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Department of General Psychology

**Bachelor's Degree Course in Techniques and Methods in Psychological
Science**

Final dissertation

**A cumulative approach to lesion mapping:
insights from optic ataxia**

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ABSTRACT

Optic ataxia is a rare neuropsychological disorder, characterized by deficits in visually guided reaching movements, typically associated with posterior parietal cortex lesions. From a neuroanatomical standpoint, optic ataxia has been extensively studied, however lesion data remain fragmented in the literature. The present study aim is to address this issue, by implementing a cumulative lesion mapping approach, reconstructing lesions from published cases, using open source softwares like MRICron and MRICroGL. The dual objective is to evaluate the reliability of this manual reconstruction approach, while building a dedicated lesion dataset on optic ataxia, useful as a foundation for future research.

We selected 14 studies out of 245, with a total of 66 patients with optic ataxia. Lesions were manually copied on a standard brain template, the MNI 152. Ratings from three independent raters were collected on lesion localization, shape, and continuity, and inter-rater reliability was assessed through intraclass correlation coefficients, which showed good agreement, supporting consistency of the protocol.

Descriptive lesion overlap analysis showed a non-random distribution, with a consistent involvement of bilateral superior and middle occipital gyri, superior and inferior parietal lobules, precuneus, cuneus, and angular gyrus, all regions strongly associated with visuomotor integration.

This protocol demonstrated a replicable, low cost approach to lesion mapping that may serve as a foundational tool for future pilot studies. Also, the resulting dataset offers a valuable starting point for upcoming works on optic ataxia. Further developments may include the integration of disconnection analysis to refine our understanding of visuomotor disorders.

INTRODUCTION

1.1 Optic Ataxia

Many experiments demonstrated the existence of two divergent visual pathways, each one with its specific function: the processing of “where” and the processing of “what”. In human beings, a neurological damage limited to a part of the posterior parietal cortex (PPC), is often associated with difficulties in directing actions toward objects in the peripheral visual field (i.e. “where”), even without any difficulty in recognizing these objects (Pisella, Rossetti & Rode, 2016).

This is a fascinating neurological deficit, also known as Optic Ataxia (OA). Patients cannot manage to reach visually guided goals in peripheral vision, even though voluntary eye movements are unaffected (Fig. 1.1). Also, primary sensory or motor deficits are not present, thus the problem is at an integrative sensorimotor level (Andersen, Andersen, Hwang & Hauschild, 2014).



FIGURE 1.1 The patient, when asked to touch the pen, misreaches it (Cogan, 1965).

Optic ataxia is considered to be one of the three defining symptoms of Balint's syndrome, first described by Rezsó Balint, in the past century, and is usually associated with major impairments in visual attention. Deficits in complex behaviors, such as reach-to-grasp or eye-hand coordination are the most common (Andersen et al., 2014).

The term *ataxia*, Greek for "lack of order", was coined by Balint himself, because he believed the deficit wasn't an apraxia, related to movement execution, but rather to a deficiency of coordination between visual input and motor output. At the beginning, OA was associated with bilateral PPC damages (Fig. 1.2), nevertheless subsequent studies have suggested that the deficit may be due to unilateral lesions and may also occur independently, in isolation from the attentional disorders typical of Balint's syndrome (Andersen et al., 2014).

In neuropsychology, brain lesions, and of course their mapping, give a key insight into the functional roles of brain areas. However, there are many negative aspects in terms of interpretation of the behavioral results and, in addition, many functional areas may be involved and there can be a large degree of variability across different patients (Andersen et al., 2014).

