVA parameters of neurotypical adults, orthopedic patients, and stroke patients without post-stroke sensory hypersensitivity.

	Neurotypical adults			Orthopedic patients			Stroke patients without post-stroke sensory hypersensitivity		
Case	t0	C	Alpha	t0	C	Alpha	t0	C	Alpha
#1	t = -.84	t = .49	**t = 34.83**	t = -1.08	t = .60	**t = 43.41**	t = -1.11	**t = 2.51**	**t = 26.53**
	Z_{cc} = -.84	Z_{cc} = .49	**Z_{cc} = 35.06**	Z_{cc} = -1.09	Z_{cc} = .60	**Z_{cc} = 43.70**	Z_{cc} = -1.12	**Z_{cc} = 2.55**	**Z_{cc} = 26.91**
	p = .41	p = .41	**p < .01**	p = .28	p = .28	**p < .01**	p = .14	**p = .02**	**p < .01**
#2	t = -1.97	t = -1.16	**t = 14.55**	**t = -2.77**	t = -1.28	**t = 18.07**	**t = -2.23**	t = -.73	**t = 10.69**
	Z_{cc} = -1.99	Z_{cc} = -1.17	**Z_{cc} = 14.64**	**Z_{cc} = -2.79**	Z_{cc} = -1.29	**Z_{cc} = 18.18**	**Z_{cc} = -2.26**	Z_{cc} = -.74	**Z_{cc} = 10.84**
	p = .05	p = .13	**p < .01**	**p < .01**	p = .10	**p < .01**	**p = .03**	p = .24	**p < .01**
#3	t = -1.97	t = -1.42	**t = 10.03**	**t = -2.77**	t = -1.58	**t = 12.42**	**t = -2.23**	t = -1.25	**t = 7.16**
	Z_{cc} = -1.99	Z_{cc} = -1.43	**Z_{cc} = 10.09**	**Z_{cc} = -2.79**	Z_{cc} = -1.59	**Z_{cc} = 12.50**	**Z_{cc} = -2.26**	Z_{cc} = -1.26	**Z_{cc} = 7.27**
	p = .05	p = .08	**p < .01**	**p < .01**	p = .06	**p < .01**	**p = .03**	p = .11	**p < .01**
#4	t = -1.97	t = -1.52	**t = 12.62**	**t = -2.77**	**t = -1.70**	**t = 15.66**	**t = -2.23**	t = -1.44	**t = 9.19**
	Z_{cc} = -1.99	Z_{cc} = -1.53	**Z_{cc} = 12.71**	**Z_{cc} = -2.79**	**Z_{cc} = -1.71**	**Z_{cc} = 15.77**	**Z_{cc} = -2.26**	Z_{cc} = -1.46	**Z_{cc} = 9.32**
	p = .05	p = .07	**p < .01**	**p < .01**	**p = .047**	**p < .01**	**p = .03**	p = .08	**p < .01**

	Neurotypical adults			Orthopedic patients			Stroke patients without post-stroke sensory hypersensitivity		
Case	t0	C	Alpha	t0	C	Alpha	t0	C	Alpha
#5	t = -1.97	t = -1.52	**t = 18.33**	**t = -2.77**	**t = -1.70**	**t = 22.79**	**t = -2.23**	t = -1.44	**t = 13.65**
	Z_{cc} = -1.99	Z_{cc} = -1.53	**Z_{cc} = 18.45**	**Z_{cc} = -2.79**	**Z_{cc} = -1.71**	**Z_{cc} = 22.94**	**Z_{cc} = -2.26**	Z_{cc} = -1.46	**Z_{cc} = 13.84**
	p = .05	p = .07	**p < .01**	**p < .01**	**p = .047**	**p < .01**	**p = .03**	p = .08	**p < .01**
#6	t = 1.86	t = -1.31	**t = 2.61**	**t = 2.91**	t = -1.46	**t = 3.15**	t = 1.57	t = -1.03	t = 1.37
	Z_{cc} = 1.88	Z_{cc} = -1.32	**Z_{cc} = 2.63**	**Z_{cc} = 2.93**	Z_{cc} = -1.47	**Z_{cc} = 3.17**	Z_{cc} = 1.59	Z_{cc} = -1.04	Z_{cc} = 1.39
	p = .07	p = .10	**p = .02**	**p < .01**	p = .07	**p < .01**	p = .19	p = .19	p = .19
#7	t = -1.77	t = -1.35	**t = 3.97**	**t = -2.46**	t = -1.50	**t = 4.85**	t = -2.03	t = -1.10	**t = 2.43**
	Z_{cc} = -1.78	Z_{cc} = -1.36	**Z_{cc} = 4.00**	**Z_{cc} = -2.48**	Z_{cc} = -1.51	**Z_{cc} = 4.88**	Z_{cc} = -2.06	Z_{cc} = -1.12	**Z_{cc} = 2.47**
	p = .08	p = .09	**p < .01**	**p = .02**	p = .07	**p < .01**	p = .05	p = .14	**p = .03**
#8	t = -.54	t = -.46	t = -.68	t = -.65	t = -.48	t = -.96	t = -.82	t = .66	t = -1.20
	Z_{cc} = -.55	Z_{cc} = -.46	Z_{cc} = -.68	Z_{cc} = -.65	Z_{cc} = -.48	Z_{cc} = -.96	Z_{cc} = -.83	Z_{cc} = .67	Z_{cc} = -1.21
	p = .75	p = .75	p = .75	p = .52	p = .52	p = .51	p = .42	p = .42	p = .36
#9	t = -.62	t = -.77	t = 1.02	t = -.77	t = -.84	t = 1.16	t = -.90	t = .04	t = .13
	Z_{cc} = -.63	Z_{cc} = -.77	Z_{cc} = 1.02	Z_{cc} = -.77	Z_{cc} = -.84	Z_{cc} = 1.17	Z_{cc} = -.91	Z_{cc} = .04	Z_{cc} = .13
	p = .47	p = .47	p = .47	p = .41	p = .41	p = .38	p = .57	p = .90	p = .90

	Neurotypical adults			Orthopedic patients			Stroke patients without post-stroke sensory hypersensitivity		
Case	t0	C	Alpha	t0	C	Alpha	t0	C	Alpha
#10	t = -.46	t = -1.09	**t = 2.33**	t = -.53	t = -1.20	**t = 2.79**	t = -.74	t = -.59	t = 1.15
	Z_{cc} = -.46	Z_{cc} = -1.09	**Z_{cc} = 2.34**	Z_{cc} = -.53	Z_{cc} = -1.21	**Z_{cc} = 2.81**	Z_{cc} = -.75	Z_{cc} = -.60	Z_{cc} = 1.16
	p = .32	p = .28	**p = .03**	p = .30	p = .23	**p < .01**	p = .47	p = .47	p = .39
#11	**t = 6.46**	t = -1.33	**t = 10.07**	**t = 9.72**	t = -1.48	**t = 12.47**	**t = 6.12**	t = -1.07	**t = 7.19**
	Z_{cc} = 6.50	Z_{cc} = -1.34	**Z_{cc} = 10.13**	**Z_{cc} = 9.78**	Z_{cc} = -1.49	**Z_{cc} = 12.55**	**Z_{cc} = 6.20**	Z_{cc} = -1.08	**Z_{cc} = 7.29**
	p < .01	p = .09	**p < .01**	**p < .01**	p = .07	**p < .01**	**p < .01**	p = .15	**p < .01**
#12	t = 1.41	t = -1.37	t = 1.15	**t = 2.24**	t = -1.53	t = 1.32	t = 1.11	t = -1.15	t = .23
	Z_{cc} = 1.42	Z_{cc} = -1.38	Z_{cc} = 1.15	**Z_{cc} = 2.25**	Z_{cc} = -1.54	Z_{cc} = 1.33	Z_{cc} = 1.13	Z_{cc} = -1.17	Z_{cc} = .23
	p = .25	p = .25	p = .25	**p = .04**	p = .13	p = .13	p = .39	p = .39	p = .41
#13	t = 1.35	t = -.94	t = -.36	t = 2.15	t = -1.03	t = -.56	t = 1.06	t = -.29	t = -.95
	Z_{cc} = 1.36	Z_{cc} = -.94	Z_{cc} = -.36	Z_{cc} = 2.17	Z_{cc} = -1.04	Z_{cc} = -.56	Z_{cc} = 1.08	Z_{cc} = -.30	Z_{cc} = -.96
	p = .27	p = .35	p = .36	p = .05	p = .31	p = .31	p = .45	p = .45	p = .45
#14	t = -.96	t = -.94	t = .61	t = -1.26	t = -1.03	t = .65	t = -1.22	t = -.30	t = -.19
	Z_{cc} = -.96	Z_{cc} = -.95	Z_{cc} = .62	Z_{cc} = -1.27	Z_{cc} = -1.04	Z_{cc} = .66	Z_{cc} = -1.24	Z_{cc} = -.30	Z_{cc} = -.19
	p = .51	p = .51	p = .51	p = .32	p = .32	p = .32	p = .34	p = .77	p = .77

	Neurotypical adults			Orthopedic patients			Stroke patients without post-stroke sensory hypersensitivity		
Case	t0	C	Alpha	t0	C	Alpha	t0	C	Alpha
#15	t = -.25	t = -.90	t = -1.63	t = -.22	t = -.99	t = 1.93	t = -.53	t = -.23	t = .61
	Z_{cc} = -.25	Z_{cc} = -.91	Z_{cc} = 1.64	Z_{cc} = -.22	Z_{cc} = -1.00	Z_{cc} = 1.94	Z_{cc} = -.54	Z_{cc} = -.23	Z_{cc} = .61
	p = .40	p = .37	p = .16	p = .41	p = .33	p = .09	p = .82	p = .82	p = .82
#16	t = -1.97	t = -1.21	**t = 8.65**	**t = -2.77**	t = -1.34	**t = 10.70**	**t = -2.23**	t = -.83	**t = 6.09**
	Z_{cc} = -1.99	Z_{cc} = -1.22	**Z_{cc} = 8.71**	**Z_{cc} = -2.79**	Z_{cc} = -1.35	**Z_{cc} = 10.77**	**Z_{cc} = -2.26**	Z_{cc} = -.84	**Z_{cc} = 6.18**
	p = .05	p = .11	**p < .01**	**p < .01**	p = .09	**p < .01**	**p = .03**	p = .21	**p < .01**

P values (one-tailed) are adjusted for multiple comparisons. Results with a significant p value are displayed in bold. Z_{cc}: estimated effect size.

Discussion

This study aimed to unravel the underlying behavioural mechanisms of sensory hypersensitivity after stroke using a computerized task based on the Theory of Visual Attention (Bundesen, 1990). The results provide first-hand evidence that selective attention impairments and, to a lesser extent, reduced sensory thresholds can be associated with post-stroke visual hypersensitivity. On a group level, stroke patients with post-stroke visual hypersensitivity showed worse selective attention as compared to stroke patients without post-stroke sensory hypersensitivity, neurotypical adults, and orthopedic patients. Moreover, stroke patients with post-stroke visual hypersensitivity had a lower sensory threshold than stroke patients without post-stroke sensory hypersensitivity. When looking at the performance of individual cases, we found that a significant number (63%) of the stroke patients with post-stroke visual hypersensitivity showed impaired selective attention as compared to stroke patients without post-stroke sensory hypersensitivity, orthopedic patients, or neurotypical adults. For six of these ten patients, impaired selective attention was coupled with a significantly lower sensory threshold as compared to stroke patients without post-stroke sensory hypersensitivity or orthopedic patients. These results help bridge the gap in our understanding of the behavioural mechanisms of post-stroke visual hypersensitivity. Filling this knowledge gap can greatly enhance clinical practice by allowing clinicians to examine and target specific underlying mechanisms during neuropsychological assessment and treatment of post-stroke visual hypersensitivity.

Visual hypersensitivity in the (sub)acute phase after stroke

16 subacute stroke patients reported an increased sensitivity to visual stimuli after their stroke (post-stroke visual hypersensitivity) and scored significantly higher on the visual subscale of the MESSY as compared to stroke patients without post-stroke sensory hypersensitivity, orthopedic patients, and neurotypical adults (after controlling for age). Post-stroke visual hypersensitivity was present across the two genders, different education levels, stroke types, and lesion locations (i.e., lesioned hemispheres) (see Table 1). Notably, the descriptions patients provided regarding their visual hypersensitivity (during the open-ended questions of the MESSY) suggested that the stimuli that triggered visual hypersensitivity were very similar across cases. For instance, all the patients with post-stroke visual hypersensitivity reported increased disturbance by lights, visual movement, or visual flashes post- as compared to pre-stroke. Conducting this type of qualitative interviews can help us uncover similarities in the experiences

of (post-stroke) sensory hypersensitivity and can help us uncover the role of specific sensory contexts in the experience of sensory hypersensitivity (Marzolla et al., 2023).

The behavioural mechanisms of post-stroke visual hypersensitivity

This study found evidence for a relationship between post-stroke visual hypersensitivity and impaired selective attention on a group and individual level (in a majority of the patients). On a group level, the patients with post-stroke visual hypersensitivity showed poorer selective attention (i.e., higher alpha values) as compared to patients without post-stroke sensory hypersensitivity, orthopedic patients, and neurotypical adults (after controlling for age). On an individual level, we found that eight (out of 16) patients with post-stroke visual hypersensitivity displayed worse selective attention as compared to age-matched stroke patients without post-stroke sensory hypersensitivity. Two additional patients with post-stroke visual hypersensitivity displayed lower selective attention abilities but this difference only reached statistical significance when comparing their performance to neurotypical adults and orthopedic patients. Interestingly, 50% of the stroke patients with post-stroke visual hypersensitivity had an alpha value above one (as compared to 11% of the stroke patients without post-stroke sensory hypersensitivity, 5% of the neurotypical adults, and 1% of the orthopedic patients). An alpha value above 1 implies that the attentional weight given to a distractor was larger than the attentional weight given to a target. In other words, when a distractor appeared, 50% of stroke patients with post-stroke visual hypersensitivity seemed to hyperfocus on the irrelevant distractor ignoring the task-relevant target.

These results seems to be contradictory with previous studies that found no evidence for a relationship between selective attention and sensory sensitivity in mild traumatic brain injury patients using pen and paper neuropsychological tests (Kumar et al., 2005; Shepherd et al., 2019). However, by using a computerized attentional task and computational modelling of behavioural data, our results might be more sensitive to subtle attention deficits (Bonato et al., 2013; Gillebert et al., 2011). This is supported by the lack of evidence for a difference in performance on a visual cancellation task in the OCS-NL between stroke patients with post-stroke visual hypersensitivity and stroke patients without post-stroke sensory hypersensitivity in the current sample.

In addition to an association between selective attention and post-stroke visual hypersensitivity, the between-group and case-control comparisons also revealed

a possible relationship between atypical sensory thresholds and post-stroke visual hypersensitivity in some patients. This aligns with previous research that found inconsistent results regarding the relationship between sensory thresholds and visual hypersensitivity in mild traumatic brain injury patients and neurotypical adults (Chang et al., 2007; Gerstenberg, 2012; Schrupp et al., 2009; Schulz & Stevenson, 2019). In this study, six patients with post-stroke visual hypersensitivity displayed an atypically low sensory threshold (as compared to stroke patients without post-stroke sensory hypersensitivity or orthopedic patients) in addition to their impaired selective attention. The combination of poor selective attention and an atypically low sensory threshold might put patients at extra risk of developing post-stroke sensory hypersensitivity since this combination causes an overflooding of the sensory cortex by two different mechanisms (e.g., by detecting more sensory input coupled with being unable to filter out irrelevant information).

There was little evidence for a relationship between post-stroke sensory sensitivity and sensory processing speed across all analyses, although the patients with post-stroke visual hypersensitivity displayed a lower sensory processing speed than neurotypical adults and orthopedic patients (on a group level). However, even though the median of the processing speed parameter (C) was lower in the patients with post-stroke visual hypersensitivity as compared to patients without post-stroke sensory hypersensitivity, this difference did not reach statistical significance (possibly due to an outlier (case #1, see Table 5)) or insufficient power.

In previous studies, a negative relationship between sensory sensitivity and processing speed was described in neurotypical adults and mild traumatic brain injury patients (Gerstenberg, 2012; Kumar et al., 2005; Shepherd et al., 2019). Since these studies used a measure of processing speed that was based on reaction time, the results might be confounded by individual differences in decision making and motor response time. The lack of evidence regarding the presence of sensory processing speed abnormalities in the stroke patients with post-stroke visual hypersensitivity in this study might be explained by the fact that the TVA-based estimate of processing speed is not confounded by these processes as it is not dependent on reaction time (Habekost, 2015). Another explanation might be a lack of power as a result of the small sample sizes and the individual case approach. A disadvantage of a single case-control analysis is that the power to detect a deficit is inevitably low to moderate (Crawford & Garthwaite, 2006). For instance, to

achieve a power of 80% using a control sample of 50 participants and a score with a reliability of .70, the score of the individual case must differ by at least three standard deviations from the mean of the control sample. Departures from normality (which were present in the current study) can negatively impact this power further. Therefore, a single case-control analysis might not be suitable for studying more subtle sensory abnormalities underlying post-stroke sensory hypersensitivity. Further research that compares the relationship between reaction-time dependent and independent measures of processing speed with post-injury sensory sensitivity in large samples of patients with different types of acquired brain injury is needed to investigate the relationship between sensory processing speed and sensory sensitivity.

Importantly, it must be noted that this study cannot determine a causal relationship between selective attention, sensory thresholds, and sensory processing speed on the one hand and post-stroke visual hypersensitivity on the other hand. We focused on selective attention, sensory thresholds, and sensory processing speed as underlying mechanisms of post-stroke visual hypersensitivity. However, it is also possible that the directionality of these relationships could be reversed (i.e., post-stroke sensory hypersensitivity may impact selective attention, sensory thresholds, or processing speed), or that these variables have complex bidirectional relationships. Future research utilizing experimental designs could potentially unravel these relationships.

The effect of hospitalization on post-stroke visual hypersensitivity

To control for the effect of hospitalization on sensory sensitivity we compared the visual sensory sensitivity scores of the stroke patients with post-stroke visual hypersensitivity to hospitalized (neurologically healthy) orthopedic patients. In contrast to 16 stroke patients with post-stroke visual hypersensitivity, none of the orthopedic patients reported an increase in their visual sensitivity post-hospitalization, indicating that post-stroke increases in sensory sensitivity cannot solely be explained by hospitalization. This notion is supported by the fact that the stroke patients with post-stroke visual hypersensitivity reported a significantly higher visual sensitivity as compared to the orthopedic patients. Interestingly, the orthopedic patients and the stroke patients without post-stroke sensory hypersensitivity had a significantly lower median score on the visual subscale of the MESSY as compared to the neurotypical adults which might imply that sensory environment (i.e., hospitalization) does affect the experienced sensory sensitivity. This was supported by the answers of some orthopedic patients and stroke patients

without post-stroke sensory hypersensitivity on the open answers of the MESSY. They indicated that instead of being overstimulated they felt that the hospital environment was understimulating and that they craved more sensory rich contexts.

Other mechanisms need to be considered

Importantly, in six patients, the TVA paradigm could not identify any underlying behavioural mechanisms that could explain their post-stroke visual hypersensitivity symptoms. These results are important in two ways. Firstly, because they show that the mechanisms of post-stroke sensory hypersensitivity might differ inter-individually. Secondly, because they show we need to explore other underlying mechanisms than the ones discussed in this study. Future research could examine the effect of other behavioural mechanisms (such as sustained attention, predictive processing, working memory, or divided attention) (Thielen et al., 2022; Ward, 2019), neural mechanisms (such as lesion location, lesion volume, type of lesion), or psychological mechanisms (such as stress, anxiety, and coping) (Callahan et al., 2018; Callahan & Storzbach, 2019; Elliott et al., 2018). Furthermore, research needs to investigate if and how these different types of mechanisms interact. For instance, the Four Quadrant Model of Sensory Processing (Dunn, 2001) stipulates that sensory hypersensitivity is caused by low sensory thresholds in combination with passive coping strategies. We propose that future research strives to build a model of the underlying mechanisms of post-stroke sensory hypersensitivity by complementing computerized cognitive tasks with brain imaging and questionnaires on possible psychological mechanisms (anxiety, stress, coping), as well as stroke characteristics (lesion type, lesion location, lesion volume, time since injury), in both subacute and chronic stroke patients.

The behavioural mechanisms of sensory hypersensitivity in orthopedic patients and neurotypical adults

Studying the underlying mechanisms of sensory sensitivity in different populations is important since to this date it remains unclear if the seemingly similar sensory hypersensitivity symptoms reported in different populations are caused by similar underlying mechanisms and, therefore, can be diagnosed and treated similarly. In contrast to the stroke population, there was no evidence for a relationship between visual sensitivity on the one hand and sensory thresholds, processing speed, and selective attention on the other hand in our sample of neurologically healthy adults and orthopedic patients (see Supplementary Analysis 2). This is also in contrast

to what was suggested by previous research and dominant theories on sensory sensitivity in neurologically healthy adults (Dunn, 2001; Gerstenberg, 2012; Panagiotidi et al., 2018; Panagopoulos et al., 2013; Smolewska et al., 2006; Trå et al., 2022). However, the lack of results could also be explained by the adaptations we made in the difficulty of the TVA task. To increase the feasibility of conducting a TVA-based assessment at the bedside of subacute stroke population we used whole and partial report tasks with a single target. This decreased task difficulty as well as task length (by decreasing the number of different trial types and the number trials per trial type) as compared to other commonly used TVA paradigms, such as the CombiTVA task (Vangkilde et al., 2011; Wang & Gillebert, 2018) or the traditional TVA paradigm described by Duncan et al. (1999), which use multiple target displays. Although a single-target TVA task was more suitable for patients with acquired brain injury, it may have been simplified too extensively for participants without brain injuries. Future research is needed to investigate the psychometric properties of the simplified TVA task described in this study and to confirm whether TVA paradigms with multiple stimulus displays (such as the CombiTVA task) have a higher sensitivity to inter-individual differences in sensory processing in neurologically healthy populations. In addition, for future research we advise using a computer with a refresh rate of 100 HZ. To allow for bedside testing, we used laptops with a refresh rate of 60 Hz, limiting our lowest exposure duration to 17ms. Using a computer with a refresh rate of 100 Hz could lower this to 10ms which might improve the estimation of low sensory thresholds (i.e., sensory thresholds that lay between 0 and 17 ms). In addition, this increased range could allow for smaller differences between the different exposure duration (i.e., differences of 10 instead of 17 ms). Using a refresh rate of 100 Hz might make the TVA model more sensitive to inter-individual differences in t0 and C values in neurologically healthy participants.

Limitations and future research

Some other limitations of the current study must be mentioned. A first limitation is that this study focused on visual sensory hypersensitivity, but post-stroke sensory hypersensitivity is known to be present across different sensory modalities (Alwawi et al., 2020; Thielen, Huenges Wajer et al., 2023). Therefore, it should be investigated whether similar bottom-up and top-down processes are related to sensory hypersensitivity in different modalities and whether underlying mechanisms are modality-specific. Furthermore, for future research it would be interesting to use cross-modal behavioural tasks (i.e.,

tasks that used stimuli from different sensory modalities, for instance a visual detection task with auditory distractors) as this better matches sensory processing in daily life.

Secondly, since we only included stroke patients that completed the TVA-based assessment, a task that placed significant cognitive demands on our participants, we could have biased our sample towards stroke patients with minor cognitive impairments (as is also apparent from the relatively low incidence of cognitive impairment as assessed using the OCS-NL, see Table 2). That being said, by adapting the TVA task we aimed to increase its suitability for studying post-stroke sensory processing abilities. Indeed, previous TVA-based studies that used multiple target displays were (mostly) conducted in chronic stroke patients with age-restricted samples (e.g., patients with an age above 60 or 70 years old were excluded) (Kraft et al., 2015; Peers et al., 2005) which limits the generalizability of their results to the entire stroke population. We believe that our task did acquire a certain level of stroke-friendliness seeing as a 90 year old stroke patient was able to complete the task, patients could be tested in the acute phase after injury (see Table 1), and just 17% of the 183 stroke patients that started the TVA-based assessment did not complete the task due to invalidating fatigue or task characteristics (participants found the task too difficult or monotonous) (see Supplementary Table 2). However, this does not mean that further improvements cannot be made. We, for instance, tried to increase the probability of task completion by allowing participants to complete the task in different sessions. To help a larger sample of stroke patients complete this type of task and to limit differences between patients in the number of sessions needed to complete the task we advise researchers to, for instance, distribute the task across two sessions of 15 minutes on succeeding days for all stroke patients. This could, in future studies, increase the number of acute and severely cognitively impaired patients that participate in studies using TVA-based assessments, seeing as these patients were still underrepresented in the current stroke sample (see Tables 1 and 2).

Another limitation of the included sample is that the majority of the included neurotypical adults (79%) obtained a degree in higher education. This in contrast, to 36% of the orthopedic and 23% of the stroke patients. For future studies it is recommended to include a higher number of neurotypical participants who did not complete higher education to investigate whether this changes the lack of evidence for a relationship between sensory sensitivity and sensory processing in neurotypical adults and to match groups based on education level.

A last limitation pertains to the different versions of the MESSY that were used. To date, the equivalence between the in- and outpatient versions of the MESSY remains unclear. Further research is planned to confirm if these two versions of the MESSY measure a similar psychological construct and to investigate the psychometric properties of the inpatient version of the MESSY. However, considering that the two versions only differ in the examples and pictograms used for nine out of 30 items, we do not expect there to be significant psychometric discrepancies.

Conclusion

This study provides important first-hand evidence that impaired selective attention and, to a lesser extent, low sensory thresholds might explain post-stroke visual hypersensitivity in some stroke patients. This provides a starting point for future research that wishes to explore the causation of sensory hypersensitivity after stroke as well as other types of acquired brain injury. Filling these knowledge gaps can further improve our understanding of post-stroke sensory hypersensitivity, allowing us to improve the treatment of these symptoms. This will ultimately improve the quality of life of patients with post-stroke visual hypersensitivity and potentially, by extension, the quality of life of patients with hypersensitivity after different types of acquired brain injury.



“When there are a lot of sensory stimuli around me I feel trapped in a small cocoon. Everything is too intense. I start to cry and don’t know anything anymore, I don’t know what to do or how to get out of the situation.”

Chapter six

The neuroanatomy of post-stroke subjective sensory hypersensitivity

Although subjective sensory hypersensitivity is prevalent after stroke, it is rarely recognized by healthcare providers, and its neural mechanisms are largely unknown. To investigate the neuroanatomy of post-stroke sensory hypersensitivity as well as the sensory modalities in which these symptoms can occur, we conducted a systematic literature review and a multiple case study of patients with post-stroke sensory hypersensitivity. For the systematic review, we searched three databases (Web Of Science, PubMed, and Scopus) for empirical articles discussing the lesion neuroanatomy of post-stroke sensory hypersensitivity in humans. We assessed the methodological quality of included studies using the Case Reports Critical Appraisal Tool and summarized the results using a qualitative synthesis. For the multiple case study, we administered a patient-friendly sensory sensitivity questionnaire to three subacute right-hemispheric stroke patients and a matched control group (n = 19), and delineated brain lesions on a clinical brain scan. Our systematic literature search resulted in four studies (describing eight stroke cases), all of which linked post-stroke sensory hypersensitivity to insular lesions. The results of our multiple case study indicated that all three included stroke patients reported a post-stroke increase in their sensitivity to different sensory modalities. The lesions of these patients overlapped with the right anterior insula, the claustrum, and the Rolandic operculum. Both our systematic literature review and our case study provide preliminary evidence for a role of the insula in post-stroke sensory hypersensitivity and suggest that post-stroke hypersensitivity can occur in different sensory modalities.

Thielen, H., Tuts, N., Lafosse, C., & Gillebert, C.R. (2023). The neuroanatomy of poststroke subjective sensory hypersensitivity. Cognitive and Behavioural Neurology, 36(2), 68-84.

The human brain is constantly bombarded with both external and internal sensory stimuli. To reach our goals in such a rich sensory environment, we must efficiently register and modulate this sensory stimulation and adapt our behaviour to continuous changes therein. Importantly, humans show large inter-individual differences in their self-reported sensitivity to sensory stimuli. Some people feel underwhelmed by sensory stimuli (i.e., they are hyposensitive) while others are easily overwhelmed by sensory stimuli (i.e., they are hypersensitive). Subjective (self-reported) sensory hypersensitivity to non-nociceptive sensory stimulation is prevalent in the neurotypical population (Greven et al., 2019) as well as in individuals with chronic pain (e.g., fibromyalgia) (López-Solá et al., 2014) and those with different neurological (e.g., Tourette syndrome, mild traumatic brain injury) (Callahan et al., 2018; Isaacs & Riordan, 2020), psychiatric (e.g., schizophrenia) (Landon et al., 2016), or neurodevelopmental disorders (e.g., autism spectrum disorder, Williams syndrome, attention deficit hyperactivity disorder (ADHD)) (Bijlenga et al., 2017; Glod et al., 2020; Tavassoli, Hoekstra et al., 2014). Subjective (self-reported) sensory hypersensitivity is known to reduce quality of life: it has been related to social isolation (Callahan & Lim, 2018; Landon et al., 2012), reduced mental health (e.g., higher negative affect and depression) (Smith, 2003; Stansfeld & Shipley, 2015), reduced physical health (e.g., sleep disturbances and fatigue) (Elliott et al., 2018; Hallberg et al., 2005; Landon et al., 2012), and difficulties carrying out activities of leisure (Callahan & Lim, 2018; Hallberg et al., 2005). Contrary to the high clinical relevance of sensory hypersensitivity, its neural mechanisms remain unclear (Ward, 2019).

Previous research on the neural mechanisms of subjective sensory hypersensitivity in neurotypical and clinical populations mainly relied on functional magnetic resonance imaging (fMRI). These studies related subjective sensory hypersensitivity to functional abnormalities in different brain areas, including the sensory cortices (e.g., Green et al., 2015; López-Solá et al., 2014), insula (e.g., López-Solá et al., 2014), thalamus (e.g., Acevedo et al., 2018), and limbic structures such as the amygdala and the hippocampus (e.g., Acevedo et al., 2018; Green et al., 2015). However, these studies varied greatly in their methodology (i.e., they studied different sensory modalities using different fMRI designs) and their population of interest (i.e., they studied neurotypical adults and different clinical populations with different comorbid symptomatology) making it difficult to interpret the variability in the reported functional neuroanatomy. In addition, given that fMRI provides only correlational information, it does not allow researchers to make causal inferences about brain-behaviour relationships. Brain regions may indeed show

task-related activation due to their anatomical or functional connection to another brain region required for the function underlying the task. In contrast, lesion studies allow researchers to identify brain regions that are crucial for performing a specific cognitive function (Adolphs, 2016; Rorden & Karnath, 2004).

Several studies have suggested a relationship between subjective sensory hypersensitivity and acquired brain injury (e.g., Alwawi et al., 2020; Callahan & Storzbach, 2019; Shepherd et al., 2020). After an acquired brain injury, some patients report a change in their sensory sensitivity, resulting in an increased sensitivity to sensory stimuli (post-injury sensory hypersensitivity). These patients, for instance, report feeling overwhelmed in crowded environments, detest bright sunlight, or feel the need to isolate themselves from sensory stimulation (Alwawi et al., 2020). Previous studies have reported a post-injury hypersensitivity to sound in 44% of 341 individuals with mild traumatic brain injury (Shepherd et al., 2021) and a post-injury hypersensitivity to light in 51% of 86 individuals with mild to severe traumatic brain injury (Goodrich et al., 2014) (for more details see Thielen et al., 2022). Sensory hypersensitivity after brain injury has been associated with longer recovery times and mental health difficulties (Callahan et al., 2018; O'Kane et al., 2014; Shepherd et al., 2021).

To date, the behavioural and neural mechanisms underlying self-reported post-injury sensory hypersensitivity remain largely unknown. Although some researchers have proposed that sensory hypersensitivity is related to reduced information processing or altered sensory thresholds (e.g., Chang et al., 2007; Shepherd et al., 2019; Schrupp et al., 2009), the available evidence is only correlational. Further research is needed to conceptualize post-injury sensory hypersensitivity into a biopsychosocial model. Studying sensory sensitivity in brain injury patients in relation to lesion neuroanatomy can help us uncover its neural basis. For lesion studies it is advised to include patients with focal lesions (De Haan & Karnath, 2018), such as those induced by stroke, since the full extent of more diffuse damage (e.g., diffuse axonal injury) cannot be detected using clinical brain scans. However, research on post-stroke sensory hypersensitivity is rare (see Thielen et al., 2022). To our knowledge, the study by Chung and Song (2016) is the only study that has investigated the prevalence of post-stroke sensory hypersensitivity in a large stroke sample. They reported that 18% of 240 stroke patients experienced a higher subjective sensory sensitivity as compared to neurologically healthy controls. The results reported by Chung and Song (2016) suggest that post-stroke subjective

sensory hypersensitivity is prevalent. However, the authors did not make inferences about the neuroanatomical substrate of post-stroke sensory hypersensitivity, nor did they disclose whether post-stroke sensory hypersensitivity was modality-specific rather than present across multiple modalities. Furthermore, it was unclear if all the patients in the sample studied by Chung and Song (2016) reported a change in their sensory sensitivity from pre- to post-stroke or whether they already experienced sensory hypersensitivity before their stroke (since this symptom is also prevalent in the neurotypical population). To characterize the properties of self-reported post-stroke sensory hypersensitivity and identify its neural mechanisms, we first conducted a systematic literature review according to the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). More specifically, we focused on studies discussing post-stroke subjective hypersensitivity in relationship to the lesion neuroanatomy, and assessed the sensory modalities in which post-stroke sensory hypersensitivity was reported. Second, we complemented the systematic literature review with a multiple case study discussing three stroke patients with post-stroke sensory hypersensitivity.

Systematic literature review

Methods

We searched the Web Of Science, PubMed, and Scopus databases from their inception through the 31st of January 2022 using a search string including different synonyms for stroke as well as terms relating to sensory sensitivity or sensory intensity. The full search string was: (stroke OR "subarachnoidal he$morrhage" OR "brain he$morrhage" OR "brain infarction" OR "cerebral infarction" OR "cerebral he$morrhage" OR "intracranial he$morrhage") AND ("sensory *sens*" OR "sensory processing disorder" OR phonophobia OR photophobia OR osmophobia OR hyperacusis OR *sensitivit* NEAR/2 (light OR visual OR auditory OR sound OR noise OR touch OR tactile OR smell OR olfactory OR gustatory OR temperature OR taste OR vestibular) OR intensity NEAR/2 (light OR visual OR auditory OR sound OR noise OR touch OR tactile OR smell OR olfactory OR gustatory OR temperature OR taste OR vestibular).

Articles were included if they discussed the lesion neuroanatomy (i.e., the location of the lesion based on a computed tomography (CT) or MRI scan) of self-reported post-stroke sensory hypersensitivity. Only empirical studies were included, meaning that review articles or book chapters were excluded. Furthermore, articles were excluded if they were not written in English, if the studied population did not include stroke

patients, if they solely consisted of animal research, or if they studied post-stroke sensory hyposensitivity (e.g., in the context of peripheral dysfunction, hemiplegia, or hemianopia). Articles regarding pain were only included if they studied post-stroke pain. More specifically, articles about chronic migraine increasing the risk of stroke incidence were excluded, as were articles on pain describing photo- or phonophobia solely during migraine episodes or describing tactile hypersensitivity or temperature allodynia limited to painful body parts. Two reviewers (HT and NT) independently reviewed the abstracts from the various databases for their relevance using the above described in- and exclusion criteria (which were set prior to abstract screening). A third reviewer (CRG) was consulted in case of disagreement. Figure 1 displays a study flow diagram of the literature review based on the PRISMA guidelines (Moher et al., 2009). We identified 462 records through database searching. After excluding duplicates, we screened 368 articles. From these articles, 13 articles fulfilled the inclusion criteria.

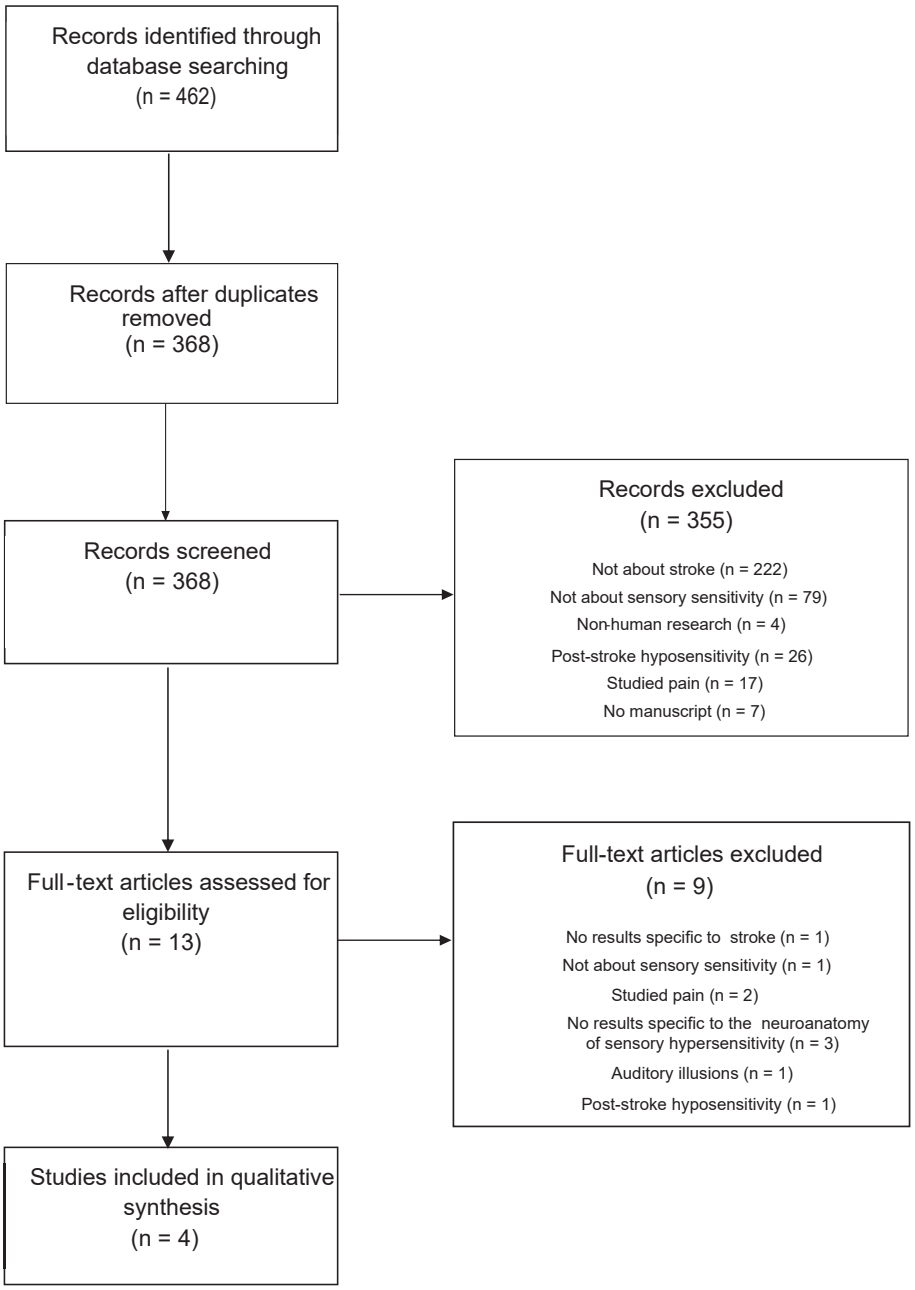


Figure 1. PRISMA flow diagram for the systematic literature review.

From the 13 included articles, we extracted the demographic characteristics (title, authors, year of publication, journal), the characteristics of the studied stroke sample (sample size, age, and gender of stroke sample, type of stroke, time since injury), the sensory modalities that were studied, and the results of the analysis relating post-stroke sensory hypersensitivity to lesion neuroanatomy. Based on the data extraction we had to exclude nine articles: one did not study sensory sensitivity (Bonan et al., 2015), one study investigated sensory sensitivity after acquired brain injury but did not provide results that were specific to the included stroke patients (Berthold-Lindstedt et al. 2017), one studied tactile hyposensitivity in hemiplegic limbs (Aikio et al., 2021), another study explored temperature allodynia limited to painful body parts (Klit et al., 2011), one study studied photophobia during a migraine episode with comorbid hemianopia (Tanev et al., 2021), three studies did not mention the neuroanatomy of post-stroke sensory sensitivity specifically (Alwawi et al., 2020; Carlsson et al., 2004, 2009), and one study described auditory illusions (palinacousis and paracusis) (Fukutake & Hattori, 1998). Since the included articles consisted of single or multiple case studies, methodological quality was assessed using the Case Reports Critical Appraisal Tool designed by Moola et al. (2020) by two independent reviewers (HT and NT). This tool includes eight criteria, of which five were applicable to our review. We used qualitative synthesis to summarize results on sensory hypersensitivity after stroke. In alignment with our research aims, we focused on lesion location and the sensory modalities that were studied. Figures were created using RStudio (2020) and Adobe Illustrator (2020). The data collection forms and the study protocol are available via 10.6084/m9.figshare.18096365. This study was not pre-registered prior to the systematic review being conducted.

Results

We identified four case reports about post-stroke sensory hypersensitivity through the systematic review (see Table 1). The quality of the included studies is presented in Table 2: two reports did not provide a detailed account of the patients' medical background. All four case reports linked insular lesions to post-stroke sensory hypersensitivity in one or two sensory modalities: visual hypersensitivity by Cantone et al. (2019), auditory hypersensitivity by Boucher et al. (2015), olfactory hypersensitivity by Mak et al. (2005), and gustatory hypersensitivity by Mak et al. (2005) and Pritchard et al. (1999). However, the two patients discussed by Boucher et al. (2015) reported comorbid tactile or olfactory hypersensitivity and the patient discussed by Mak et al. (2005) reported a comorbid hypersensitivity to environmental temperature.

Table 1. Overview of studies relating post-stroke sensory hypersensitivity to lesion neuroanatomy based on a systematic literature review.

Study	Case	Case descriptions	Stroke type	Lesioned hemisphere	Lesion location based on MRI or CT scan	Assessment of subjective sensory hypersensitivity	Studied sensory modality	Results
Pritchard et al. (1999)	Case 1 (G.B)	Age: 52 Gender: Female Months since stroke: 18	Not reported	Right-hemispheric lesion	Right rostral insula, frontal, parietal, and temporal opercula, and putamen	Self-reported intensities of gustatory stimuli	Gustatory	Three stroke cases (G.B., M.L. and P.G.) reported lower taste intensities on the ipsilesional as compared to the contralesional side of the tongue. Case M.K. showed no taste intensity differences between the ipsilesional and contralesional side of the tongue.
	Case 2 (M.L.):	Age: 56 Gender: Female Months since stroke: 6	Subarachnoid haemorrhage	Left-hemispheric lesion	Left posterior and rostral insula, left parietal and temporal lobes as well as the left putamen and internal capsule			
	Case 3 (P.G.):	Age: 65 Gender: Male Months since stroke: 2	Not reported	Left-hemispheric lesion	Lesion in the left rostral insula, orbitofrontal cortex, caudate nucleus, putamen, and internal capsule			
	Case 4 (M.K.):	Age: 61 Gender: Female Months since stroke: 8	Ischemic stroke	Left-hemispheric lesion	Lesion in the left posterior insula, parietal lobe, putamen, and internal capsule. Signs of global atrophy			

Mak et al. (2005)		Age: 70 Gender: Male Months since stroke: 13 (Follow up at 18 months)	Ischemic stroke	Left-hemispheric lesion	Left posterior insular	Rating of the intensity of gustatory and olfactory stimuli	Gustatory and olfactory	Increased intensity rating of gustatory and olfactory stimuli especially when stimuli were presented to the contralesional nostril or the contralesional side of the tongue.
Boucher et al. (2015)	Case 1	Age: 29 Gender: Female Months since stroke: 16	Ischemic stroke	Left-hemispheric lesion	Left posterior insular	Hearing Sensitivity Questionnaire, loudness discomfort task	Auditory	Self-reported auditive hypersensitivity and heightened loudness discomfort as compared to a matched control group.
	Case 2	Age: 40 Gender: Female Months since stroke: 52	Not reported	Right-hemispheric lesion	Right insula			
Cantone et al. (2019)		Age: 62 Gender: Male Months post-injury: Not reported	Ischemic stroke	Right-hemispheric lesion	Right temporal-insular, periventricular white matter damage	Subjective description	Visual	Facial expression of fear and disgust with a neurovegetative reaction and horripilation in response to visual stimuli.

Pritchard et al. (1999) described taste intensity ratings in two patients with insular damage as a result of a tumour. Boucher et al. (2015) additionally described a patient who suffers from hyperacusis after a resection of the insula as a treatment to drug-resistant epilepsy.

Table 2. Critical appraisal of the included studies.

Study	1	2	3	4	5
Pritchard et al. (1999)	+	-	+	+	+
Mak et al. (2005)	+	+	+	+	+
Boucher et al. (2015)	+	-	+	+	+
Cantone et al. (2019)	+	+	+	+	+

The critical appraisal criteria (based on Moola et al. (2020)): a clear description of the 1) demographic characteristics of the case, 2) the patient's history presented as a timeline, 3) the current clinical condition, 4) diagnostic tests or assessment methods, and 5) does the case report takeaway lessons.

Multiple case study

Methods

Participants

Stroke patients who were admitted to RevArte Rehabilitation hospital in June through October 2018 and whose medical files mentioned post-stroke sensory hypersensitivity were recruited to participate in this study after referral by a clinical neuropsychologist. If a patient complained of post-stroke sensory hypersensitivity to their clinical neuropsychologist during an intake, neuropsychological assessment, or neuropsychological rehabilitation, a description of their sensory hypersensitivity was added to their medical file. Patients who were unable to give informed consent, or had a formal diagnosis of autism spectrum disorder, ADHD, schizophrenia, or post-traumatic stress disorder were excluded from the study. No exclusion was made based on stroke type, lesion location, cognitive profile, or time since stroke. Out of 59 stroke patients who were admitted to the RevArte Rehabilitation Hospital during the stated time, three patients were referred for our study. All three patients fulfilled the in- and exclusion criteria, consented to take part in the study, and reported that Flemish was their dominant language. Each of the stroke patients reported having intact hearing and vision and did not have epilepsy. The gender, age, and years of completed education (starting from the age of six years) of each participant were recorded (see Table 3). Figure 2 shows lesion maps for each individual case as well as a lesion overlap for the three cases.

Since demographic characteristics such as age and gender are associated with subjective sensory sensitivity (e.g., Benham, 2006; Ueno et al., 2019), we matched a control group based on age, gender, and education level to each case. To this end, we recruited 19 neurotypical volunteers by employing a participant database of adults who had previously participated in research. Exclusion criteria were having a formal diagnosis of autism spectrum disorder, ADHD, schizophrenia, or post-traumatic stress disorder, or a probable history of neurological disease. We excluded one control participant because of a probable history of mild traumatic brain injury. The in- and exclusion criteria were set prior to data collection.