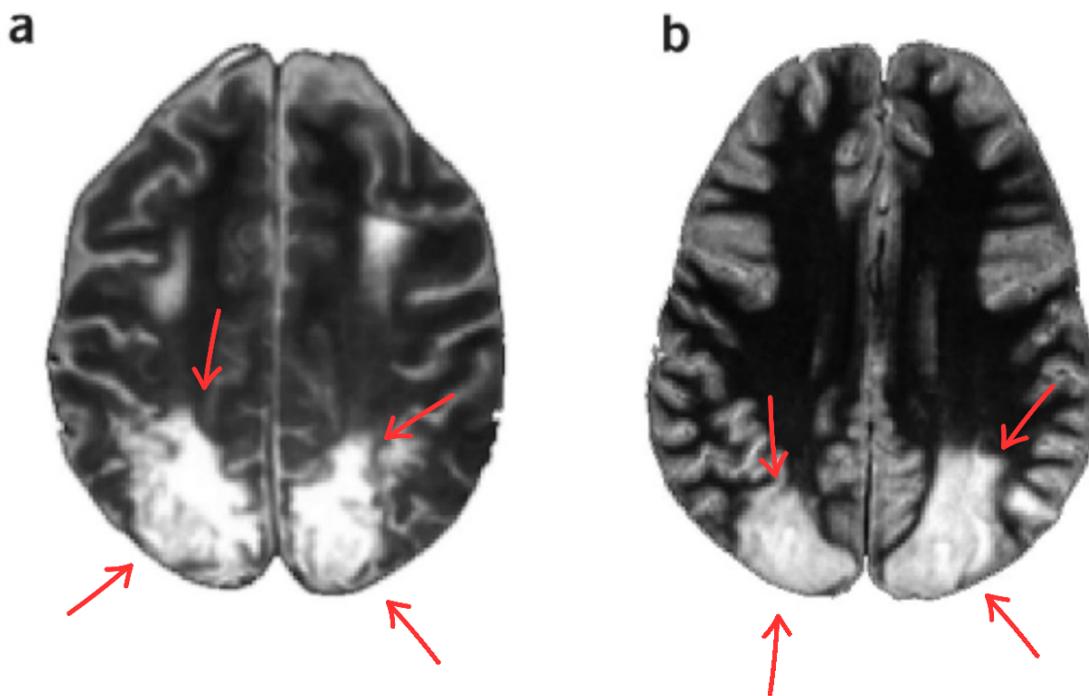


FIGURE 1.2 Bilateral posterior parietal cortex lesions, associated with OA (Schindler et al., 2004).

1.2 Lesion Mapping in Neuropsychological Research

Lesion mapping is one of the main methodologies employed by classical neuropsychologists to infer brain-behavior relationships and to build theoretical models of neurological diseases. The location of brain lesions in an individual or group of patients can be used, in combination with a statistical approach, to identify specific areas that, when damaged, lead to peculiar behavioral impairments (Moore, Demeyere, Rorden & Mattingley, 2024). In the context of neuroimaging data analysis, the brain tissue is measured in terms of voxels, and a voxel is a three dimensional unit of space (i.e. the building blocks of a 3D image) that represents a specific volume of brain tissue. When we group many voxels we identify a ROI or Region of Interest, a portion of the brain that we can then associate to specific cortical or subcortical areas.

1.2.1 Structural Lesion Mapping

For many years neuropsychologists studied brain lesions that occurred as a result of strokes, hemorrhages, or tumors and patients with overlapping lesions generally had similar symptoms, associating those specific behavioral deficits to that brain region. Traditionally, structural lesion mapping began with very simple overlays or subtraction analysis. These approaches were first applied back in the 19th century, when neuroanatomists like Broca and Wernicke discovered brain areas involved in language dysfunctions. However, with technological advancements, computational tools allowed Voxel-based Lesion-Symptom Mapping or VLSM. With this new statistical approach we are now able to test if each brain voxel, across all patients, is statistically associated with worst performance (Karnath, Sperber & Rorden, 2018). This method is useful to create statistical maps of significant voxels, identifying which anatomical areas differ between patients and control groups.

Despite a huge number of functions related to precise brain areas have been identified through these methods, nowadays the scientific community agrees that many symptoms cannot be traced back to a single region, but instead they involve a network of connected regions. Indeed, deficits may also arise if two critical regions are preserved, but disconnected (Nabizadeh & Aarabi,

2023). This refers to a complementary approach, that is structural disconnection mapping, that consists in identifying white matter pathways that may be disrupted by specific lesions. This method provides useful insights to voxel-based methods, helping to explain deficits caused by the interruption of long range connections instead of cortical damages (Joutsa, Corp & Fox, 2022).

1.2.2 Lesion Network Mapping

Recently, lesion network mapping (LNM) has emerged as a novel approach that implements traditional lesion mapping by considering the interconnected networks of the brain. With traditional lesion mapping we intend a fully structural lesion mapping, where we highlight the specific portion of brain tissue examined/damaged. Based on traditional lesion mapping, LNM provides additional information on the structural and functional brain networks, allowing us to identify common circuits associated with lesions in different areas. The assumption here is that disruptions occurring within a specific network, can lead to similar clinical symptoms, even if the lesion is in a different anatomical region (Nabizadeh et al., 2023).