Two neurotypical control groups were formed: one consisting of females and the other of males (in order to match the gender of the different cases). To compare the age and years of education of each case to the mean of the matched control group, we followed the recommendations of Crawford and Garthwaite (2002) for significance testing. The age of each case did not differ significantly from the mean age of their respective control group (Case #1: $t = .6$, $p = .3$; Case #2: $t = 1$, $p = .2$; Case #3: $t = .9$, $p = .2$). The completed years of education of the cases also did not differ significantly from the mean years of education of their respective control group (Case #1: $t = -1.6$, $p = .07$; Cases #2 and #3: $t = -.5$, $p = .3$).

Table 3. Characteristics of the included participants.

	Stroke patients			Neurologically healthy controls (n = 19)	
	Case #1	Case #2	Case #3	Matched control group Case #1	Matched control group Cases #2 and #3
n	1	1	1	10	9
Age (in years)	67	72	71	Mean (Sd): 60 (11) Range: 46-77	Mean (Sd): 60 (11) Range: 46-77
Years of education	12	12	12	Mean (Sd): 15 (2)	Mean (Sd): 14 (4)
Gender	Female	Male	Male	Female	Male
Time since stroke (in months)	6[1]	2	3		
Type of stroke	Ischemic Stroke	Ischemic Stroke	Ischemic Stroke		
Lesioned hemisphere	Right-hemispheric	Right-hemispheric	Right-hemispheric		

Sd: Standard deviation.

[1] *Case #1 had a previous infarction with a lesion in the right temporal-occipital region (visible on slices z = -12 in Figure 2). For this infarction Case #1 did not receive rehabilitation and the medical file did not mention motor or cognitive deficits related to this infarction.*

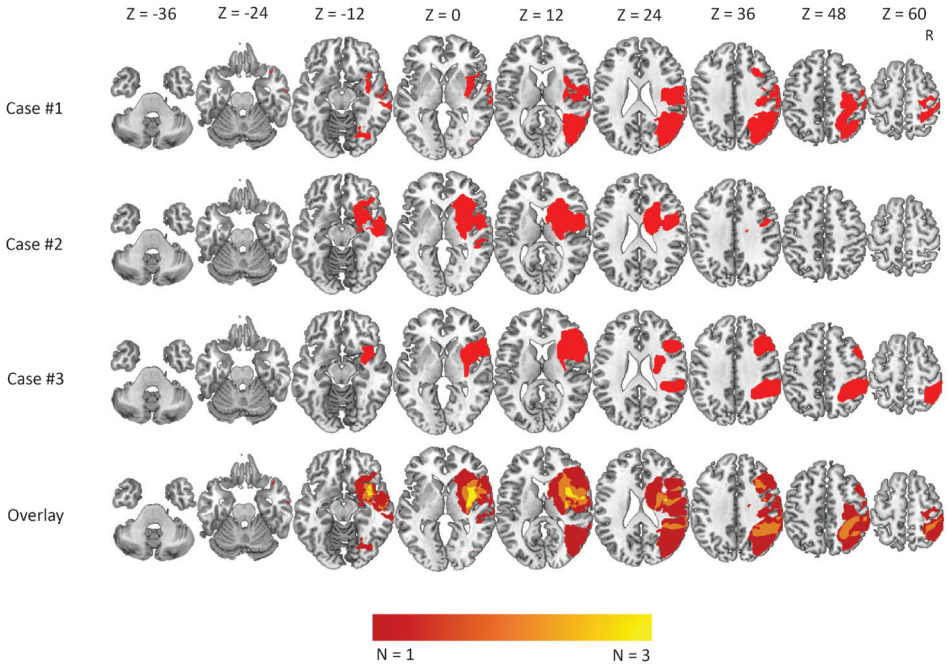


Figure 2. Lesion maps of the individual lesions of each stroke patient and a lesion overlay plot projected on axial slices of the T1-weighted Ch2 template from the Montreal Neurological Institute (MNI). Lesions were delineated on clinical Fluid Attenuated Inversion Recovery (FLAIR) scans for Cases #1 and #2 using the Clusterize toolbox (De Haan et al., 2015). Due to lower quality of the clinical computed tomography (CT) scan from Case #3 we manually delineated his lesion following the procedure outlined by Biesbroek et al. (2019). Normalisation of CT and MRI scans was performed using the Clinical Toolbox (Rorden et al., 2012) under SPM12. MNI coordinates of each transverse section (z-axis) are given. The colour scale indicates the number of cases having a lesion in this voxel. Lesion overlap across the three cases was found in the right anterior insula, the claustrum, and the Rolandic operculum.

Materials

Patient-friendly sensory sensitivity questionnaire

To date, there is no validated sensory sensitivity questionnaire that is adapted to stroke patients and assesses all sensory modalities (for an overview of the diagnostical tools used to assess subjective sensory sensitivity after acquired brain injury, see Thielen et al. (2022)). Therefore, in order to systematically assess post-stroke sensory sensitivity across different modalities (i.e., multisensory, visual, auditory, tactile, olfactory, gustatory,

and vestibular sensitivity as well as a sensitivity to temperature and pain), we developed a stroke-friendly questionnaire. This sensory sensitivity questionnaire consists of two parts. The first part contains 83 multiple-choice items assessing subjective sensory sensitivity across several modalities (see Table 4). Since it is unclear what the underlying mechanisms of subjective sensory hypersensitivity after brain injury are, we asked experts (clinical neuropsychologists from the department of neuropsychology at RevArte) to identify items from existing sensory sensitivity questionnaires that match the experience of sensory hypersensitivity in stroke patients as well as add items if they felt that certain experiences were lacking. We included some items from the English versions of the Highly Sensitive Person Scale (Aron & Aron, 1997), the Sensory Hypersensitivity Scale (Dixon et al., 2016), and the Sensory Perception Quotient (Tavassoli, Hoekstra et al., 2014), and had them translated to Dutch using back translation by two independent translators. Additionally, we included items based on the Dutch versions of the Adolescent/Adult Sensory Profile (Brown & Dunn, 2002; Rietman, 2007) and the Glasgow Sensory Questionnaire (Robertson & Simmons, 2013).

The sensory sensitivity questionnaire included multiple modalities assessing visual, auditory, tactile, olfactory, gustatory, environmental temperature, vestibular, and pain sensitivity. Items that could represent a sensitivity to multiple sensory stimuli across different modalities (i.e., 'I get irritated when there is a lot going on around me') were included to form the subscale multisensory sensitivity. In order to prevent acquiescence bias, the tendency to agree with all items without this reflecting the responder's actual opinion, we included four items that were reverse-coded. Each item could be answered using a five-point Likert scale (almost never, seldom, sometimes, frequently, and almost always). Completion of the first part of the questionnaire resulted in a total sensory sensitivity score as well as modality-specific sensitivity scores. Example items are provided in Table 4.

The second part of the questionnaire contains ten open-ended questions that assess whether stroke patients experienced a change in their sensory sensitivity from pre- to post-stroke and provide a detailed description of the changes in sensory sensitivity that they experienced. These items were also used to acquire data on the impact of post-stroke sensory hypersensitivity on daily functioning (i.e., "Do you feel sensory hypersensitivity has impacted your life? In what manner?"). Completion of the entire questionnaire took approximately 20 minutes.

Table 4. Example items of the sensory sensitivity questionnaires per modality.

Multisensory sensitivity I get easily overwhelmed by strong sensory stimuli
Visual sensory sensitivity I am sensitive to bright light
Auditory sensory sensitivity I get overwhelmed by loud sounds
Tactile sensory sensitivity I cut the labels from my clothes
Olfactory sensitivity I have a strong sense of smell
Gustatory sensitivity I do not eat food with a strong taste (for example: very spicy, sour, or sweet food)
Vestibular sensitivity I avoid elevators and/or escalators because I do not like the movement
Sensitivity to temperature I get overwhelmed when I feel too hot or too cold
Pain sensitivity I can handle a large amount of pain

The Oxford Cognitive Screen - NL

To screen cognition, we used version A of the Dutch version of the Oxford Cognitive Screen (OCS-NL) (Huygelier et al., 2019). The OCS-NL is a short neuropsychological battery that uses 11 tasks to assess impairment in five cognitive domains (attention, memory, language, praxis, and numeracy). Additionally, the OCS-NL includes a clinical confrontation test to assess visual field deficits. A detailed description of the tasks including the OCS-NL and the cut-off values for each task can be found in Huygelier et al. (2019). The OCS-NL can be completed within 20 minutes.

Amnestic interview

To assess each patient's match to the in- and exclusion criteria, we conducted an anamnestic interview consisting of questions regarding their medical background. Additional questions regarding lesion location and time since stroke were answered by studying the stroke patients' medical files.

Procedure

This study was approved by the ethical committee of the GasthuisZusters Antwerpen (application number: 180606MASTER) and the Social and Societal Ethics Committee of the KU Leuven (application number: G- 2019031604). Informed consent was obtained in accordance to the World Medical Association Declaration of Helsinki.

Stroke patients

Data of stroke patients were collected at RevArte Rehabilitation hospital in a quiet room without distraction. After requesting written informed consent, patients completed the sensory sensitivity questionnaire and the OCS-NL (Huygelier et al., 2019). The session ended with the structural anamnesis interview and debriefing, during which questions of participants were answered. Participation consisted of one session that lasted maximally one and a half hours. Sufficient breaks were offered during the session to promote feasibility. It was possible to split participation in two sessions if needed.

Neurotypical controls

After acquiring informed consent, neurotypical adults were sent the link to an online version of the sensory sensitivity questionnaire. We also asked these participants for 1) basic demographic information (age, gender, and education level), 2) if they had a probable history of neurological or psychiatric disease, and 3) if they had a formal diagnosis of autism spectrum disorder or ADHD. Participation consisted of a single online session that lasted maximally 25 minutes.

Data analysis

To compare the sensory sensitivity of the three cases to their matched control group, we ran three different analyses. Firstly, since sensory sensitivity is a continuous trait, and neurologically healthy adults can also be hypersensitive (Greven et al., 2019; Kuiper et al., 2019), we considered percentile scores. We assessed the point estimate of the percentage of the control population that would score lower than the stroke cases (i.e., the estimated population percentile of the stroke case) following the recommendations of Crawford and Garthwaite (2002) using the software package Singlims_ES[2] . This statistical method is suitable even in very small control samples (i.e., n = 5) (Crawford & Howell, 1998). Secondly, we assessed the point and interval estimates of the effect size of the difference between the sensory sensitivity of each case and the mean sensory sensitivity of the matched control group (as described by Crawford et al. (2010)). Crawford et al. (2010) recommend focusing on the

[2] *The t-statistic described by Crawford and Garthwaite (2002) allows for comparing the raw score of a case to that of a matched control group. In addition, it computes an estimate of the effect size and an estimate of the percentage of the control population that would obtain a score lower than the patient's (as well as the 95% confidence limits) (Crawford et al., 2010).*

effect size in case-control designs since it is not dependent on sample size (in contrast to significance testing) (see also Sullivan & Fein, 2012). We considered an estimated population percentile equal to or above the 95th percentile and an estimated effect size equal to or higher than 2 to indicate exceptionally high sensory sensitivity (similar to Kuiper et al. (2019) and Hendriks et al. (2020)). Lastly, we compared the raw scores of each case to the mean of the matched control group. Since we were interested in hypersensitivity (instead of both hypo- and hypersensitivity) the reported p-values are one-tailed. To correct for multiple comparisons, we used the adjustment method proposed by Benjamin and Hochberg (1995). No analyses were pre-registered prior to data collection. The dataset acquired and analysed during the current study is available on figshare at https://doi.org/10.6084/ m9.figshare.14140988.v2

Results

Sensory sensitivity questionnaire

Case #1

Case #1 reported a post-stroke increase in her visual, auditory, olfactory, environmental temperature, and pain sensitivity (for details see Table 5). In an attempt to cope with her post-stroke hypersensitivity to bright lights and flashing or moving images, she reported wearing sunglasses while watching television. In the days following her stroke, Case #1 had an intense hypersensitivity to smell, which had since normalized. During sensory overload, Case #1 expressed feeling tired, nauseated, and anxious. Due to her perceived hypersensitivity to background chatter, Case #1 could not attend social gatherings, causing her to feel socially isolated.

Regarding visual, environmental temperature, pain, and general sensory sensitivity (the total score on the sensory sensitivity questionnaire), Case #1's raw scores on the questionnaire were indicative of exceptionally high sensory sensitivity because her estimated percentiles fell above the 95th percentile and the point estimates of the effect sizes were higher than 2 (see Figure 3A and Table 6). Case #1's total score was significantly higher as compared to the mean total score of a matched control group (n = 10). When looking at the sensory modalities separately, Case #1 scored significantly higher on the items assessing visual, environmental temperature, and pain sensitivity as compared to the mean sensory sensitivity of a matched control group (see Figure 3A). These differences were no longer significant after adjustment for multiple comparisons using the adjustment method of Benjamin and Hochberg (1995). Details of the statistical test values and the 95% confidence intervals of the estimates can be found in Table 6.

Case #2

Case #2 reported a post-stroke increase in his sensitivity to multisensory (especially the combination of visual and auditory stimulation), olfactory, and vestibular stimuli (e.g., when standing or sitting in a moving elevator), as well as to environmental temperature and pain (for details see Table 5). He had difficulty concentrating in the presence of irrelevant visual or auditory stimuli. At moments of sensory overload, Case #2 described feeling tired and uneasy, as well as having the urge to seek out privacy. Like Case #1, Case #2 had less social contact as a result of his post-stroke sensory hypersensitivity.

Regarding general, multisensory, olfactory, environmental temperature, pain, and vestibular sensitivity, Case #2's raw scores were indicative of exceptionally high sensory sensitivity because his estimated percentiles fell above the 95th percentile and the point estimates of the effect sizes were higher than 2 (see Figure 3B and Table 6). Case #2's total score was significantly higher as compared to the mean total score of a matched control group (n = 9). When looking at the sensory modalities separately, Case #2 scored significantly higher on the items assessing multisensory, olfactory, environmental temperature, vestibular, and pain sensitivity as compared to the mean sensory sensitivity of a matched control group. Case #2 reported a significantly lower gustatory sensitivity as compared to a matched control group. However, he did not report post-stroke changes in his gustatory sensitivity. Except for sensitivity to environmental temperature, these differences were no longer significant after adjustment for multiple comparisons using the adjustment method of Benjamin and Hochberg (1995). Details of the statistical test values and the 95% confidence intervals of the estimates can be found in Table 6.

Case #3

Case #3 reported a post-stroke increase in his sensitivity to auditory and pain stimuli (for details see Table 5). He reported especially high distractibility as a result of auditory stimulation. When overloaded by sensory stimulation, Case #3 recounted getting a severe headache and feeling anxious.

For general, multisensory, auditory, and pain sensitivity, Case #3's raw scores were indicative of exceptionally high sensory sensitivity because his estimated percentiles fell above the 95th percentile and the point estimates of the effect sizes were higher than 2 (see Figure 3C and Table 6). Case #3's total score was significantly higher as

compared to the mean total score of a matched control group (n = 9). When looking at the sensory modalities separately, Case #3 scored significantly higher on the items assessing multisensory, auditory, and pain sensitivity as compared to the mean sensory sensitivity of a matched control group. The differences between Case #3's raw scores and the mean of the control group were no longer significant after adjustment for multiple comparisons using the adjustment method of Benjamin and Hochberg (1995). Details of the statistical test values and the 95% confidence intervals of the estimates can be found in Table 6.

Cognitive profile of the cases

Table 7 provides an overview of the performance of the cases on the OCS-NL. Scores indicating an atypical score based on the cut-off values specified by Huygelier et al. (2019) are presented in bold. The stroke patients performed near ceiling level on the tasks regarding language, orientation, memory, and praxis (see Table 7). Cases #1 and #2 showed an impairment on one of the numeracy tasks. All three stroke patients showed an impaired score on the broken hearts cancellation task, assessing visual attention. For two stroke patients performance on the OCS-NL may have been disrupted by their sensory hypersensitivity. Case #1 could not complete the broken hearts cancellation task because she reported feeling overwhelmed by the large number of items on the page. Case #2 had difficulty completing the executive set-switching task because he reported finding it hard to ignore the distractors during the baseline condition. In contrast to what is expected based on the cognitive demands of the different conditions within the executive task (with the set-switching condition being more cognitively demanding than the baseline conditions), Case #2 performed better on the set-switching condition than the baseline condition due to high distractibility during the baseline condition.

Structural Anamnesis

None of the cases (or their medical files) reported having a neurological, psychiatric, or other medical condition that could explain their post-stroke sensory hypersensitivity.

Table 5. Stroke patients' answers on the open-ended questions of the sensory sensitivity questionnaire.

	Case #1	Case #2	Case #3
Do you experience an increase in your sensitivity to sensory stimuli from pre- to post-stroke?	**Yes**	**Yes**	**Yes**
Multisensory stimuli	No	**Yes**	No
Visual stimuli	**Yes**	No	No
Auditory stimuli	**Yes**	No	**Yes**
Tactile stimuli	No	No	No
Olfactory stimuli	**Yes**	**Yes**	No
Gustatory stimuli	No	No	No
Vestibular stimuli	No	**Yes**	No
Environmental temperature	**Yes**	**Yes**	No
Pain	**Yes**	**Yes**	**Yes**
Detailed descriptions of the experienced sensory hypersensitivity and its impact on daily life.	"After my stroke I had to start wearing sunglasses while watching television because of my hypersensitivity to the bright light of the television screen and the flashing images on the screen."	"I feel extremely overwhelmed when I am in situations where there is visual and auditory stimulation (for example when I have to listen to my therapist during my physical therapy while there is also a radio playing in the background and a lot of people moving around me). I never experienced this before my stroke."	"I get my physical therapy in a special room where there are no other people or other noises. Due to my hypersensitivity to noises it is impossible for me to practice or eat in the same room as other patients."

	Case #1	Case #2	Case #3
	"Since my stroke I started disliking everyday noises (for example the sound from the television or a group of people who are talking)." "My sense of smell had heightened extremely in the first few days after my stroke. This has improved after the first week." "I do not tolerate warmer temperatures (e.g., a room where the heating is on) as well as before my stroke. Just a small increase in temperature causes me to feel overwhelmed. I do not like when my husband turns on the heating in our house, even when it is cold outside." "It has become much harder for me to ignore pain. I have the feeling that I am much more sensitive for pain. I experience pain more intensely as compared to before my stroke." "I avoid social gatherings." "When I am surrounded by a lot of sensory stimuli I feel tired, nauseous, and anxious."	"I hate being in the presence of people who wear perfume, even when they do not wear a lot of perfume. I am also more sensitive to the smell of soaps or detergent as compared to before my stroke." "After my stroke I started noticing small changes in environmental temperature. I often feel like it is too warm in certain rooms while my family members and other patients are not bothered by the temperature" "When I sit in a moving elevator or wheelchair I feel very uncomfortable. The feeling of those movements is terrible." "I need time alone to recover from the sensory stimulation that I get throughout the day. So I ask my visitors to visit me very shortly or not as often as I would like. I get less and less social contact."	"My family wanted to take me to the hospital cafeteria to drink a coffee. After fifteen minutes I had to leave my family behind to go back to my room to recover from the overload of sounds that I experienced. My family was very surprised because before my stroke I loved going to cafes." "I find it much harder than before my stroke to ignore low levels of pain." "When I am surrounded by a lot of noise I feel very nervous, stressed. It feels very uncomfortable" "I try to avoid situations where there is a lot of noise."

Table 6. The scores on the sensory sensitivity questionnaire of the stroke patients compared to scores from their respective matched control group.

Score	Controls (n = 10)		Case score	Estimated percentile		Estimated effect size (Z_{cc})		Significance test		
	Mean	Sd		Point	95% CI	Point	95% CI	t	p	Adj. p
Case #1										
Total score	199	43	289	96	[83 ; 100]	2.1	[1.0 ; 3.2]	2.0	.04*	.1
Multisensory	17	7	29	94	[78 ; 100]	1.8	[0.8 ; 2.8]	1.7	.1	.11
Visual	24	10	44	95	[81 ; 100]	2.0	[0.9 ; 3.1]	1.9	.046*	.1
Auditory	28	9	42	93	[75 ; 100]	1.7	[0.7; 2.6]	1.6	.1	.1
Tactile	30	9	39	84	[62 ; 97]	1.1	[0.3; 1.9]	1.1	.2	.2
Olfactory	22	7	31	89	[68 ; 99]	1.4	[0.5 ; 2.2]	1.3	.1	.2
Gustatory	18	1	19	83	[60 ; 96]	1.0	[0.2 ; 1.8]	1.0	.2	.2
Temperature	24	5	35	95	[81 ; 100]	2.0	[0.9 ; 3.1]	1.9	.045*	.1
Vestibular	11	4	13	63	[39 ; 84]	0.4	[-0.3 ; 1]	0.3	.4	.4
Pain	26	4	37	98	[88 ; 100]	2.4	[1.2 ; 3.7]	2.3	.02*	.1
Case #2										
Total score	162	26	236	99	[91 ; 100]	2.9	[1.3 ; 4.4]	2.7	.01*	.1
Multisensory	15	5	27	97	[85 ; 100]	2.3	[1.0 ; 3.6]	2.2	.03*	.1
Visual	19	8	26	81	[56 ; 96]	1.0	[0.1 ; 1.8]	0.9	.2	.2
Auditory	22	7	21	47	[23 ; 72]	-0.1	[-0.7 ; 0.6]	-0.1	.5	.5
Tactile	27	8	40	91	[71 ; 99]	1.6	[0.6 ; 2.6]	1.5	.1	.1
Olfactory	18	6	31	97	[84 ; 100]	2.3	[1.0 ; 3.5]	2.2	.03*	.1
Gustatory	16	2	10	1	[0 ; 8]	-3.0	[-4.6 ; -1.4]	-2.9	.01*	.1
Temperature	17	2	31	100	[100;100]	6.0	[3.0 ; 8.9]	5.7	.0002 ***	.007*
Vestibular	7	3	16	99	[94 ; 100]	3.3	[1.6 ; 5]	3.1	.007 **	.1
Pain	22	5	34	97	[86 ; 100]	2.4	[1.1 ; 3.8]	2.3	.03*	.1

Case #3										
Score	Controls (n = 9)		Case score	Estimated percentile		Estimated effect size (Z_{cc})		Significance test		
	Mean	Sd		Point	95% CI	Point	95% CI	t	p	Adj. p
Total score	162	26	226	98	[87 ; 100]	2.5	[1.1 ; 3.8]	2.4	.02*	.1
Multisensory	15	5	27	97	[85 ; 100]	2.3	[1.0 ; 3.6]	2.2	.03*	.1
Visual	19	8	26	81	[56 ; 96]	1.0	[0.1 ; 1.8]	0.9	.2	.2
Auditory	22	7	45	99	[95 ; 100]	3.4	[1.6 ; 5.2]	3.2	.006**	.1
Tactile	27	8	29	59	[34 ; 82]	0.3	[-0.4 ; 0.9]	0.2	.4	.4
Olfactory	18	6	22	74	[49 ; 93]	0.7	[0 ; 1.4]	0.7	.3	.3
Gustatory	16	2	18	80	[55 ; 96]	0.9	[0.1 ; 1.7]	0.9	.2	.2
Temperature	17	2	19	80	[55 ; 96]	0.9	[0.1 ; 1.7]	0.9	.2	.2
Vestibular	7	3	4	14	[2 ; 38]	-1.2	[-2.1. ; -0.3]	-1.1	.1	.2
Pain	22	5	36	99	[90 ; 100]	2.8	[1.3 ; 4.3]	2.7	.01*	.1

* Significant at $p < .05$. ** Significant at $p < .01$. *** Significant at $p < .001$.

P values were adjusted for multiple comparisons using the adjustment method of Benjamin, & Hochberg (1995). Sd: Standard deviation, CI: Confidence interval, Adj. p: adjusted *p* value

Table 7. Stroke patients' performance on the OCS-NL.

	Range of possible scores	Case #1	Case #2	Case #3
Language				
Picture naming	[0 – 4]	4	4	3
Semantics	[0 – 3]	3	3	3
Sentence reading	[0 – 15]	15	15	15
Numeracy				
Number writing	[0 – 3]	3	**2**	3
Calculations	[0 – 4]	**2**	3	4
Praxis				
Meaningless gesture imitation	[0 – 12]	11	12	12
Memory				
Orientation	[0 – 4]	4	4	4
Verbal memory: free recall and recognition	[0 – 4]	4	3	4
Episodic memory: recognition	[0 – 4]	4	3	4
Attention				
Broken hearts cancellation:				
• Total score	[0 – 50]	**14**[3]	**35**	**23**
• Object asymmetry	[-50 – 50]	**5**	0	**1**
• Space asymmetry	[-20 – 20]	**12**	-2	0
Executive score	[-12 – 12]	**4**	**-2**	3

Scores that indicate impaired functioning (based on the cut-off values specified by (Huygelier et al. (2019)) are presented in bold.

[3] *The broken hearts cancellation task was discontinued due to experiences of sensory overload.*

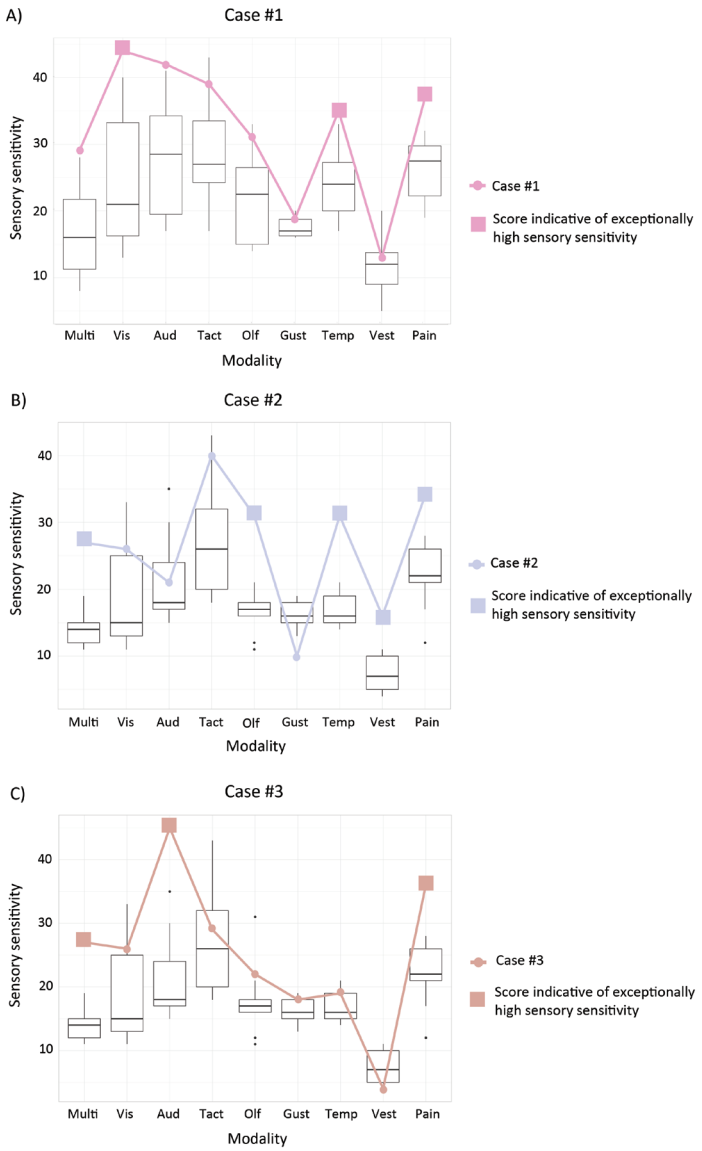


Figure 3. The scores on the sensory sensitivity questionnaire of Cases #1, #2, and #3 as compared to a matched control group. The boxplots represent the distribution of the scores of the neurotypical controls. The lines visualize the scores of the stroke cases. The squares indicate scores of which the estimated percentile of the case is equal to or above the 95th percentile and of which the effect size is ≥ 2. Multi = multisensory, Vis = visual, Aud = auditory, Tact = tactile, Olf = olfactory, Gust = gustatory, Temp = environmental temperature, Vest = vestibular.

Discussion

Systematic literature review

Our systematic literature review on post-stroke sensory sensitivity identified four case reports that linked insular lesions to sensory hypersensitivity in one or two sensory modalities (Table 1). It is noteworthy that only four studies could be identified by our systematic search of the available literature, which indicates the lack of scientific attention for the neuroanatomy of post-stroke sensory hypersensitivity. This lack of scientific attention clearly contrasts with the clinical impact of these symptoms reported by the stroke patients in out multiple case study (see Table 5) and the prevalence mentioned by Chung and Song (2016).

Of the four case reports, Mak et al. (2005) focused on olfactory and gustatory hypersensitivity, Boucher et al. (2015) focused on auditory hypersensitivity, and Cantone et al. (2019) focused on visual hypersensitivity (i.e., post-stroke feelings of fear and disgust in response to complex visual stimuli). However, close reading of the case reports showed evidence for multi-modal hypersensitivity after insular damage. Even though Boucher et al. (2015) focused on post-stroke hyperacusis, their two cases also reported being hypersensitive to other sensory modalities (i.e., comorbid tactile and olfactory hypersensitivity), and the case discussed by Mak et al. (2005) reported a comorbid post-stroke change in his sensitivity to environmental temperature in addition to gustatory and olfactory hypersensitivity.

The results reported by Pritchard et al. (1999) are more difficult to interpret. They compared self-reported taste intensity between the ipsilesional and contralesional side of the tongue for different taste stimuli. Three of their four cases with insular lesions reported a lower taste intensity when taste stimuli were applied to the ipsilesional side of the tongue as compared with taste stimuli applied to the contralesional side of the tongue. The authors interpreted this as evidence for an ipsilesional taste deficit after insular damage. However, these results could also indicate a hypersensitivity to taste on the contralesional side of the tongue (similar to Mak et al. (2005); Table 1). From the article by Pritchard et al. (1999) we can only deduce difference ratings (i.e., ipilesional rating compared to contralesional rating); absolute intensity rating for each hemibody separately are not included, thereby complicating interpretation of these results. Overall, our systematic literature review suggests that post-stroke sensory hypersensitivity can extend across several sensory modalities (visual, auditory, olfactory, gustatory), although

it remains unclear in the aforementioned studies whether post-stroke hypersensitivity was uni- or multi-modal within one patient.

Multiple case study

Regarding this remaining uncertainty, we used a multiple case design to extend the results of previous case studies (Boucher et al., 2015; Cantone et al., 2019; Mak et al., 2005) (Table 1) by presenting three cases with self-reported post-stroke multi-modal hypersensitivity. A stroke-friendly sensory sensitivity questionnaire showed that the self-reported sensitivity of these stroke patients could be considered as exceptionally high as compared to a matched control group (see Figure 3 and Table 6). In our study, Case #1 was found to be exceptionally sensitive to visual stimuli, environmental temperature, and pain; Case #2 was found to be exceptionally sensitive to multisensory, olfactory, and vestibular stimuli as well as to environmental temperature and pain; and Case #3 was found to be exceptionally sensitive to multisensory, auditory, and pain stimuli. The modalities in which the patients experienced post-stroke hypersensitivity were variable suggesting that post-stroke hypersensitivity is a complex, idiosyncratic symptomatology. Due to their sensory hypersensitivity, the stroke patients reported reduced quality of life across several life domains (i.e., social contact, mental, and physical well-being) emphasizing the clinical importance of diagnosing post-stroke sensory hypersensitivity.

The neural basis of post-stroke sensory hypersensitivity

The lesions of the three stroke patients overlapped in the right anterior insula, the claustrum, and the Rolandic operculum. An association between insular damage and post-stroke sensory hypersensitivity is supported by previous case studies (see Table 1). Although the previous studies focused mostly on uni-modal subjective sensory hypersensitivity, we provide preliminary evidence for multi-modal sensory hypersensitivity after an insular lesion as well as self-reported heightened interoception (e.g., heightened sensitivity to pain; reported by all three stroke patients).

The role of the insula in the subjective interpretation of multi-modal sensory stimulation is complemented by fMRI data. Hyperactivation of the insula in response to sensory stimulation has been linked to sensory hypersensitivity in fibromyalgia patients (López-Solá et al., 2014; for a meta-analysis see Dehghan et al. (2016)). Additionally, insula abnormalities have been mentioned in other populations with atypical sensory sensitivity such as patients with mild traumatic brain injury (Li et al., 2020), autism

spectrum disorder (Di Martino et al., 2014), schizophrenia (Wylie & Tregellas, 2010), Tourette syndrome (Cavanna et al., 2017), or attention hyperactivity deficit disorder (Lopez-Larson et al., 2012).

However, because stroke leads to both structural damage as well as impaired functionality due to diaschisis or disconnection, the neural mechanisms of sensory sensitivity might include disruption of a larger neural network instead of focal damage to a specific structure. Two recent reviews (Greven et al., 2019; Ward, 2019) proposed large-scale brain networks as neural markers of subjective sensory hypersensitivity, with a strong emphasis on the salience network. The insula is an important hub of the salience network and it is often coactivated with the rest of the network (Menon & Uddin, 2010). Because the salience network is involved in the detection of relevant sensory input as well as attentional filtering of irrelevant input (Menon, 2015), it is indeed plausible that disruption of this network can lead to sensory hypersensitivity, especially when multiple regions of this network are compromised. Functional salience network abnormalities (not solely limited to the insula) were previously linked to sensory hypersensitivity in children with autism spectrum disorder (Green et al., 2016). To this date, it remains unclear if structural damage to other hubs of the salience network (not encompassing the insula) can also result in sensory hypersensitivity.

All three stroke patients that we studied sustained right-hemispheric brain damage, which could suggest an association between right insular damage and subjective sensory hypersensitivity. Indeed, previous fMRI research associated functional abnormalities in the right insula to sensory hypersensitivity in patients with chronic pain (i.e., fibromyalgia) (López-Solá et al., 2014). However, to date, it remains unclear if there is a differential hemispheric contribution to subjective sensory hypersensitivity since several case studies suggest that sensory hypersensitivity is also present after a left insular lesion (Boucher et al., 2015; Mak et al., 2005; Pritchard et al., 1999). Furthermore, all three included stroke patients had sustained an ischemic stroke, and just one of the cases described in Table 1 sustained a haemorrhagic stroke. Although overrepresentation of ischemic stroke (vs. haemorrhagic stroke) in the case studies could suggest an association between ischemic stroke and subjective sensory hypersensitivity, these results may just reflect the difference in prevalence between ischemic and haemorrhagic strokes (e.g., Krishnamurthi et al., 2015). Furthermore, the stroke type of three cases identified by the systematic review was unclear, limiting our available data on the relationship between stroke type and post-stroke sensory hypersensitivity. As such, further research is needed to investigate the prevalence

of subjective sensory hypersensitivity after ischemic and haemorrhagic stroke respectively, as well as how this might relate to the underlying neuroanatomy.

Given that brain damage does not respect the boundaries of neuroanatomical structures, it is possible that damage to structures or white matter tracts adjacent to the insula belong to the neural underpinnings of sensory sensitivity. A possibility is the insular-claustrum region (including the external and extreme capsule). Due to their proximity and their shared vascularization it is hard for fMRI and lesion studies to distinguish between these structures (Crick & Koch, 2005). Therefore, previous research focusing on the involvement of the insula in nociceptive hypersensitivity might reflect involvement of the entire insular-claustrum region. The claustrum, a neglected region, is known to support the processing and integration of multi-modal sensory information (Crick & Koch, 2005; Reser & Picard, 2020), and claustrum lesions have been shown to result in sensory abnormalities (Maximov et al., 2018). A recent rodent study (Qadir et al., 2018) showed that the claustrum is involved in the detection of salient stimuli and is bidirectionally connected to important hubs of the salience network (e.g., the anterior cingulate cortex). Damage to white matter tracts that are adjacent to the insula and the claustrum and that connect these two regions (e.g., the extreme capsule) or connect these regions to other cortical regions (e.g., the external capsule), might increase vulnerability for post-stroke sensory hypersensitivity. This hypothesis is supported by studies reporting external capsule abnormalities in clinical populations with sensory processing disorders, such as patients with mild traumatic brain injury (Kraus et al., 2007; Narayana et al., 2015) and patients with chronic pain (Lieberman et al., 2015). Further research allowing for investigation of the relationship between neuroanatomy and post-stroke sensory hypersensitivity with high structural resolution is needed. Lastly, Haroutounian et al. (2018) suggested that tactile hypersensitivity in the context of central post-stroke pain originates from a maladaptive sensitization of central neurons to peripheral input, causing non-nociceptive input to cross a nociceptive threshold (that it would not cross under normal circumstances). It would be interesting to study if a similar interaction between the central and peripheral nervous systems can be found for post-stroke hypersensitivity to other sensory modalities as well as without comorbid pain.

A relationship between post-stroke sensory hypersensitivity and selective attention

It must be noted that our three stroke patients all presented with both post-stroke sensory hypersensitivity and indications of selective attention impairments. In Cases #1 and #2, sensory hypersensitivity hindered cognitive functioning during the attention-based tasks

of the OCS-NL, and performance on these tasks was impaired in all three stroke patients. A relationship between attention and sensory sensitivity has previously been proposed in the neurotypical population and in other clinical groups (autism spectrum disorder, ADHD, schizophrenia) (Marco et al. 2011; Micoulaud-Franchi et al., 2015; Panagiotidi et al., 2018). The described link between post-stroke sensory hypersensitivity and insular lesions might reflect this relationship between attention and sensory sensitivity since the salience network is involved in attentional filtering (Menon, 2015). Post-stroke sensory hypersensitivity might be indicative of underlying selective attention difficulties which would explain why patients report the most intense impairments when encountering multi-modal stimulation and that the impacted sensory modality is idiosyncratic and possibly arbitrary (Thielen & Gillebert, 2019). Because we used only paper-and-pencil tasks to screen for deficits in selective attention, subtle attentional impairments may have been missed. Previous research has indeed shown that computer-based attentional testing is more sensitive to these subtle attention deficits (Bonato et al., 2013; Gillebert et al., 2011). Further research including a comprehensive neuropsychological assessment (preferably including computerized attentional testing) is needed to determine if attention impairments are indeed part of the behavioural mechanisms of subjective sensory hypersensitivity.

Study limitations

A limitation of the review process was that a grey literature search was not conducted which could lead to neglecting recent emerging research. Our case study also had limitations, one of which was the small sample size. A larger control sample matched in gender, age, and education level to each case would be preferable. Furthermore, we studied stroke patients with self-reported sensory hypersensitivity in the subacute stage after stroke (i.e., minimally 2 months after stroke), which limits our understanding of the relationship between lesion location and subjective symptoms because of the influence of functional reorganization. All three of the included stroke patients had a right-hemispheric lesion biasing our results towards a right-hemispheric dominance for subjective sensory sensitivity. We recommend that future studies include patients with left-, right-, and bilateral strokes in order to expand our knowledge on hemispheric contribution to subjective sensory sensitivity.

Lastly, since isolated insula lesions are rare and the insula is commonly damaged after middle cerebral arteries strokes due to its location and vasculature (Caviness et al., 2002), the suggested relationship between the insula and subjective sensory sensitivity might merely reflect differential vulnerability. For future research, we suggest using a technique

that can study the relationship between structural lesions and subjective sensory sensitivity at a small structural scale while controlling for lesion volume. For instance, voxel-based lesion-symptom mapping (VLSM) can be used to investigate the relationship between structural lesions and subjective sensory hypersensitivity at the level of an individual voxel (Mirman et al., 2018; Rorden et al., 2007; Varjacic et al., 2018). It allows us to determine which regions are crucial for post-stroke alterations in sensory sensitivity and to predict behavioural deficits from lesion location without having to a priori exclude patients based on the presence or absence of a certain behavioural deficit. In this study, we included patients based on a report of post-stroke sensory hypersensitivity in their medical files causing a sampling bias where patients with a higher symptom severity or greater introspective and communicative abilities had a larger chance to be included in the study. VLSM could provide a better understanding of the neural mechanisms of post-stroke sensory hypersensitivity by comparing the lesion location of patients with and without post-stroke sensory hypersensitivity in a larger stroke sample. VLSM has previously successfully been used in stroke patients to examine the neural markers of a variety of cognitive functions including attention and executive functions (e.g., Karnath & Rennig, 2017; Varjacic et al., 2018). This promising technique could help us to determine which regions play a role in post-stroke sensory hypersensitivity.

Conclusion

By presenting three cases with post-stroke sensory hypersensitivity, we hope to raise awareness for the clinical importance of recognizing multi-modal hypersensitivity as a possible consequence of stroke as well as to outline some of the outstanding questions surrounding the neuroanatomy of these subjective symptoms. Gaining more insight on the neural basis of post-stroke sensory hypersensitivity as well as its behavioural mechanisms will be of high importance for adequate diagnosis and rehabilitation of these symptoms. To date, it remains unclear if post-stroke sensory hypersensitivity reflects an abnormal affective interpretation of sensory stimulation (i.e., the perceived unpleasantness or perceived intensity), attentional difficulties (i.e., poorer selective attention, high distractibility), or abnormal bottom up processing of sensory stimulation (i.e., abnormal sensory thresholds). Systematic research on post-stroke subjective sensory hypersensitivity and its behavioural and neural mechanisms in a heterogenous stroke sample can provide further answers to these outstanding questions.



“Since my stroke I am hypersensitive to
the noises my children make when they are playing.
It makes me feel like an awful mother.
It feels like something in my brain has changed.”

Chapter seven

Unravelling the neural basis of sensory hypersensitivity after stroke: evidence from lesion-symptom and structural disconnection mapping

A post-injury increase in sensory sensitivity is frequently reported by acquired brain injury patients (including stroke patients). These symptoms are related to poor functional outcomes, but their underlying neural mechanisms remain unclear. Since stroke results in focal lesions that can easily be visualized on imaging, the lesions of stroke survivors can be used to study the neural basis of post-injury sensory hypersensitivity. We used multivariate support vector regression lesion-symptom mapping and indirect structural disconnection mapping to uncover the lesion location and white matter tracts related to post-stroke sensory hypersensitivity. A total of 103 patients were included in the study, of which 48% reported post-stroke sensory hypersensitivity across different sensory modalities. The lesion-symptom and structural connectivity mapping identified the basal ganglia, thalamus and insula in the grey matter as well as the fronto-insular tract, and the uncinate fasciculus in the white matter as neural structures potentially involved in post-stroke sensory hypersensitivity. By examining the neuroanatomy of post-stroke sensory hypersensitivity in a large stroke sample, this study offers a significant advancement in our understanding of the neural basis of post-stroke sensory hypersensitivity.

Thielen, H., Tuts, N., Welkenhuyzen, L., Lemmens, R., Wibail, A., Huenges Wajer, I.M.C., Lafosse, C., Mantini, D., & Gillebert, C.R. (2023). Unravelling the neural basis of sensory hypersensitivity after stroke: evidence from lesion-symptom and structural disconnection mapping. Submitted to Cortex.

Successful participation in society requires an adequate processing of sensory rich environments (e.g., buying groceries in a busy supermarket, working in an open office, having a conversation at a family gathering). Stroke can affect sensory sensitivity, resulting in a post-injury increase in sensory sensitivity (i.e., post-stroke sensory hypersensitivity) (Chung & Song, 2016; Thielen, Huenges Wajer, et al., 2023). In a previous study, it was found that 76% of 204 chronic stroke patients reported post-stroke sensory hypersensitivity for one (uni-modal post-stroke sensory hypersensitivity) or multiple sensory modalities (multi-modal post-stroke sensory hypersensitivity) (Thielen, Huenges Wajer, et al., 2023). Importantly, post-stroke sensory hypersensitivity can also be present in the subacute phase after stroke (Thielen, Tuts, et al., 2023). Patients with post-stroke sensory hypersensitivity are easily overwhelmed by sensory rich environments which can negatively impact their mental well-being, social functioning, and physical health (Alwawi et al., 2020; Thielen, Tuts, et al., 2023).

These symptoms are not specific to stroke patients but are also seen after other types of acquired brain injury (traumatic brain injury, brain tumours), in the neurotypical population, and in several clinical populations, including individuals with autism spectrum disorder, attention deficit hyperactivity disorder, or chronic pain (Bijlenga et al., 2017; López-Solá et al., 2014; Ochi et al., 2022; Tavassoli, Miller et al., 2014; Thielen, Huenges Wajer, et al., 2023). Across these populations, the underlying mechanisms contributing to self-reported sensory hypersensitivity remain largely unknown. More specifically, it is uncertain whether inter-individual differences in subjective (self-reported) sensory sensitivity are related to inter-individual differences in behavioural (i.e., the ability to detect or discriminate between different sensory stimuli) or neural sensory sensitivity (i.e., the neural response to sensory stimuli) (Ward, 2019). Characterizing the underlying behavioural and neural mechanisms of subjective sensory sensitivity is necessary for developing rehabilitation protocols that can limit the negative impact of high sensory sensitivity on daily functioning.

Stroke patients are ideal candidates for studying the neural basis of sensory hypersensitivity after acquired brain injury since stroke results in focal lesions that can be easily visualized on routine clinical imaging (in contrast to the lesions caused by traumatic brain injuries or brain tumours). In a previous systematic review that investigated the neuroanatomy of post-stroke sensory hypersensitivity (Thielen, Tuts, et al., 2023), we described four case studies that linked uni-modal post-stroke sensory

hypersensitivity (hypersensitivity to visual, auditory, gustatory, olfactory stimuli) to insular damage (Boucher et al., 2015; Cantone et al., 2019; Mak et al., 2005; Pritchard et al., 1999). We complemented these results with a multiple case study describing three right-hemispheric stroke cases with multi-modal post-stroke sensory hypersensitivity whose lesions overlapped in the right anterior insula, the claustrum, and the Rolandic operculum (Thielen, Tuts, et al., 2023).

However, the results of the systematic review and the multiple case study might be biased. On the one hand, the sample of our multiple case study was limited to patients with self-reported post-stroke sensory hypersensitivity after right-hemispheric damage. On the other hand, the insula is commonly damaged after a middle cerebral artery stroke (Caviness et al., 2002). To mitigate these limitations, the brain lesions of left- and right-hemispheric patients with and without post-stroke sensory hypersensitivity should be compared to investigate which region, when damaged, could result in post-stroke sensory hypersensitivity. Lesion-symptom mapping is a powerful technique that examines the relationship between behaviour and brain damage without a priori defining a region of interest or excluding patients with or without certain behavioural profiles (Baldo et al., 2022). Lesion-symptom mapping offers a topological approach that identifies specific grey matter regions that are necessary for certain functions. However, it does not consider that brain lesions can have structural and functional impacts on non-damaged parts of brain networks (Gillebert & Mantini, 2013). In addition, since white matter tracts are spatially distributed, a disconnection at different locations among this tract can have similar behavioural consequences (Gleichgerrcht et al., 2022). White matter integrity can be directly assessed using Diffusion Tensor Imaging but this technique is hard to implement in a large patient sample due to its reliance on high-quality nonclinical brain imaging (Kuceyeski & Boes, 2022; Salvalaggio et al., 2020). To overcome these limitations, indirect structural disconnection mapping can be used to map individual lesions (normalized to a common template) onto a database of structural networks in neurologically healthy adults to estimate the disruptions in white matter integrity caused by the lesion (Foulon et al., 2018; Kuceyeski & Boes, 2022; Sperber et al., 2022).

This study aimed to investigate the neuroanatomy of post-stroke sensory hypersensitivity in a first-ever subacute stroke sample. To assess whether stroke survivors experienced post-stroke sensory hypersensitivity they completed the Multi-Modal Evaluation of Sensory Sensitivity (MESSY) (Thielen, Huenges Wajer, et al., 2023). To investigate the

neuroanatomy of post-stroke sensory hypersensitivity the lesions and white matter integrity of patients with and without post-stroke sensory hypersensitivity were compared using multivariate lesion-symptom and indirect structural disconnection mapping.

Methods

Participants

Stroke patients were recruited between December 2019 and January 2023 from the acute stroke unit of University Hospitals Leuven and the rehabilitation units of RevArte Rehabilitation Hospital and Hospital East-Limburg. Recruitment was halted between March 2020 and June 2020 due to the COVID-19 pandemic. Stroke patients were included when (1) they were able to provide informed consent, (2) they were adult (aged 18 years or older), (3) they completed the MESSY, (4) at least one clinical brain scan was available, and (5) they were first-ever stroke survivors. Additional exclusion criteria were (1) not having a visible lesion on clinical imaging, (2) the presence of major microvascular damage (defined as Fazekas grade 3)[1] (Fazekas et al., 1987), (3) having a subdural or subarachnoid haemorrhage, (4) presence of Wallerian degeneration, (5) having a pre-existing neurological disorder (previous traumatic brain injury, stroke, tumour), (6) having a formal diagnosis of autism spectrum disorder, ADHD or schizophrenia, and (7) having a psychiatric disorder that could impact their sensory sensitivity. We did not exclude patients based on their lesion location, cognitive profile, or time since stroke.

102 participants were excluded based on the a priori set exclusion criteria (see Table 1). Three additional participants were excluded due to poor quality of the normalization of their scans because of motion artefacts. This resulted in a final sample of 103 participants. Scans were acquired on average six days after stroke (standard deviation: 12) and there were on average 17 days between acquisition of the scan and completion of the MESSY (standard deviation: 26). The majority of the included stroke patients (77%) had an ischemic stroke.

[1] *The Fazekas grade was defined based on a radiologic report or by having two independent researchers reach a consensus after examining the clinical brain imaging.*

Table 1. Overview of the number of patients that were excluded based on a priori set exclusion criteria, ordered from most to least common.

Exclusion criteria	Number of excluded stroke patients
Having a previous stroke	31
Presence of major microvascular damage	21
Having a subdural or subarachnoid haemorrhage	13
Participant did not have a stroke	9
No clinical brain scan was available	8
Participant did not complete the MESSY	7
Not having a visible lesion on clinical imaging	5
Having a pre-existing neurological disorder	5
Presence of Wallerian degeneration	1
Having a formal diagnosis of autism spectrum disorder or ADHD	1
Having a psychiatric disorder that could impact sensory sensitivity	1
Total number of excluded stroke patients	102

Materials

MESSY

The MESSY is a patient-friendly questionnaire that assesses the sensitivity to sensory stimuli across several modalities (i.e., multisensory, visual, auditory, tactile, olfactory, gustatory, and motion sensitivity as well as sensitivity to environmental temperature) (Thielen, Huenges Wajer, et al., 2023). Multisensory sensitivity refers to the sensitivity to stimuli from different sensory modalities that are present at the same time (i.e., for example the simultaneous presence of visual, auditory, olfactory, and gustatory stimuli in a restaurant). Per modality, the MESSY assesses whether patients experience an increase in their sensory sensitivity after their brain injury using open questions (i.e., “Since your brain injury, have you become more sensitive to sounds? How did you notice this or in which situations did you notice this?”). These open questions are used to determine

whether high sensory sensitivity was linked to stroke onset (i.e., to differentiate post-stroke symptoms from pre-existing sensory hypersensitivity). In addition, the MESSY uses 30 multiple-choice items which are answered on a five-point Likert-scale (ranging from never/not at all to very often/extremely). The multiple-choice items are summed to assess the severity of the sensory sensitivity per modality or across all modalities (i.e., total score of the MESSY). The MESSY can be seen as aphasia-friendly since it uses pictograms, places one item per page, and displays key concepts in a question in bold (Dalemans et al., 2009). In this study we used the pen-and-paper version of the MESSY that was developed for an inpatient acquired brain injury population.

If a stroke patient indicated that they experienced a post-stroke increase in their sensitivity to one or multiple sensory modalities on the open-ended questions of the MESSY, they were considered as having post-stroke sensory hypersensitivity. Accordingly, patients in the group without post-stroke sensory hypersensitivity reported no post-stroke increase in their sensory sensitivity to any sensory modality. To assess the severity of post-stroke sensory hypersensitivity, we compared the total score of the MESSY in patients with post-stroke sensory hypersensitivity to that of patients without post-stroke hypersensitivity.

The Oxford Cognitive Screen-NL

To assess post-stroke cognition, we administered the Dutch version of the Oxford Cognitive Screen (OCS) (version A) (Huygelier et al., 2019). This cognitive screening tool consists of 11 subtests assessing visual field deficits and various cognitive domains such as attention, memory, language, praxis, and numeracy. In contrast to other commonly used screening tools (such as the Montreal Cognitive Assessment), the OCS provides domain-specific test scores and is thought to be aphasia- and neglect-friendly (Huygelier et al., 2022). The parallel-form reliability and convergent validity of the OCS were deemed satisfactory by previous studies (Demeyere et al., 2015; Huygelier et al., 2022).

Structural anamnesis

During a structural anamnesis participants answered questions regarding several demographic variables (i.e., their age, gender, education level) and their medical background. Stroke type, time since stroke, and the number of previous strokes were gathered from the electronic medical files of the stroke patients.

Procedure

This study is part of a larger study assessing post-stroke sensory sensitivity. Ethical approval for this study was granted by the Medical Ethics Committee of the Hospital of East-Limburg (application number: CTU2019055), the Ethics Committee Research UZ/KU Leuven (application number: S63063), and Medical Ethics Committee of the GasthuisZusters Hospital Antwerp (application numbers: 190904ACADEM). Participation consisted of three sessions which were completed in a distraction-free room. During the first session written informed consent was obtained in accordance with the World Medical Association Declaration of Helsinki. Afterwards, participants completed the MESSY and the structural anamnesis. Clinical imaging was acquired from the electronic medical files of the stroke patients. During the three sessions, that lasted approximately 60 minutes each, patients completed additional neuropsychological tasks and questionnaires that are beyond the scope of the current study.

Data analysis

Analyses were conducted in R (version 4.2.2) (RStudio Team, 2020) and Matlab2018b (The MathWorks Inc., 2018). Figures were created using Adobe Photoshop (2020).

Behavioural data analysis

During the analyses of behavioural data, alpha was set to .05 and all reported p values were corrected for multiple comparisons using the Holm method (Holm, 1979).

Lesion delineation and preprocessing

Lesions were delineated manually on the axial plane of a clinical brain scan (Fluid Attenuated Inversion Recovery (FLAIR): n = 46, Diffusion Weighted Imaging (DWI): n = 37, Computed Tomography (CT): n = 20) using MRIcron and a Wacom Cintiq Pro tablet by trained investigators (HT, NT) (for details see Table 2). A recent study indicated that there was no evidence for a difference in accuracy between CT- and MRI-based lesion delineation (Moore et al., 2023). If multiple brain scans were available for one patient, the scan used for lesion delineation was selected following the procedure outlined by Biesbroek et al. (2019). We used SPM12 (https://www.fil.ion.ucl.ac.uk/spm) to smooth the lesion masks at 8 mm full width half maximum, resliced them to 2 mm isotropic voxels, and normalized them to Montreal Neurological Institute (MNI) space by applying a non-linear deformation calculated on the brain scan using the 'old segment' function. All normalized lesion masks were visually inspected by comparing them both with the

normalized brain scan and with a template image in MNI space. If a small lesion focus was removed due to smoothing, this focus was manually added to the normalized lesion mask (Biesbroek et al., 2019; Lugtmeijer et al., 2021; Zhao et al., 2018).

Table 2. The resolution of the included scans per scan type.

Scan type	n	Mean voxel size [Range] (in mm)		
		X	Y	Z
FLAIR	46	1.52 [.49 – 6.45]	.84 [.45 – 4.01]	1.34 [.46 – 6.5]
DWI	37	.99 [.57 – 1.2]	2.28 [.57 – 6.43]	3.28 [.9 – 6.48]
CT	20	1.04 [.33 – 2.99]	.52 [.32 – 2.61]	1.71 [.32 – 3]

Multivariate lesion-symptom mapping

To investigate the relationship between post-stroke sensory hypersensitivity and lesion location we performed a support vector regression-based multivariate lesion-symptom mapping (SVR-LSM) (Zhang et al., 2014) using the SVR-LSM toolbox (DeMarco & Turkeltaub, 2018). SVR-LSM uses machine learning and support vector regressions (with a radial basis function) to compute, for each voxel, a feature weight (a beta value) that represents the strength of the relationship between that voxel and the behaviour of interest. Since these feature weights cannot be interpreted directly, permutation testing is used to assess their statistical significance. Previous research has shown that multivariate lesion-symptom mapping using SVR-LSM has a higher sensitivity and specificity for identifying lesion-behaviour relationships than univariate (voxelwise) approaches (Zhang et al., 2014). In line with recommendations from Zhang et al. (2014), the hyperparameter values of the machine learning algorithms were set a priori at a cost of 30 and a gamma of 5. Only voxels that were lesioned in at least five participants (5% of the sample) were considered in the analysis. To control for multiple comparisons, we used a permutation-based continuous family wise error correction (with 2000 permutations, $p = .05$, and $v = 10$) which permitted 10 false positive voxels (similar to Faulkner & Wilshire, 2020; Mirman et al., 2018). Anatomic labelling was performed using the Automated Anatomical Labelling Atlas 3 (Rolls et al., 2020). We compared in SVR-LSM the groups of patients with and without post-stroke sensory hypersensitivity.

Since lesion volume did not differ significantly between the patients with or without post-stroke sensory hypersensitivity (see below, Table 3) and since there was no evidence for a relationship between the severity of post-stroke sensory hypersensitivity and lesion volume (see below), we did not apply a correction for lesion volume.

Indirect structural disconnection mapping

To investigate the relationship between behaviour and white matter integrity we used the Tractotron software of the BCBtoolkit (www.toolkit.bcblab.com) (Foulon et al., 2018). This software determines to what extent a lesion damages white matter tracts by mapping individual lesion maps on existing white matter atlases based on 7T DWI imaging data in 179 neurotypical adults (Vu et al., 2015). Tractotron calculates, for each participant, the probability that a lesioned voxel intersected with a specific white matter tract. When this probability is above 50%, the white matter tract is considered disconnected (de Schotten et al., 2014). We used logistic regressions to examine whether tract disconnection was related to the presence of post-stroke sensory hypersensitivity. In line with the SVR-LRM analyses, analyses were limited to white matter tracts that were disconnected in at least five patients, permutation testing (with 2000 permutations) was used to assess the significance of the results, and a Holm correction was used to correct for multiple comparisons (Ludbrook, 1998). Since we were interested in a positive relationship between tract disconnection and post-stroke sensory hypersensitivity, Table 7 is limited to tracts that were damaged more frequently in patients with post-stroke sensory hypersensitivity as compared to patients without post-stroke sensory hypersensitivity. Descriptives of the other tracts can be found in Supplementary Table 1.

Results

Participants

49 stroke patients (48% of the final sample) reported a post-stroke increase in their sensitivity to sensory stimuli. The characteristics of stroke patients with and without post-stroke sensory hypersensitivity are displayed in Table 3. There was no evidence for a significant difference between patients with and without post-stroke sensory hypersensitivity in age, lesion volume, days between stroke onset and clinical imaging, days between stroke onset and MESSY completion, the proportion of patients who completed higher education (Fisher's exact test: Holm adjusted $p = 1$) and cognitive performance (assessed using the OCS-NL) (see Tables 3 and 4). Furthermore, there

was no evidence for a relationship between the sensory sensitivity severity (the total score of the MESSY) on the one hand, and lesion volume (spearman rho: 22435, Holm adjusted $p = 1$), age (spearman rho: 19004, Holm adjusted $p = 1$), or gender (Wilcoxon test: W: 172.5, Holm adjusted $p = .10$) on the other hand in patients with post-stroke sensory hypersensitivity.

36 of the 49 patients with post-stroke sensory hypersensitivity (73%) reported experiencing multi-modal post-stroke sensory hypersensitivity (their increase in sensory sensitivity was present in more than one sensory modality). The number of patients who experienced an increased sensitivity per sensory modality as well as a description that participants gave to describe their heightened sensitivity to that sensory modality are given in Table 5. The total MESSY score of patients with post-stroke sensory hypersensitivity was significantly higher as compared to stroke patients without post-stroke sensory hypersensitivity (see Table 3).

Table 3. Characteristics of the patients with and without post-stroke sensory hypersensitivity.

	Patients without post-stroke sensory hypersensitivity	Patients with post-stroke sensory hypersensitivity	Results of non-parametric Wilcoxon rank-sum test	
			W	Adjusted *p*
Number of patients	54	49		
Age: mean (sd), in years	69 (12)	62 (15)	1721	.07
Age range: in years	29 - 89	26 - 90		
Number of male patients (%)	34 (63%)	29 (60%)		
Number of patients who completed higher education (%)[2]	15 (28%)	19 (40%)		
Number of patients with a ischemic / haemorrhagic stroke (%)	47 (87%) / 7 (13%)	36 (73%) / 13 (27%)		
Lesioned hemisphere: left / right / bilateral: number of patients (%)	22 (41%) / 26 (48%) / 6 (11%)	22 (45%) / 25 (51%) / 2 (4%)		
Lesion volume: mean (sd), in cc	42 (60)	36 (53)	1417.5	1
Time between MESSY completion and clinical imaging: mean (sd), in days	11 (12)	25 (33)	1248	1
Time between stroke onset and clinical imaging: mean (sd), in days	4 (8)	7 (16)	952.5	.10
MESSY Total Score - Possible range [30-150]	44 (13)	65 (17)	446	< . 01

Sd: standard deviation. Higher education: at least a bachelor degree awarded by a college or university. Cc: cubic centimetre. P values were adjusted for multiple comparisons using a Holm correction (Holm, 1979).

[2] *The education level of one patient without post-stroke sensory hypersensitivity and one patient with post-stroke sensory hypersensitivity was not reported.*

Table 4. The cognitive profile of the stroke patients with and without post-stroke sensory hypersensitivity assessed using the OCS-NL.

OCS subtest per cognitive domain	Range of possible scores	Incidence of impairment per group (%)		Median score		Results of the Mann Whitney U Test		
		Without SH (n = 50)	With SH (n = 45)	Without SH (n = 50)	With SH (n = 45)	W	Adjusted p	Effect size
Visual Field test	[0 - 4]	12%	4%	4	4	1038	1	.14
Language								
Picture naming	[0 - 4]	4%	7%	4	4	1037.5	1	.07
Semantics	[0 - 3]	6%	7%	3	3	1132.5	1	.01
Sentence reading	[0 - 15]	12%	4%	15	15	937.5	.39	.23
Numeracy								
Number writing	[0 - 3]	4%	2%	3	3	1229.5	1	.01
Calculations	[0 - 4]	2%	7%	4	4	1183	1	.06
Praxis								
Meaningless gesture imitation	[0 - 12]	12%	7%	11	11	860.5	.53	.21
Memory								
Orientation	[0 - 4]	12%	13%	4	4	1137	1	.02
Verbal memory: free recall and recognition	[0 - 4]	16%	18%	3	4	972	1	.13

OCS subtest per cognitive domain	Range of possible scores	Incidence of impairment per group (%)		Median score		Results of the Mann Whitney U Test		
		Without SH (n = 50)	With SH (n = 45)	Without SH (n = 50)	With SH (n = 45)	W	Adjusted p	Effect size
Episodic memory: recognition	[0 - 4]	4%	4%	4	4	1016	1	.12
Attention								
Broken hearts cancellation:								
• Total score	[0-50]	32%	20%	44	47	884	.86	.19
• Object asymmetry	[-50 – 50]	28%	18%	0	0	1061	1	.06
• Spatial asymmetry	[-20 – 20]	26%	16%	0	0	1148	1	.02
Trail making task	[-12 – 12]	20%	11%	0	-1	1309.5	1	.15

SH = Post-stroke sensory hypersensitivity. Eight stroke patients did not complete the OCS-NL and were removed from this analysis. *P* values were adjusted for multiple comparisons using a Holm correction (Holm, 1979).

Table 5. The number of patients with post-stroke sensory hypersensitivity for a specific modality as well as examples of descriptions patients gave to describe their symptoms.

Sensory modality	Number of patients with post-stroke sensory hypersensitivity for a specific modality	Examples of descriptions patients gave to describe their symptoms
Multisensory	33	"I get overwhelmed during my physical therapy. I feel like there is too much happening all at once (listening to my therapist, other people moving around me, the sunlight that shines through the windows, and the radio that is on)." "I detest having visitors: it makes me feel anxious and stressed when there are too many people around me. Before my stroke I was very social."
Visual	29	"Since my stroke I started disliking bright sunlight and fast moving images on the television."
Auditory	21	"I notice that I experience typical sounds, such as the sound of my playing grandchildren or music, as highly aversive. Being surrounded by these sounds gives me a headache and makes me feel exhausted."
Motion	16	"When I am seated in a moving car or when I am driven around in my wheelchair, it feels like everything around me is moving. This makes me incredibly nauseous and feels very unstable (like I am going to tip over)."
Environmental temperature	11	"I get overwhelmed by the slightest increase in temperature."
Olfactory	8	"My sense of smell has increased since my stroke. Smells of detergent or makeup are much more intense than before more stroke."
Gustatory	2	"Sweet or sour foods taste incredibly intense. I have stopped eating certain foods due to this increase in taste."
Tactile	1	*"Since my stroke I feel overwhelmed by brushing my hair (when the comb lightly touches my scalp) or when my wife touches my arm. I avoid physical contact."*

Patients who reported multi-modal post-stroke sensory hypersensitivity are counted multiple times in this table. Sensory modalities were ordered from most to least prevalent.

Multivariate lesion-symptom mapping

Figure 1 shows an overlay of the lesions (for the entire sample, and the patients with and without post-stroke sensory hypersensitivity separately) as well of the voxels that were included in the analysis (i.e., voxels that were lesioned in at least five participants). The SVR-LSM identified a relationship between post-stroke sensory hypersensitivity and clusters of voxels in the left insula, thalamus, and basal ganglia (caudate nucleus and putamen) (see Figure 2 and Table 6).

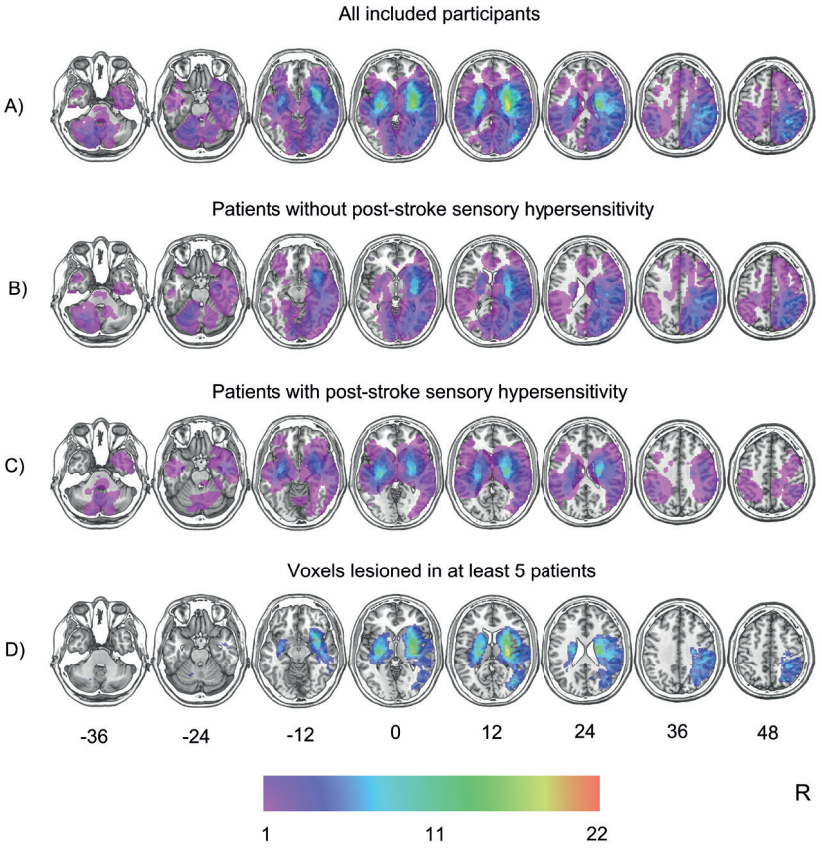


Figure 1. A: Lesion overlap map of all included participants (n = 103). B: Lesion overlap map of patients without post-stroke sensory hypersensitivity (n = 54). C: Lesion overlap map of patients with post-stroke sensory hypersensitivity (n = 49). D: Lesion coverage map displaying the voxels that were lesioned in at least five patients. The lesion maps are visualized on axial slices of the T1-weighted template from the Montreal Neurological Institute (ch2-template). The numbers refer to the MNI coordinates of the z-axis. The colour scale indicates the number of patients with a lesion in a specific voxel.

Table 6. Descriptive statistics of the significant clusters identified by SVR-LSM.

	Number of voxels	MNI centre of mass coordinates			Peak Z value in MNI coordinates	Anatomical location
		X	Y	Z	Z	
Cluster 1	649	-23	2	-3	-19	Left caudate nucleus, Putamen, Insula
Cluster 2	79	-8	-17	-3	-9	Left Mediodorsal Thalamus
Cluster 3	76	-24	-2	4	3	Left Putamen
Cluster 4	17	-27	-12	4	1	Left Putamen

Anatomical location was determined using the Automated Anatomical Labelling Atlas 3 (Rolls et al., 2020).

Indirect structural disconnection mapping

The logistic regressions revealed a significant association between post-stroke sensory hypersensitivity and disconnection in the left fronto-insular tract 3 and the left uncinate fasciculus (see Figure 2 and Table 7).

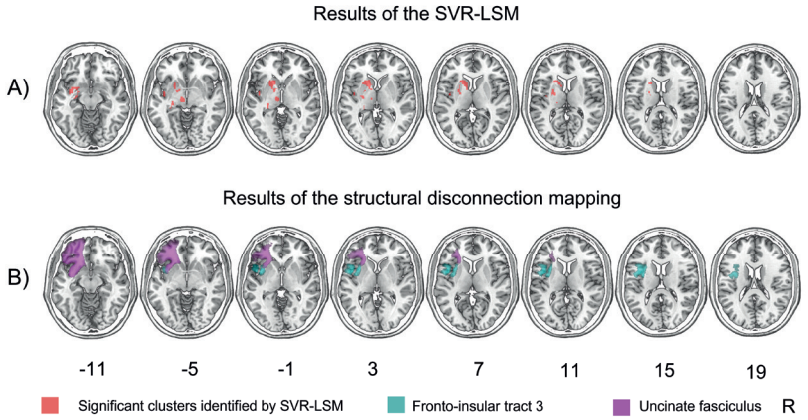


Figure 2. A: Significant voxels identified by SVR-LSM. B: Significant tracts identified by indirect disconnection mapping with the left fronto-insular tract 3 shown in cyan and the left uncinate fasciculus shown in violet. The lesion maps and white matter tracts are visualized on axial slices of the T1-weighted template from the Montreal Neurological Institute (ch2-template). The numbers refer to the MNI z-coordinates of the corresponding slices.

Table 7. Results of the logistic regression models examining the association between tract disconnection and post-stroke sensory hypersensitivity.

Tract name	Number of patients with a disconnection in the specified tract (%)		Odds ratio	95% CI	Adjusted p value
	Without SH (n = 54)	With SH (n = 49)			
Anterior Commissure	33%	43%	1.5	[.68 ; 3.37]	1
Arcuate Fasciculus - Anterior Segment					
Left	6%	20%	4.36	[1.24 ; 20.42]	.36
Arcuate Fasciculus - Long Segment					
Left	15%	27%	2.08	[.79 ; 5.76]	1
Arcuate Fasciculus - Posterior Segment					
Left	7%	18%	2.81	[.85 ; 11]	1
Anterior Cingulum					
Left	13%	14%	1.12	[.36 ; 3.52]	1
Posterior Cingulum					
Left	7%	8%	1.11	[.25 ; 4.95]	1
Cortico-spinal Tract					
Left	39%	41%	1.08	[.49 ; 2.39]	1
Right	44%	49%	1.20	[.55 ; 2.62]	1
Face U Tract					
Left	2%	6%	3.46	[.43 ; 71.20]	1
Right	13%	14%	1.12	[.36 ; 3.52]	1
Fornix	30%	39%	1.50	[.66 ; 3.45]	1

Frontal Aslant Tract					
Left	19%	20%	1.13	[.42 ; 3.03]	1
Right	28%	33%	1.26	[.54 ; 2.95]	1
Fronto-inferior Longitudinal Tract					
Left	9%	12%	1.37	[.39 ; 5.05]	1
Fronto-Insular Tract 2					
Right	15%	16%	1.12	[.38 ; .3.31]	1
Fronto-Insular Tract 3					
Left	6%	22%	4.92	[1.42 ; 22.87]	**.04**
Right	17%	22%	1.45	[.54 ; 3.95]	1
Fronto-Insular Tract 4					
Left	19%	24%	1.43	[.55 ; 3.74]	1
Right	19%	27%	1.59	[.63 ; 4.13]	1
Fronto-Insular Tract 5					
Left	13%	24%	2.18	[.80 ; 6.37]	1
Fronto-Striatal Projections					
Right	43%	45%	1.10	[.50 ; 2.40]	1
Hand Inferior U tract					
Left	7%	8%	1.11	[.25 ; 4.95]	1
Inferior Fronto-occipital Fasciculus					
Left	26%	27%	1.03	[.42 ; 2.49]	1
Optic Radiations					
Left	19%	22%	1.27	[.49 ; 3.38]	1

Tract name	Number of patients with a disconnection in the specified tract (%)		Odds ratio	95% CI	Adjusted p value
Right	24%	27%	1.14	[.47 ; 2.79]	1
Uncinate Fasciculus					
Left	4%	18%	5.85	[1.41 ; 39.79]	**.04**

Left: left-hemispheric. Right: right-hemispheric. The one-tailed p values were based on permutation testing (with 2000 permutations) and corrected for multiple-comparisons using a Holm correction (Holm, 1979). Significant p values are displayed in bold. For more information on the location of the specific tracts see Rojkova et al. (2016). The results discussed in this table are limited to tracts that were disconnected more frequently in patients with post-stroke sensory hypersensitivity as compared to patients without post-stroke sensory hypersensitivity.

Discussion

The aim of this study was to examine the neuroanatomy of post-stroke sensory hypersensitivity in a subacute stroke sample using state-of-the-art techniques. We found evidence for a relationship between post-stroke sensory hypersensitivity and damage to the insula as well as disconnection of fronto-insular tracts (see Figure 2, Tables 6 and 7). This corresponds with previous case studies that described uni- or multi-modal post-stroke sensory hypersensitivity after insular damage (Boucher et al., 2015; Cantone et al., 2019; Mak et al., 2005; Thielen, Tuts, et al., 2023). In addition, our results suggest a role for other structures such as the thalamus, basal ganglia, and uncinate fasciculus (see Figure 2, Tables 6 and 7). This study provides a significant advancement in our understanding of the neural basis of post-stroke sensory hypersensitivity since it is the first time that the neuroanatomy of these symptoms is studied in a large stroke sample. Furthermore, this study is among the first to assess the prevalence of multi-modal post-stroke sensory hypersensitivity in a (sub)acute stroke population. Noteworthy, the prevalence of post-stroke sensory hypersensitivity in the current sample (48%) was lower than in a chronic stroke sample that also used the MESSY (75%) (Thielen, Huenges Wajer, et al., 2023). This might be due to methodological differences such as the self-selection bias of the chronic stroke study as well as the different in- and exclusion criteria between the two studies. Indeed, the exclusion of certain stroke types (i.e., subarachnoid haemorrhage and subdural hematoma) as well as patients with major microvascular damage or with previous strokes limits the extent to which the current sample represents the entire stroke population. On the other hand, the difference in prevalence of post-stroke sensory hypersensitivity between the acute and chronic sample might also reflect true changes in prevalence across time. For instance, it is possible that sensory hypersensitivity symptoms are not always noticeable in the subacute phase and only become apparent when participation demands increase in the chronic phase after stroke (e.g., returning to work, driving in traffic, taking part in large social gatherings). Learning more about the prevalence of post-stroke sensory hypersensitivity as well as its neural basis can greatly enhance our understanding of the underlying mechanisms of these subjective symptoms as well as help identify patients that are at risk of developing post-stroke sensory hypersensitivity.

The neural basis of post-stroke sensory hypersensitivity

Previous research has suggested a relationship between sensory hypersensitivity and selective attention (Panagiotidi et al., 2018; Panagopoulos et al., 2013; Thielen &

Gillebert, 2019). The involvement of the insula, basal ganglia, and thalamus in post-stroke sensory hypersensitivity can accordingly be understood through their role in sensory filtering. Indeed, the thalamus is seen as a relay station that receives incoming sensory information from different senses and selects information to send to the cortex for further processing (Torrico & Munakomi, 2023). Higher cortical regions project onto the thalamus to drive this sensory filtering towards goal-directed information (John et al., 2016; Zikopoulos & Barbas, 2007). One of these feedback loops projects from the prefrontal cortex to the thalamus through the basal ganglia (Nakajima et al., 2019). The insula, in turn, serves as a key hub of the salience network, which is involved in the detection of relevant sensory input and the filtering of irrelevant sensory input (Menon & Uddin, 2010). These findings are further supported by functional neuroimaging research in other populations. Research, for instance, shows a relationship between insular and basal ganglia activation on the one hand and sensory sensitivity on the other hand (in fibromyalgia patients and neurotypical adults respectively) (López-Solá et al., 2014; Stoffers et al., 2014). Additionally, abnormal functional connectivity of the thalamus during sensory processing has been observed in children with autism spectrum disorder, indicating its potential role in sensory hypersensitivity in this population (Green et al., 2017). From this perspective, the findings of the current study complement previous findings on the potential role of selective attention and neural structures related to selective attention (thalamus, insula, basal ganglia) in sensory hypersensitivity.

In addition to a relationship between selective attention and post-stroke sensory hypersensitivity, researchers have also proposed an involvement of psychosocial mechanisms. One such hypothesis, known as the negative affect hypothesis, posits that sensory hypersensitivity may arise from a negative evaluation of sensory stimuli, influenced by a general inclination for negative affectivity (Shepherd et al., 2019). The insula is involved in sensory appraisal through its connection with the prefrontal cortex (Namkung et al., 2017). Disruptions in frontal-insular connections may result in distortions in how sensory information is interpreted and assigned emotional significance. This could explain why we found a positive relationship between post-stroke sensory hypersensitivity and disconnection of the left posterior fronto-insular tract 3 which connects the insula to the orbitofrontal cortex (Rojkova et al., 2016) (see Table 7 and Figure 2). Using indirect structural connectivity mapping we also found evidence for a relationship between post-stroke sensory hypersensitivity and the left uncinate fasciculus. The uncinate fasciculus connects the primary auditory cortex to the

orbitofrontal cortex and has previously been related to auditory sensitivity in neurotypical adults (Shiotsu et al., 2021).

In summary, our results provide evidence that post-stroke sensory hypersensitivity is related to damage to different neural structures and white matter tracts that are involved in selective attention, sensory appraisal, and auditory processing.

Limitations of the current study

Firstly, to increase statistical power of the multivariate lesion-symptom mapping analysis, only voxels that were lesioned in at least five participants were included in the analysis (De Haan & Karnath, 2018; Sperber & Karnath, 2022). The lesions of our sample overlapped in middle cerebral artery regions (in the left and right hemisphere) but did not reach sufficient coverage in other areas that might be of interest (such as the frontal or sensory cortices). As a result, the conclusions of this study are spatially limited and biased towards the regions in which we had sufficient lesion coverage. This limited lesion coverage is not specific to our study but is a common occurrence in lesion-symptom mapping studies (e.g., Feldman et al., 2023; Meyer et al., 2016; Oostra et al., 2016). It does, however, limit the sensitivity of our analyses and impedes us from studying the relationship between post-stroke sensory hypersensitivity and some large-scale neural networks. In addition, it makes it hard to draw conclusions about a hemispheric dominance for post-stroke sensory hypersensitivity. When considering both hemispheres in our analyses, we only found evidence for significant results in the left hemisphere. The lack of significant results in the right hemisphere could be attributed to a difference in lesion volume and lesion distribution between the included left- and right hemispheric lesions. Post-stroke sensory hypersensitivity has indeed been reported after both left- and right hemispheric stroke, hence a hemispheric dominance for sensory sensitivity seems unlikely (Thielen, Huenges Wajer, et al., 2023; Thielen, Tuts, et al., 2023).

A second limitation of this study is that we focused solely on the structural consequences of stroke without considering influences of neuroplasticity or recovery (Wilson, 2017). Previous research has shown that within the first few days after stroke the brain engages in functional reorganization (Grefkes & Fink, 2020; Rehme et al., 2011). This functional reorganization includes both lesion-related functional changes as well as secondary compensatory responses (where other brain regions take over the functions

performed by the lesioned area). These effects could not be explored using the current methodology. To provide insight on the functional neural mechanisms of post-stroke sensory hypersensitivity, future studies should conduct fMRI research, possibly combined with lesion-symptom mapping.

A last limitation, that is not specific to our study but to lesion-symptom mapping in general, is that lesion-symptom mapping techniques induce a spatial misplacement of their results (oriented towards the middle and posterior arteries) (Mah et al., 2014; Sperber et al., 2018). To gain more certainty about the reliability of the spatial location of our results, we encourage replication studies using larger heterogenous samples. As an additional benefit, studying a larger sample might provide important information about whether the neuroanatomy of post-stroke sensory hypersensitivity is related to symptom severity, differs according to the sensory modality that is affected, as well as if there are differences in neuroanatomy between uni-modal and multi-modal sensory hypersensitivity. Due to the limited number of patients with (uni-modal) sensory hypersensitivity, our sample did not allow for such analyses.

In conclusion, this study provides evidence for a relationship between post-stroke sensory hypersensitivity and damage to the insula, basal ganglia, and thalamus as well as different white matter tracts (fronto-insular tract 3 and the uncinate fasciculus). This provides us with important information about which patients are at risk for developing post-stroke sensory hypersensitivity but can also teach us something about which neural regions play a role in sensory sensitivity, making it of interest for other clinical groups. Furthermore, since the insula, basal ganglia, and thalamus are all involved in sensory filtering, these results provide indirect evidence for a relationship between post-stroke sensory hypersensitivity and selective attention.



“It’s too much — so many stimuli are coming at me — it feels like I have a completely different brain.”

Chapter eight

General Discussion

After meeting Ann, a patient who suffered from post-stroke sensory hypersensitivity, and witnessing the detrimental impact of these symptoms on her quality of life (see Chapter 1), I felt compelled to contribute to the scientific understanding of these symptoms. This doctoral thesis aimed to achieve several objectives: (1) to provide an overview of the current knowledge regarding sensory sensitivity after acquired brain injury through a systematic literature review, (2) to improve the assessment of subjective sensory sensitivity after acquired brain injury by developing a patient-friendly sensory sensitivity questionnaire, and to unravel the underlying (3) behavioural and (4) neural mechanisms of sensory hypersensitivity after acquired brain injury using state-of-the-art techniques. This general discussion, reviews our findings regarding each objective, summarizes the key discoveries in a biopsychosocial model, and outlines remaining questions and recommendations for future research.

Subjective sensory sensitivity after acquired brain injury

From the systematic review (in Chapter 2) we learned that previous literature mainly focused on light and noise hypersensitivity after mild traumatic brain injury. We hypothesized that this emphasis on specific sensory modalities and a specific type of brain injury was potentially driven by the absence of validated diagnostic tools that can assess changes in sensory sensitivity in other modalities and that are adapted to acquired brain injury patients with language or cognitive impairments. As a first step to help us achieve our remaining objectives, we, therefore, aimed to improve the assessment of sensory hypersensitivity after acquired brain injury.

Assessment of subjective sensory hypersensitivity after acquired brain injury

The assessment of sensory sensitivity is complicated by the fact that it is a subjective experience that cannot be directly observed by others. When developing the Multi-

Modal Evaluation of Sensory Sensitivity (MESSY) (Chapter 3) we placed a central focus on the subjective experience of acquired brain injury patients with post-injury sensory hypersensitivity by involving these patients with lived experience in the designing process. The MESSY has several strengths: it offers a valid and reliable evaluation of sensory sensitivity across several sensory modalities, was sensitive to changes in sensory sensitivity after different types of brain injury, and was successfully used in acute and chronic acquired brain injury patients (Chapters 3, 5, and 7). Nevertheless, there are certain limitations of the MESSY that need to be addressed. To capture whether patients suffered from a change in their sensory sensitivity post- as compared to pre-injury we relied on open questions. The reliability of the answers to these open questions as well as the equivalence between the in- and outpatient versions of the MESSY have not been formally evaluated thus far.

By using the MESSY in a large sample of chronic acquired brain injury patients (Chapter 3), we learned that sensory hypersensitivity was present after different types of brain injury including stroke, mild to severe traumatic brain injury, and brain tumours. Importantly, the severity of post-injury sensory hypersensitivity was found to be comparable across these different types of brain injury. This implies that the scientific community should aim to reduce the bias towards mild traumatic brain injury in future research and clinicians should be made aware that these symptoms can also be present after more severe and other types of acquired brain injury. In support of this latter objective, we initiated several outreach projects, allowing us to communicate our research findings to a broad audience of healthcare professionals (see pages 282 and 283).

A high prevalence of post-injury sensory hypersensitivity in chronic and (sub)acute stroke samples (75% and 48% respectively) was reported in Chapters 3 and 7. These prevalence rates might be influenced by sampling bias (in Chapter 3) and the in- and exclusion criteria of the respective study (in Chapter 7). Noteworthy, for Chapter 7, the influence of strict in- and exclusion criteria seems to be limited as an (unpublished) data analysis in a larger and more representative sample showed that 42% of 186 (sub)acute stroke patients experienced post-stroke sensory hypersensitivity. Future research in representative samples of (sub)acute and chronic patients with different types of acquired brain injury is needed to provide more comprehensive information on the prevalence of post-injury sensory hypersensitivity.

Noticeably, both Chapter 3 and Chapter 7 indicated that if patients experienced post-injury sensory hypersensitivity, it was often present in more than one modality and prevalences differed according to the affected sensory modalities. Both in a chronic (Chapter 3) and subacute sample (Chapter 7) of acquired brain injury patients, hypersensitivity for noise, light, motion, and multisensory stimuli was more prevalent than hypersensitivity for sensory stimuli from other modalities. The reasons for these differences require further investigation, but may be related to certain characteristics of the sensory stimuli in question such as the amount of exposure to certain stimuli, the experienced control over the stimulus, or the experienced time pressure related to the stimulus (Marzolla et al., 2023). For instance, it could be that stimuli in social contexts (such as people talking, people moving around) are harder to control or avoid and place larger demands on the timing of sensory processing than, for instance, tactile, gustatory, or olfactory stimuli.

In this thesis, the MESSY was only completed by Dutch or Belgian participants. As the subjective experience of sensory hypersensitivity might differ across cultures (Caron et al., 2012; Greven et al., 2019; Weyn et al., 2021), it would be beneficial to study the measurement equivalence of the MESSY across different cultural groups. This can teach us more about culturally relevant factors that can influence the experience of sensory hypersensitivity, which will expand our understanding of sensory sensitivity as a psychological construct as well as facilitate the development of culturally sensitive assessment and treatment protocols.

Having succeeded in developing a valid, reliable, and patient-friendly assessment of subjective sensory sensitivity, we were better equipped to examine the behavioural and neural mechanisms of subjective sensory hypersensitivity in stroke patients.

The behavioural mechanisms of post-injury sensory hypersensitivity

When considering the underlying behavioural mechanisms of post-injury sensory hypersensitivity, the systematic review (Chapter 2) suggested that abnormal information processing speed and sensory thresholds are promising candidates (Chang et al., 2007; Shepherd et al., 2019). In a commentary (Chapter 4), we argued that selective attention might also be important to consider. Indeed, in Chapter 5, we found evidence, both at the group and at the individual level, for impaired selective attention (combined with

lowered sensory thresholds) in stroke patients with post-stroke visual hypersensitivity as compared to stroke patients without post-stroke visual hypersensitivity, hospitalized orthopedic patients, or neurotypical adults. In contrast to prior research (Gualtieri & Johnson, 2006), we found no evidence for a difference in information processing speed, which could possibly be attributed to a reduced sensitivity of the behavioural assessment, or the way in which information processing speed was operationalized. These results represent a significant advancement in our understanding of the underlying mechanisms of post-stroke sensory hypersensitivity and can serve as a valuable source of inspiration for future investigations into interventions aimed at addressing post-stroke visual hypersensitivity.

Future research is needed to replicate these findings in other acquired brain injury populations and in other sensory modalities to see how well they generalize beyond the stroke population and the visual modality. In addition, given that the computerized TVA-based assessment used in Chapter 5 placed significant cognitive demands on our patients, future studies should investigate if and how this task can be made more stroke-friendly. By doing so, researchers can ensure that the assessment of sensory thresholds, sensory processing speed, and selective attention can be used in a broader range of patients with varying cognitive abilities, guaranteeing its clinical applicability. Lastly, given that this thesis was limited to only three potential underlying behavioural mechanisms, it is essential to keep exploring other potential mechanisms that contribute to sensory hypersensitivity.

Other potential behavioural mechanisms

Although selective attention and sensory thresholds are plausible candidate behavioural mechanisms for post-stroke visual hypersensitivity, Chapter 5 also showed us that these constructs alone could not explain sensory hypersensitivity symptoms in all stroke patients. Other behavioural mechanisms that could be considered are sustained attention, predictive coding, and multisensory integration. Exploring these related concepts might contribute to a more comprehensive understanding of sensory hypersensitivity after acquired brain injury.

Sustained attention

Sustained attention is the ability to maintain focus on a certain task for an extended period of time and is known to affect lower-level perception (Fortenbaugh et al., 2017).

For instance, focusing on a visual stimulus initially enhances the neural response to that stimulus (Carrasco, 2011; Carrasco et al., 2004). However, this effect is not stable over time. As focus is prolonged, sustained attention leads to increased sensory adaptation characterized by a reduced response to sensory stimuli after extended exposure (Ling & Carrasco, 2006). As sustained attention impairments are prevalent after acquired brain injury (Brosnan et al., 2022; Molenberghs et al., 2009; Pearce et al., 2016), it is possible that post-injury impairments in sustained attention result in diminished sensory adaptation. This could place higher demands on sensory and cognitive resources, resulting in increased mental fatigue and a faster depletion of attentional resources throughout a task, which, in turn, can lead to information processing overload and feeling hypersensitive (Neigel et al., 2019). Indeed, previous research has suggested an association between sustained attention and sensory sensitivity in neurotypical adults and in children with autism spectrum disorder (Mazor-Karsenty et al., 2019; Pastor-Cerezuela et al., 2020).

Predictive coding

Predictive coding refers to a theoretical framework stating that the brain continuously generates predictions about upcoming sensory input based on prior expectations (Friston, 2005; Ward, 2019). Since the neural response to an expected stimulus is smaller than to an unexpected stimulus, making accurate responses about upcoming expected stimuli lowers the demands placed on sensory processing systems (Kok et al., 2012; Ward, 2019). However, since sensory environments are continuously changing, predictions are not always accurate and need to be continuously updated. Mismatches between actual and expected sensory input (i.e., prediction errors) are used to update subsequent expectations so that future inferences better match the sensory environment. Importantly, not every prediction error should be given equal weight: rather, weights should be based on the ambiguity and certainty of the sensory input that it is based on (Van de Cruys et al., 2017). The predictive coding theory has mostly been used in the autism population and implies that impaired prediction of upcoming sensory input or inflexible weighting of prediction errors leads to symptoms of sensory hypersensitivity (Pellicano & Burr, 2012; Van de Cruys et al., 2014). Inflexible or impaired prediction of upcoming sensory input could put people at higher risk of being surprised by sensory input, causing people to depend more on their sensory input than previous expectations, in turn possibly making them hyperattentive or -sensitive to sensory environments. Little research has been done regarding the relationship between acquired brain injury and

predictive coding (Asko et al., 2023; Doricchi et al., 2021), making this an interesting area for further research.

Multisensory integration

Our environment is multisensory in nature (i.e., stimuli of different sensory modalities are presented simultaneously). Multisensory integration is needed to integrate information from different modalities pertaining to the same sensory stimulus (Colonius & Diederich, 2020). For instance, because of multisensory integration the sound of a person clapping their hands and the actual hand movements are processed as one single stimulus instead of two. Difficulty in perceiving the relationship between cross-modal inputs may overload the sensory system by increasing the number of stimuli that need processing (Hebert & Filley, 2022; Ward, 2019). Reduced multisensory integration as an underlying mechanism of sensory hypersensitivity might explain why, in our studied samples, the prevalence of multisensory hypersensitivity was higher than hypersensitivity to a single modality (see Chapters 3 and 7). To date, there is little direct evidence for a relationship between multisensory integration impairments and sensory hypersensitivity. Nevertheless, abnormal multisensory integration is seen in several clinical groups in which sensory hypersensitivity is prevalent (stroke, traumatic brain injury, autism spectrum disorder) (De Sain et al., 2023; Könings et al., 2017; Stevenson et al., 2014; Van der Stoep et al., 2019).

The neural mechanisms of post-injury sensory hypersensitivity

In addition to investigating the behavioural mechanisms of post-stroke sensory hypersensitivity, this thesis also considered the relationship between neuroanatomy and post-injury sensory hypersensitivity. Using a systematic review (Chapter 6), a multiple case study (Chapter 6), and lesion-symptom and indirect structural disconnection mapping techniques (Chapter 7), we discovered that post-stroke sensory hypersensitivity was possibly related to damage to different neural structures such as the insula, thalamus, and basal ganglia in the grey matter, and the fronto-insular tract and uncinate fasciculus in the white matter. These results complement previous research describing post-stroke sensory hypersensitivity after insular damage as well as research in other populations linking damage in these regions and white matter tracts to sensory sensitivity, sensory processing, sensory appraisal, or selective attention (Boucher et al., 2015; Cantone et al., 2019; López-Solá et al., 2014; Mak et al., 2005; Nakajima et al., 2019; Namkung et al., 2017; Shiotsu et al., 2021; Stoffers et al., 2014; Torrico & Munakomi, 2023).

Importantly, a comprehensive account of the neural markers of post-injury sensory hypersensitivity should also consider functional abnormalities as well as abnormalities at a cellular or molecular level.

Other potential neural mechanisms

Functional neural mechanisms

As brain injury can result in functional disturbances and decreased activity in neural regions that are not lesioned (i.e., diaschisis) (Gillebert & Mantini, 2013; Seitz et al., 1999; Wawrzyniak et al., 2022), examining the relationship between post-injury sensory hypersensitivity and functional neural mechanisms is necessary. Out of the 82 studies identified by the systematic literature review in Chapter 2, only one study investigated the relationship between brain activity and post-injury sensory hypersensitivity (Astafiev et al., 2016). This study found that patients with light hypersensitivity after mild traumatic brain injury displayed higher brain activity in the visual cortex during a visual tracking task as compared to mild traumatic brain injury patients without light hypersensitivity. Previous research in neurotypical adults, adults with chronic pain, and individuals with autism spectrum disorder found abnormal brain activity in other regions such as the insula, thalamus, amygdala, hippocampus, and orbito-frontal cortices in relation to sensory hypersensitivity (Acevedo et al., 2018; Green et al., 2013; Greven et al., 2019; López-Solá et al., 2014).

Importantly, as studies rarely include an extensive assessment of subjective sensory sensitivity and often limit themselves to sensitivity in one sensory modality, it is important for future studies to incorporate a multi-modal subjective evaluation and a multi-modal task in task-related functional magnetic resonance imaging (fMRI). Furthermore, to mimic the sensory hypersensitivity experienced in multisensory real-world settings, future fMRI research might focus on naturalistic neuroimaging using ecological multisensory stimuli (e.g., movies) (Aliko et al., 2020; Gal et al., 2022).

Since conducting fMRI research in a large sample of acquired brain injury patients with sensory hypersensitivity poses some challenges (especially due to the noise that the fMRI machine makes), future research could make use of modern indirect measures such as indirect functional connectivity mapping (Joutsa et al., 2022). In this technique, lesions delineated on routine clinical imaging, are overlaid onto a freely available dataset of resting state fMRI data from neurotypical adults, to identify a network of brain regions

that are functionally related to the brain lesion and might display abnormalities post-injury. These identified networks are then compared between patients with and without a certain symptoms to investigate whether functional abnormalities in certain regions are related to behaviour (Boes, 2021).

In addition to functional abnormalities at a system level, abnormalities at a micro scale including a neurotransmitter disbalance or neuroinflammation may play a role in post-injury sensory hypersensitivity.

Gaba / glutamate disbalance

Findings from functional MRI research in children with autism spectrum disorder have suggested that their brains exhibit a hyperreactivity in response to sensory stimuli (as compared to typically developing children) (Green et al., 2013). This hyperactivity could potentially be attributed to an imbalance between the main inhibitory and excitatory neurotransmitters: gamma-aminobutyric acid (GABA) and glutamate respectively (Ward, 2019; Wood et al., 2021). This hypothesis proposes that a GABA-glutamate imbalance may lead to hyperarousal and hyperattentiveness to the sensory environment, subsequently resulting in sensory hypersensitivity. Support for this hypothesis is found in research investigating children with autism spectrum disorder where elevated glutamate in sensorimotor regions and decreased GABA in thalamic regions were related to subjective sensory hypersensitivity (He et al., 2021; Wood et al., 2021). Regarding acquired brain injury patients, there is evidence for GABA-glutamate abnormalities after brain injury (Carmichael, 2012; Guerriero et al., 2015), but, to our knowledge, there is, to date, no study that investigated a direct link between neurotransmitter imbalances and subjective sensory sensitivity.

Neuroinflammation

After a brain injury, an immediate inflammatory response involving the activation of microglial occurs (Wang et al., 2022; Xiong et al., 2016). Microglia are the primary immune cells of the central nervous system and can serve both degenerative and reparative functions (Zhang et al., 2020). While initial microglial activation after brain injury is beneficial as it removes cellular debris and promotes neuroplasticity, excessive or prolonged microglial activation can have detrimental effects resulting in secondary injuries that can persist for up to 17 years post-injury (Gentleman et al., 2004; Ramlackhansingh et al., 2011). As an in vivo measurement of microglial activation in humans is challenging,

research on the relationship between sensory sensitivity and neuroinflammation after brain injury is, to date, limited to animal models. In rats, a link between microglial proliferation and sensory sensitivity after traumatic brain injury (whisker sensitivity) has been suggested (Cao et al., 2012). However, since our knowledge regarding the role of neuroinflammation in post-injury sensory hypersensitivity is limited, further research is needed to understand this complex interplay and to investigate if these results can be replicated in humans.

A biopsychosocial model of sensory hypersensitivity after acquired brain injury

When Ward (2019) reviewed the state of the literature on sensory sensitivity in different populations an important research question emerged. It remained unclear whether subjective symptoms of sensory hypersensitivity were related to behavioural or neural markers. By using a multi-level approach, this thesis found evidence for a relationship between subjective, behavioural, and neural sensitivity in an acquired brain injury population. Specifically, this thesis provides evidence that post-injury subjective sensory hypersensitivity is related to selective attention impairments (Chapter 5) as well as to damage in neural regions that play a role in selective attention (e.g., the thalamus, insula, and basal ganglia) (Chapters 6 and 7). However, we acknowledge that studying a limited number of specific neural and behavioural mechanisms poses a risk of diminishing the diversity and complexity of sensory hypersensitivity after acquired brain injury. Therefore, other mechanisms, particularly psychosocial mechanisms, need to be considered to fully understand sensory sensitivity.

The role of psychosocial mechanisms

In their examination of noise hypersensitivity after mild traumatic brain injury, Shepherd et al. (2019) posit two hypotheses that describe its relationship with psychological factors. Firstly, the negative affect hypothesis suggests that post-injury sensory hypersensitivity is a result of a negative appraisal of sensory stimuli mediated by a general tendency to critically evaluate situations or the self. This hypothesis is supported by studies that found a relationship between sensory sensitivity on the one hand and somatization and the perception of recovery on the other hand in acquired brain injury patients (Callahan et al., 2018; Nelson et al., 2018; Shepherd et al., 2019). Secondly, the anxiety hypothesis proposes that stress and anxiety can result in a hyperaroused sympathetic nervous system, which subsequently leads to hypervigilance towards the sensory environment.

This hypothesis is supported by the widespread evidence for a relationship between post-injury sensory sensitivity on the one hand and anxiety and post-traumatic stress on the other hand (Al-Ozairi et al., 2015; Assi et al., 2018; Callahan et al., 2018; Callahan & Storzbach, 2019; Elliott et al., 2018; Goodrich et al., 2014; Shepherd et al., 2019). Since the acquisition of an acquired brain injury is a stressful and traumatic life event, it seems logical that having to experience such an event (regardless of the outcomes of the brain injury) might lead to anxiety or post-traumatic stress symptoms. In Chapter 5, we made an effort to control for the influence of hospitalization and recovery from a medical event by comparing the visual sensitivity of hospitalized (sub)acute stroke patients to that of hospitalized orthopedic patients. However, since the included orthopedic patients were often hospitalized after a planned surgery, we recognize that this particular group does not fully control for the trauma of experiencing a sudden medical emergency. Further research investigating the relationship between sensory sensitivity on the one hand and the appraisal of life events or the self, hyperarousal, and post-traumatic stress symptoms on the other hand is needed to investigate to what extent these psychological factors can explain sensory hypersensitivity symptoms after acquired brain injury. In addition, social factors such as socioeconomic status, cultural expectation, access to healthcare, and social support should be considered.

The role of fatigue and sleep quality

In semi-structured interviews, patients with acquired brain injury often report an association between post-injury sensory hypersensitivity and post-injury fatigue (Alwawi et al., 2020; De Sain et al., 2023; Hallberg et al., 2005; Landon et al., 2012; Marzolla et al., 2023). It has been hypothesized that this relationship forms a negative feedback loop, where sensory hypersensitivity leads to fatigue which in turn worsens the sensory hypersensitivity (Landon et al., 2012; Marzolla et al., 2023). However, to our knowledge, there is currently no quantitative research examining this complex causal interplay between fatigue and post-injury sensory hypersensitivity. Nonetheless, there is correlational evidence suggesting a positive relationship between fatigue and sensory hypersensitivity after mild traumatic brain injury (Chandran et al., 2020; Shepherd et al., 2019). Several explanations for the relationship between post-injury fatigue and post-injury sensory hypersensitivity are possible. One possibility is that poor sleep quality mediates the relation between fatigue and sensory hypersensitivity (Elliott et al., 2018; Howell et al., 2019). Again, the relationship between sensory hypersensitivity and sleep might be bidirectional as post-injury sensory hypersensitivity might make it

more difficult to fall asleep. Another explanation is that fatigue, poor sleep quality, and sensory hypersensitivity may be linked through identical underlying mechanisms (such as selective attention, hyperarousal, hypothalamic-pituitary-adrenal axis dysregulation, anxiety, coping strategies, and illness perceptions) (Arm et al., 2021; Cellini et al., 2017; Faber et al., 2012; Papadopoulos & Cleare, 2012; Ponsford et al., 2012; Rakers et al., 2021; Schoormans et al., 2020; Wang et al., 2015). Therefore, fatigue, poor sleep quality, and sensory hypersensitivity after acquired brain injury could potentially be symptoms of an overarching disorder. For instance, all three symptoms align with those of a stress-related hyperarousal disorder (Riemann et al., 2010; Shepherd et al., 2019; Wang et al., 2015). Further research is needed to assess these relationships.

The role of sustaining mechanisms

Longitudinal research on sensory hypersensitivity after acquired brain injury showed that for some patients sensory hypersensitivity symptoms recover in the first year after injury, while for others symptoms are persistent after the first year (Barker-Collo et al., 2019; Marzolla et al., 2022; Shepherd et al., 2021). Indeed, in Chapter 3 we found a high prevalence of post-injury sensory hypersensitivity in chronic patients and saw that symptoms can persist for several decades after brain injury. Since post-injury sensory hypersensitivity recovers in some patients but not others, it is important to explore the role of mechanisms that influence the maintenance of these symptoms. The fear-avoidance model has previously successfully explained the persistence of post-concussion symptoms and functional impairment in mild traumatic brain injury patients (Silverberg et al., 2018; Wijenberg et al., 2017). This model, that originates from the chronic pain literature, suggests that the way individuals interpret their symptoms plays a crucial role in determining their impact on daily functioning (Leeuw et al., 2007; Vlaeyen & Linton, 2000).

In the context of sensory hypersensitivity, the same initial experience of post-injury sensory hypersensitivity might elicit different levels of symptom-related fear in different patients (see Figure 1). Those who interpret their sensory hypersensitivity symptoms as threatening (e.g., a sign of severe brain pathology) and engage in symptom-related catastrophizing, may develop a fear of sensory stimuli. This, in turn, may result in a hypervigilance towards and avoidance of sensory stimulation, which results in disuse and disability. By avoiding sensory stimuli, patients might give their sensory systems less chance to habituate to sensory stimuli (e.g., sensory deconditioning), resulting in a

negative feedback loop where catastrophizing and sensory avoidance worsen symptoms over time. Since the acquisition of a brain injury is often sudden and leads to overall shock, sensory hypersensitivity might be an adaptive response to acute brain injury. Experiencing sensory hypersensitivity might be the brain's way to communicate its need for rest and recovery. In that sense, short-term avoidance of sensory stimuli might be beneficial. However, a long-term avoidance might disable an individual to engage in activities of daily life. Research is needed to investigate to what extent recovery of sensory hypersensitivity symptoms is related to catastrophizing and avoidance-behaviours in acquired brain injury patients. If evidence is found for this model, it could pave the way for implementing preventive measures (e.g, psycho-education about this model as well as psychological treatment focused on coping) to limit functional impairment.

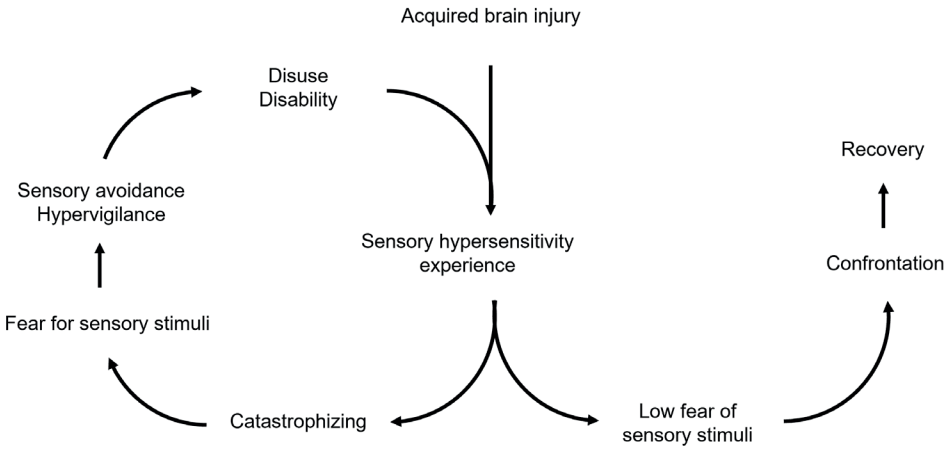


Figure 1. Fear-avoidance model of post-injury sensory hypersensitivity, adapted from Vlaeyen & Linton (2000).

The role of pre-morbid vulnerabilities

To add to the complexity, it could be that pre-morbid vulnerabilities such as pre-existing preferences for maladaptive coping styles, exposure to stressful life events, or psychiatric disturbances might predispose certain patients for developing post-injury sensory hypersensitivity (Van Veldhoven et al., 2011). Indeed, a reduced resilience might disturb successful adaptation after acquired brain injury, resulting in higher symptoms severity and persistence of symptoms. Though the assessment of pre-morbid vulnerabilities is challenging as it relies on extensive retrospective (hetero)amnestic interviews or questionnaires, this information could prove to be crucial to fully understand post-injury sensory hypersensitivity and thus warrants scientific attention.

A complex biopsychosocial model

As is clear from the previous paragraphs, our understanding of the underlying mechanisms of sensory hypersensitivity after acquired brain injury is still limited. Similar to recent approaches in mental health research (Fried, 2022), we propose that sensory hypersensitivity should be seen as a complaint that results from complex within-person interdependent biopsychosocial processes. In the previous paragraphs we discussed different types of mechanisms (behavioural, neural, psychosocial) separately. However, isolated study of particular mechanisms of post-injury sensory hypersensitivity can result in explanatory reductionism (Borsboom et al., 2019). Indeed, psychological mechanisms (e.g., a post-traumatic stress response) have cognitive and neural consequences and, vice versa, cognition and psychological functioning are dependent on neurological substrates (Driscoll et al., 2012; Günther et al., 2022; Sagnier et al., 2019; Stark et al., 2015). Importantly, the complex interplay between biopsychosocial processes should not be considered stable, as, for instance, neural mechanisms might be highly influential initially after brain injury, while psychosocial mechanisms could gain in importance in the subacute and chronic stages after brain injury. In addition, the underlying mechanisms do not only interact with one another but possibly also with sensory hypersensitivity, as a bidirectional relationship between sensory hypersensitivity and mechanisms such as selective attention and fatigue has not been ruled out (e.g., Marzolla et al., 2023). In the future, unravelling the interdependence of different mechanisms will allow us to better understand, prevent, predict, and treat post-injury sensory hypersensitivity, as well as to build elaborate theoretical models to explain post-injury sensory hypersensitivity (for an example see Figure 2).

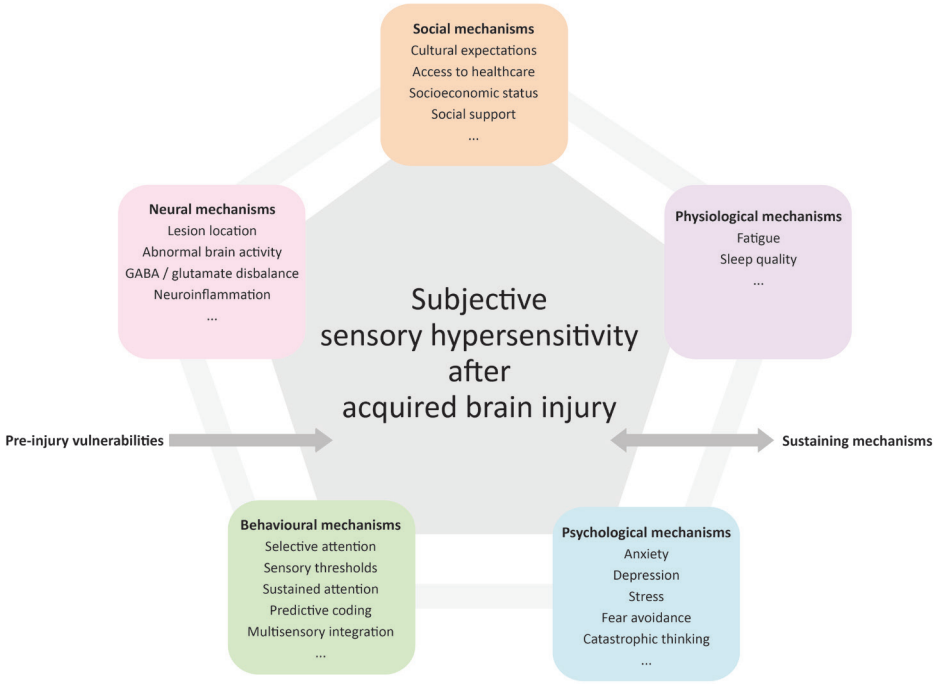


Figure 2. An example of a potential biopsychosocial model of post-injury sensory hypersensitivity. In this figure, the relationships between post-injury sensory hypersensitivity and the different mechanisms as well as the relationships between the different mechanisms are bidirectional.

Multidimensional approach to sensory hypersensitivity after acquired brain injury

Recognizing sensory hypersensitivity as a manifestation of complex interdependent biopsychosocial processes has implications for its assessment and treatment.

Multidimensional assessment

Subjective measures are often seen as less reliable than objective measures, especially in patients with cognitive difficulties. This raises the question whether or not future assessment of post-injury sensory sensitivity should progress towards objective quantifiable measures of sensory sensitivity after learning more about the underlying mechanisms of sensory hypersensitivity after acquired brain injury. We propose a multidimensional assessment of

sensory sensitivity (similar to the multidimensional assessment of pain published by Wideman et al. (2019)) where the subjective experience of sensory sensitivity is complemented by data regarding established behavioural, neural, and psychosocial correlates. This does not mean that the validation of the subjective experience should be sought through identification of potential mechanisms: subjective, behavioural, and neural sensory sensitivity should be seen as different processes that might or might not be related within a single individual. Furthermore, failure to consider an individual's subjective experience could lead to important risks such as causing patient distress, degrading therapeutic alliance, and undermining patient autonomy, and compassion-based care (Wideman et al., 2019). During a multi-modal assessment of sensory sensitivity, clinicians and researchers would integrate the subjective experience of sensory sensitivity with other biopsychosocial mechanisms (see Figure 2) through, for instance, (computerized) assessment investigating both lower-level sensory processing abilities and higher-level cognitive functions, neuroimaging (e.g., indirect measures of functional and structural connectivity), physiological measures of stress and hyperarousal (e.g., cortisol levels, heart rate, skin conductance), as well as patient-friendly questionnaires and structured interviews assessing psychosocial influences. Such a comprehensive assessment can help clinicians identify why a certain patient experiences post-injury sensory sensitivity (by uncovering potential underlying mechanisms in the individual patient), determine the severity of the sensory sensitivity, and identify factors that might exacerbate and alleviate symptoms. Taken together, this approach, can aid clinicians to decide whether treatment is needed, and to tailor treatment towards the individual person.

Treatment of sensory hypersensitivity after acquired brain injury

A multidimensional assessment that considers patient-specific underlying mechanisms of post-injury sensory hypersensitivity can facilitate patient-tailored rehabilitation. However, as research on the treatment of sensory hypersensitivity after acquired brain injury is limited, and since the different underlying mechanisms of sensory hypersensitivity and their interdependence still need to be identified, we can only speculate about appropriate treatment strategies. The systematic review in Chapter 2 identified that research regarding the treatment of sensory hypersensitivity, to date, mainly focused on the use of tools (i.e., coloured glasses, contact lenses) to minimize sensory hypersensitivity in an experimental context (in the presence of an observer) (Clark et al., 2017; Mansur et al., 2018; Truong et al., 2014). The ecological validity of these tools, as well as their long-term impact, remain unknown. One study by Hallberg et al. (2005) focused on a psychological intervention that consisted of a combination of gradual desensitization and cognitive behavioural therapy. Even though this treatment resulted

in a self-reported decrease in sensory hypersensitivity-related disabilities, considerable methodological limitations (e.g., the study did not include a control group, a quantitative outcome measure, or follow-up assessments) restrict the validity of these results. Seeing that sensory hypersensitivity possibly depends on a complex interplay between biopsychosocial mechanisms, it is essential to investigate treatment strategies at multiple levels (see Figure 2). For instance, in the long term, treatments could consist of a combination of psychological (e.g., cognitive behavioural therapy targeted towards gradual exposure to sensory stimuli and coping, relaxation techniques), neurobiological (e.g., transcranial magnetic stimulation, medication), and cognitive (e.g., the use of cognitive compensatory strategies) therapies targeted towards an individual patient.

Outstanding questions

It is evident that there are still a lot of unknowns regarding the underlying mechanisms, assessment, and treatment of sensory hypersensitivity after acquired brain injury. In addition to these questions specific to the acquired brain injury population, broader questions regarding the concept of sensory hyposensitivity and the transdiagnostic value of sensory hypersensitivity need to be answered.

What is sensory hyposensitivity?

The systematic review in Chapter 2 focused on both sensory hyper- and hyposensitivity while the rest of the thesis focused on sensory hypersensitivity. Sensory hyposensitivity (a reduced sensitivity to sensory stimuli) is hard to differentiate from common brain injury symptoms such as motor disabilities (e.g., hemiparesis) (Lawrence et al., 2001; Wallen et al., 2001), sensory difficulties (e.g., hemispatial neglect, hemianopia) (Esposito et al., 2021; Goodwin, 2014), or motivation impairments (e.g., apathy) (Worthington & Wood, 2018). Sensory hyposensitivity is mainly described in individuals with autism spectrum disorder and is operationalized as a desire to stimulate the senses by performing sensory-motor repetitions such as repeatedly spinning around or flicking your fingers in front of your eyes (Kuiper et al., 2019). In autism spectrum disorder, there is evidence that sensory hypo- and hypersensitivity are present within the same individuals (Sapey-Triomphe et al., 2018). However, more research is needed to check whether hyposensitivity is present to the same extent in other clinical groups as well as how these symptoms should be defined and assessed in an acquired brain injury population (in order to differentiate them from other common motor, sensory, and motivational impairments after brain injury).

Is sensory hypersensitivity a transdiagnostic symptom?

Sensory hypersensitivity occurs in various populations, including acquired brain injury patients, neurotypical individuals, and different clinical groups (e.g., autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), schizophrenia, Tourette syndrome) (Bijlenga et al., 2017; Dixon et al., 2016; Greven et al., 2019; Isaacs & Riordan, 2020; Kamath et al., 2020; Tavassoli, Hoekstra et al., 2014; Weiland et al., 2020; Zhou et al., 2020). However, the definition, assessment, and research methods used to study sensory hypersensitivity vary significantly among these groups (see Chapter 1; Ward, 2019), making it unclear whether sensory hypersensitivity is expressed similarly across groups (e.g., do different sensory sensitivity questionnaires measure a similar latent construct? Does sensory hypersensitivity even refer to the same latent construct in different populations?) as well as whether there are similarities across groups in the underlying mechanisms of sensory hypersensitivity. To address these questions, future research should employ identical questionnaires, behavioural assessments, and neural paradigms across different populations to study the equivalence of the subjective experience and identify commonalities and differences in its underlying mechanisms. For instance, we found evidence that the multiple-choice items of the MESSY measure the same latent construct in neurotypical adults and adults with acquired brain injury (Chapter 3). It would be valuable to investigate whether the MESSY also shows measurement equivalence across other clinical groups (such as adults with autism spectrum disorder, ADHD, or Tourette syndrome) and shows a similar relationship to selective attention and sensory thresholds measured using a TVA-based assessment. We advocate for transdisciplinary research to undertake a comprehensive, multi-level approach to sensory hypersensitivity across different populations. This approach is essential to comprehend the complexity of this subjective symptom, to advance scientific knowledge, and to improve clinical practice.

Conclusion

This thesis has made noteworthy theoretical and clinical contributions by improving the assessment of sensory hypersensitivity after acquired brain injury and providing evidence for a relationship between subjective, behavioural, and neural sensory sensitivity. Additionally, through outreach projects (for an overview see pages 282 and 283), we raised awareness about post-injury sensory hypersensitivity as well as combated misinformation by providing accessible, evidence-based information. Although, future work is needed, this thesis has the potential to pave the way for future research and improved care of patients with sensory hypersensitivity after acquired brain injury.

Supplementary materials

Chapter 2: Sensory sensitivity after acquired brain injury: a systematic review

The supplementary materials for Chapter 2 are available via:
https://doi.org/10.6084/m9.figshare.14785293.v2

Chapter 3: The Multi-Modal Evaluation of Sensory Sensitivity (MESSY): assessing a commonly missed symptom of acquired brain injury

The supplementary materials for Chapter 3 are available via:
https://doi.org/10.6084/m9.figshare.23433972.v1

Chapter 5: Why am I overwhelmed by bright lights? The behavioural mechanisms of post-stroke visual hypersensitivity

Supplementary Table 1. Results of Kruskal-Wallis Tests that examine if there is a difference in TVA performance between the four target positions per exposure duration and per group.

Exposure duration	Neurotypical adults		Orthopedic patients		Stroke patients	
	X^2	*p* value	X^2	*p* value	X^2	*p* value
Whole Report						
17ms	7.39	.97	3.48	1	.67	1
33ms	1.55	1	9.03	.49	11.86	.14
50ms	4.09	1	6.14	1	6.09	1
83ms	1.85	1	1.88	1	2.33	1
100ms	.53	1	6.99	1	4.36	1
Partial Report						
83ms	3.15	1	3.65	1	2.79	1

The degree of freedom for all Kruskal-Wallis Tests were 3. *P* values were adjusted for multiple comparisons.

Supplementary Table 2. The reasons why participants did not complete the TVA-based assessment.

	Neurotypical adults	Orthopedic patients	Stroke patients
Dropout (e.g., due to hospital dismissal)	1	0	63
COVID-19 isolation	14	0	1
Technical error	0	0	12
Asked to quit (due to fatigue, finding the task too difficult or boring)	5	7	31
Colour discrimination difficulties	0	0	1
Expression deficits	0	0	4
Total number of participants	20	7	112

Supplementary Analysis 1

The relationship between eye movements and TVA parameters

To examine the relationship between eye movements outside of a region of central fixation and TVA performance we fitted simple regression models with the TVA parameters as dependent variables and the percentage of trials with eye movements as an independent variable. Firstly, during the preprocessing of the eyetracking data we deleted trials in which more than 30% of the eye samples recorded during target presentation were missing. We then calculated the distance between the centre of the screen and each eye sample using the Pythagorean theorem[11] to determine whether there were any eye movements (of at least 10ms) outside of a circle of 1.2 visual degrees around central fixation (to avoid that any part of the target stimuli was inside the region of fixation). Finally, we divided the number of trials with eye movements by the total number of trials remaining after preprocessing. Since the assumption of normal distribution of the errors was violated and to limit the influence of outliers we conducted robust regressions (Field & Wilcox, 2017).

We recorded the eye movements of 41 neurotypical adults, 55 orthopedic patients, and 11 stroke patients. Across participants, eye tracking data was missing on average in 32% (standard deviation: 30%) of the trials. Across participants, eye movements of more than 10ms outside of the central fixation region were recorded on average in 44% (standard deviation: 36%) of the trials. There was no evidence that the proportion of trials with eye movements outside of the central fixation region (of at least 10ms) predicted the estimated TVA parameters (adjusted p value > .05) in the neurotypical adults, orthopedic, and stroke patients.

[11] *The distance between two points is computed using Pythagorean Theorem:*

$$\sqrt{|X_{point1} - X_{point2}|^2 + |y_{point1} - y_{point2}|^2}$$

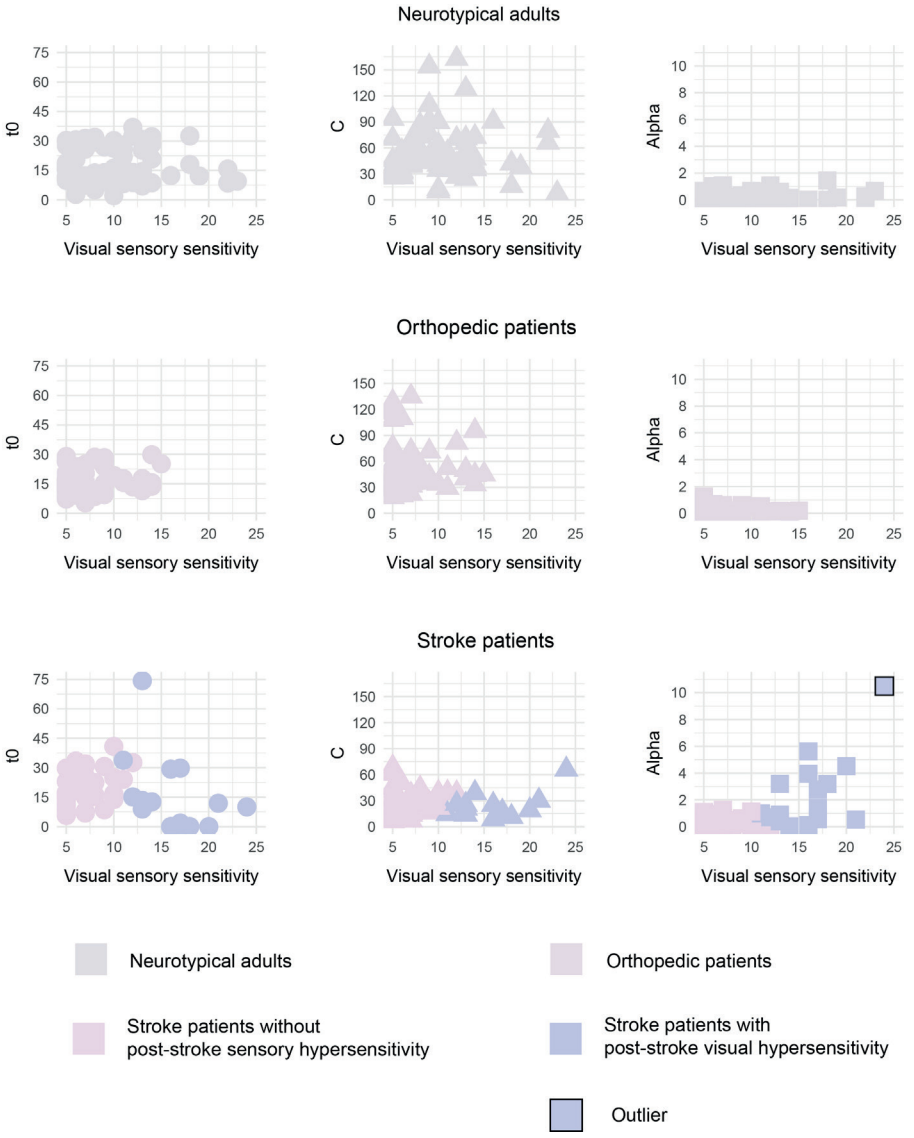
Supplementary Analysis 2

The relationship between the TVA parameters and sensory sensitivity

We examined whether sensory thresholds (t0), sensory processing efficiency (C), and selective attention (alpha) predicted the severity of subjective visual sensitivity (i.e., the score for the multiple-choice items of the visual subscale of the MESSY) by conducting multiple regressions in all stroke patients (pooled across patients with and without post-stroke sensory hypersensitivity), orthopedic patients, and neurotypical adults. To control for the potential impact of demographic variables (age, gender, and education level) these variables were added to the regression analyses. Since the assumption of normal distribution of the errors was violated and to limit the influence of outliers we conducted robust regressions (Field & Wilcox, 2017). There was no evidence for a violation of the assumptions of multicollinearity or homogeneity (checked via the Breusch-Pagan Test) (Breusch & Pagan, 1979). The variables gender and education level were dummy coded with men and lower education (individuals with maximally a high school diploma) as reference categories.

A robust multiple regression indicated that, across all stroke patients, visual sensory sensitivity had a positive relationship with the alpha values after controlling for the influence of t0, C, and the demographic variables (see Supplementary Figure 1, for details see Supplementary Table 3)[12] . There was no evidence for a relationship between visual sensory sensitivity and the other TVA parameters (t0, C) in the stroke patients and between visual sensory sensitivity and all TVA parameters in the neurotypical adults and orthopedic patients. The regression model that included both demographic variables and the TVA parameters explained a significant amount of the variance in visual sensory sensitivity in the stroke patients ($R_{adjusted}$ = .75). This proportion of explained variance dropped to .23 when removing the TVA parameters from the regression model.

[12] *This relationship remained significant after removing the stroke patients with an alpha value above [10] (see the purple cube with a black outline in Supplementary Figure [1]).*



Supplementary Figure 1. Scatterplots visualizing the relationships between visual sensory sensitivity and t0, C, and alpha in neurotypical adults, orthopedic patients, and stroke patients (with and without post-stroke sensory hypersensitivity).

Supplementary Table 3. Multiple regressions investigating the relationship between visual sensory sensitivity and the TVA parameters (t0, C, alpha) in neurotypical adults, orthopedic patients, and stroke patients.

	β	95% Confidence interval	Standard Error	t	Adjusted p
Neurotypical adults					
Intercept	10.63	[5.68 ; 15.58]	2.48	4.28	< .01
Gender	2.52	[.89 ; 4.14]	.82	3.09	.05
Age	-.05	[-.11 ; .01]	.03	-1.71	1
Education level	-.65	[-2.63 ; 1.33]	.99	-.66	1
t0	.01	[-.10 ; .13]	.06	.20	1
C	.003	[-.03 ; .03]	.01	.20	1
Alpha	2.43	[-1.21 ; 6.08]	1.83	1.33	1
Orthopedic patients					
Intercept	6.70	[1.58 ; 11.83]	2.57	2.61	.17
Gender	.04	[-.81 ; .90]	.43	.10	1
Age	.002	[-.07 ; .07]	.03	.05	1
Education level	-.66	[-1.55 ; .22]	.45	-1.49	1
t0	.04	[-.04 ; .12]	.04	.98	1
C	-.01	[-.03 ; .01]	.01	-1.20	1
Alpha	-.88	[-2.90 ; 1.14]	1.01	-.87	1
Stroke patients					
Intercept	12.85	[8.87 ; 16.84]	1.98	6.5	< .01
Gender	.67	[-.99 ; 2.33]	.82	.81	1
Age	-.10	[-.14 ; -.06]	.02	-4.84	< .01
Education level	2.87	[1.03 ; 4.71]	.91	3.14	.05
t0	.004	[-.05 ; .06]	.03	.14	1
C	-.02	[-.06 ; .02]	.02	-1.21	1
Alpha	1.75	[1.42 ; 2.07]	.16	10.90	< .01

P values were adjusted using the Holm-Bonferroni method (Holm, 1979).

Chapter 7: Unravelling the neural basis of sensory hypersensitivity after stroke: evidence from lesion-symptom and structural disconnection mapping

Supplementary Table 1. Results of the logistic regression models examining the association between tract disconnection and post-stroke sensory hypersensitivity.

Tract name	Number of patients with a disconnection in the specified tract (%)		Odds ratio	95% CI
	Without SH (n = 54)	With SH (n = 49)		
Anterior Thalamic Projections				
Left	39%	37%	.91	[.41 ; 2.07]
Right	43%	41%	.93	[.42 ; 2.04]
Arcuate Fasciculus - Anterior Segment				
Right	39%	13%	.57	[.23 ; 1.30]
Arcuate Fasciculus – Long Segment				
Right	41%	24%	.47	[.20 ; 1.09]
Arcuate Fasciculus – Posterior Segment				
Right	30%	16%	.46	[.17 ; 1.18]
Cingulum				
Left	26%	20%	.73	[.28 ; 1.83]
Right	31%	16%	.43	[.16 ; 1.07]
Anterior Cingulum				
Right	28%	14%	.43	[.15 ; 1.14]
Posterior Cingulum				
Right	17%	6%	.33	[.07 ; 1.17]
Corpus Callosum	85%	69%	.39	[.14 ; 1.01]
Frontal Commissural Tract	59%	49%	.66	[.30 ; 1.44]
Fronto-inferior Longitudinal Tract				
Right	19%	18%	.99	[.36 ; 2.70]

Tract name	Number of patients with a disconnection in the specified tract (%)		Odds ratio	95% CI
	Without SH (n = 54)	With SH (n = 49)		
Fronto-superior Longitudinal Tract				
Left	9%	6%	.64	[.13 ; 2.75]
Right	19%	16%	.86	[.30 ; 2.39]
Fronto-orbito Polar Tract				
Right	11%	10%	.91	[.25 ; 3.22]
Fronto-Insular Tract 5				
Right	31%	31%	.96	[.41 ; 2.22]
Fronto-Striatal Projections				
Left	35%	35%	.98	[.43 ; 2.21]
Hand Inferior U tract				
Right	28%	12%	.36	[.12 ; .99]
Hand Middle U tract				
Right	22%	8%	.31	[.08 ; .97]
Hand Superior U tract				
Left	9%	4%	.42	[.06 ; 2.04]
Right	20%	12%	.55	[.17 ; 1.57]
Inferior Fronto-occipital Fasciculus				
Right	39%	29%	.63	[.27 ; 1.43]
Inferior Longitudinal Tract				
Left	20%	20%	1	[.38 ; 2.63]
Right	30%	27%	.86	[.36 ; 2.03]
Fronto-pontine projections				
Left	43%	41%	.93	[.42 ; 2.04]
Right	50%	47%	.88	[.41 ; 1.92]

Superior Longitudinal Fasciculus 3				
Left	30%	27%	.86	[.36 ; 2.03]
Right	44%	39%	.79	[.36 ; 1.74]
Superior Longitudinal Fasciculus 2				
Left	26%	24%	.93	[.38 ; 2.26]
Right	43%	31%	.59	[.26 ; 1.33]
Superior Longitudinal Fasciculus 1				
Left	19%	12%	.61	[.19 ; 1.80]
Right	33%	22%	.58	[.24 ; 1.38]
Uncinate Fasciculus				
Right	19%	18%	.99	[.36 ; 2.70]

Left: left-hemispheric. Right: right-hemispheric. For more information on the location of the specific tracts see Rojkova et al. (2016). The results in this table are limited to white matter tracts that were disconnected less or equally frequent in patients with post-stroke sensory hypersensitivity as compared to patients without post-stroke sensory hypersensitivity.

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Published journal articles

Thielen, H., Huenges Wajer, I. M. C., Tuts, N., Welkenhuyzen, L., Lafosse, C., & Gillebert, C. R. (2023). The Multi-Modal Evaluation of Sensory Sensitivity (MESSY): Assessing a commonly missed symptom of acquired brain injury. *The Clinical Neuropsychologist*, 1–35. https://doi.org/10.1080/13854046.2023.2219024

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Submitted journal articles

Thielen, H., Welkenhuyzen, L., Tuts, N., Vangkilde, S., Lemmens, R., Wibail, A., Lafosse, C., Huenges Wajer, I.M.C., & Gillebert, C.R. (2023). Why am I overwhelmed by bright lights? The behavioural mechanisms of post-stroke visual hypersensitivity. Manuscript submitted for publication.

Thielen, H., Tuts, N., Welkenhuyzen, L., Lemmens, R., Wibail, A., Huenges Wajer, I.M.C., Lafosse, C., Mantini, D., & Gillebert, C.R. (2023). Unravelling the neural basis of sensory hypersensitivity after stroke: evidence from lesion-symptom and structural disconnection mapping. Manuscript submitted for publication.

Conference contributions

Thielen, H., Welkenhuyzen, L., Tuts, N., Huenges Wajer, I., Lafosse, C., Gillebert, C. (2022). Assessing sensory sensitivity after acquired brain injury: the Multi-Modal Evaluation of Sensory Sensitivity (MESSY). Presented at the 19th NR-SIG-WFNR Conference, Maastricht, The Netherlands, October 2022.

Thielen, H., Tuts, N., Welkenhuyzen, L., Huenges Wajer, I., Lafosse, C., Lemmens, R., Wibail, A., Gillebert, C. (2022). The Multi-Modal Evaluation of Sensory Sensitivity (MESSY): how to assess a commonly missed stroke symptom. Presented at the 2022 International Neuropsychological Society Mid-Year Meeting, Barcelona, Spain, July 2022.

Thielen, H., Welkenhuyzen, L., Tuts, N., Huenges Wajer, I., Lafosse, C., Gillebert, C. (2022). Normative data and validation of the Multi-Modal Evaluation of Sensory Sensitivity (MESSY). Presented at the Annual Meeting of the Organisation for Psychological Research into Stroke in the Lowlands, Leuven, Belgium, May 2022.

Thielen, H., Tuts, N., Welkenhuyzen, L., Huenges Wajer, I., Lafosse, C., Gillebert, C. (2021). Atypical subjective sensory sensitivity after acquired brain injury: insights on the underlying mechanisms, prevalence and treatment. Presented at the European Congress of NeuroRehabilitation 2021, Virtual meeting, December 2021.

Thielen, H., Tuts, N., Lafosse, C., Gillebert, C. (2021). Sensory hypersensitivity after stroke: insights from a systematic review and case representations. Presented at the Belgian Stroke Scientific Workshop, Brussels, Belgium, September 2021.

Thielen, H., Welkenhuyzen, L., Tuts, N., Lafosse, C., Lemmens, R., Wibail, A., Gillebert, C. (2021). Multi-modal evaluation of sensory sensitivity after stroke: how to assess a commonly missed stroke symptom. Presented at the Annual Meeting of the Organisation for Psychological Research into Stroke, Virtual meeting, September 2021.

Thielen, H., Welkenhuyzen, L., Tuts, N., Lemmens, R., Wibail, A., Lafosse, C., Gillebert, C. (2021). The Multi-modal Evaluation of Sensory Sensitivity: a questionnaire to assess post-stroke sensory hypersensitivity. Presented at the The 7th European Stroke Conference, Virtual meeting, September 2021.

Thielen, H., Welkenhuyzen, L., Lafosse, C., Gillebert, C. (2020). Sensorische sensitiviteit na een niet-aangeboren hersenletsel. Presented at the Translation meeting on sensory sensitivity organized by the University of Maastricht, Virtual meeting, November 2020.

Thielen, H., Welkenhuyzen, L., Lemmens, R., Wibail, A., Lafosse, C., Gillebert, C. (2020). Stroke survivors experience a reduced quality of life as a result of atypically high sensory sensitivity. Presented at the Leuven Brain Institute Scientific Meeting, Leuven, Belgium. November 2020.

Thielen, H., Welkenhuyzen, L., Lemmens, R., Wibail, A., Lafosse, C., Gillebert, C. (2020). Post-stroke atypical sensory sensitivity is a clinically important symptom. Presented at the Belgian Stroke Scientific Workshop, Gent, Belgium, September 2020.

Thielen, H., Lafosse, C., Gillebert, C. (2020). Post-stroke sensory sensitivity reduces quality of life: exploratory data. Presented at the International Neuropsychological Society Mid-year conference, Virtual meeting, July 2020.

Thielen, H., Verleysen, G., Huybrechts, S., Lafosse, C., Gillebert, C. (2019). Age-associated verbal memory impairment differs according to education level. Presented at the 7th Meeting of the Federation of the European Societies of Neuropsychology (FESN), Milan, Italy, September 2019

Thielen, H., Verleysen, G., Huybrechts, S., Lafosse, C., Gillebert, C. (2019). Verbal memory performance in the Flemish population: normative data for the Buschke Selective Reminding Test. Presented at the Annual Meeting of the Belgian Association for Psychological Sciences (BAPS) 2019, Liège, Belgium, May 2019.

Thielen, H., Van der Donck, S., Vettori, S., Dzhelyova, M., Steyaert, J., Rossion, B., Boets, B. (2018). Investigating emotional face processing in children with autism using fast periodic visual stimulation EEG. Presented at the BAPS 2018, Gent, Belgium, May 2018.

List of outreach activities

Outreach presentations regarding post-injury sensory hypersensitivity

Table 1. Overview of outreach presentations ordered chronologically.

Place	Targeted audience	Date
University Hospital UZ Leuven (Campus Pellenberg)	Brain injury patients and their family members	11/3/2019
RevARte Rehabilitation Hospital	Healthcare professionals, brain injury patients and their family member	14/03/2019
Hospital of East-Limburg	Healthcare professionals	01/04/2019
RevARte Rehabilitation Hospital	Healthcare professionals	22/10/2019
RevARte Rehabilitation Hospital	Healthcare professionals	4/11/2019
University of Maastricht	Healthcare professionals	12/11/2020
Hospital of East-Limburg	Healthcare professionals	08/03/2021
RevARte Rehabilitation Hospital	Healthcare professionals	22/06/2021
PraxisP, Practice Center of the Faculty of Psychology and Educational Sciences (KU Leuven)	General public, healthcare professionals, brain injury patients and their family member	23/02/2022
RevARte Rehabilitation Hospital	Healthcare professionals	10/03/2022
Hospital of East-Limburg	Brain injury patients and their family members	17/05/2022

National Conference about acquired brain injury (NAH-congres, Beveren-Waas)	Healthcare professionals, brain injury patients and their family members	11/10/2022
University Hospital UZ Leuven (Campus Pellenberg)	Brain injury patients and their family members	14/03/2023
University Hospital UZ Leuven (Campus Gasthuisberg)	Healthcare professionals	02/05/2023
Artevelde University of Applied Sciences	Healthcare professionals	04/05/2023
RevArte Rehabilitation Hospital	Brain injury patients and their family members	27/05/2023
National Conference about sensory hypersensitivity (Nationaal Congres Overprikkeling, Zeist)	General public, healthcare professionals, brain injury patients and their family members	22/06/2023
Heilig-Hart Hospital Lier	Healthcare professionals, brain injury patients and their family members	12/10/2023
General Hospital Brugge	Healthcare professionals, brain injury patients and their family members	27/10/2023

Published outreach materials regarding post-injury sensory hypersensitivity

Table 2. Overview of published outreach materials ordered chronologically.

Type of material	Targeted audience	Date published
Informational brochure	Brain injury patients and their family members	7/07/2021
Infographic	Brain injury patients and their family members	23/06/2022
Informational brochure	Healthcare professionals	6/10/2022