The process of conducting LNM involves typically many steps:

1. Lesion identification and standardization, through delineation of lesions into a standardized brain atlas (to ensure consistency across analysis);
2. Connectivity analysis, through the use of functional or structural connectome data (like Human Connectome Project data);
3. Network mapping, by correlating lesion locations with brain connectivity patterns.

This type of methodology has been applied across several conditions (Nabizadeh et al., 2023), offering innovative possibilities to further investigate the functions of brain networks.

1.3 Modern Neuroimaging Techniques

Lesion mapping methods have been revolutionized by the advent of modern neuroimaging techniques. Technologies like computed tomography (CT) and magnetic resonance imaging (MRI) allow ‘in vivo’ visualization of brain structures with high resolution, facilitating the identification of lesions. A diagram of the main neuroimaging techniques is provided in Fig. 1.3.

We identify two main neuroimaging fields, structural and functional neuroimaging. The former refers to the analysis of anatomical structures and properties of the brain and can be useful to diagnose lesions caused, for example, by tumors. Computed tomography utilizes X-rays to visualize brain slices, however nowadays magnetic resonance imaging offers greater resolution, thanks to powerful magnets (instead of ionizing radiations). On the other hand, functional imaging allows the identification of brain processes, thanks to different recordings of neural activity. Electroencephalography (EEG), for example, identifies electrical activity, while PET measures alterations in glucose levels in response to metabolic activity, and fMRI allows to observe blood flow and blood oxygen levels (Erol & Hunyadi, 2022, chap.12).

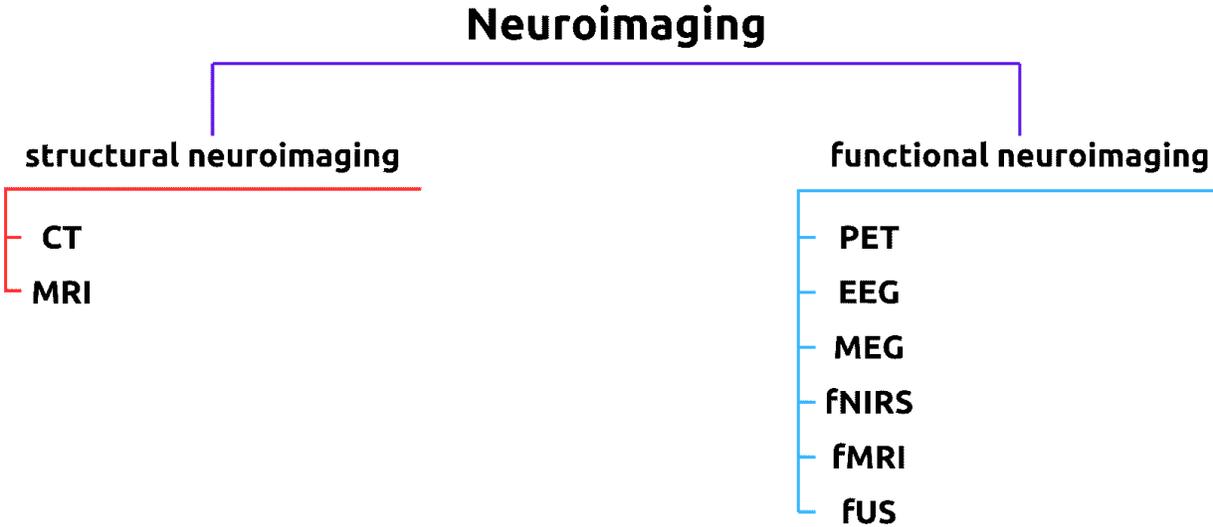


FIGURE 1.3 Neuroimaging modalities

THE PRESENT STUDY

2.1 Study Aim

Brain lesion analysis has been one of the major foundations of neuropsychological research, helping to understand the neural mechanisms underlying cognitive and motor deficits. In scientific literature, many studies present lesion data in 2D formats, from MRI or CT scans, making it difficult to infer the 3D structure lesion distribution across patients. With this study we would like to explore the potential of a new approach, using manual lesion reconstruction with MRICron as a tool to reproduce and analyze lesion data from previous studies on Optic Ataxia. The final aim is dual:

- to determine if manual lesion tracing can contribute to neuropsychological research, as a preliminary step to a more sophisticated network analysis;
- to build a reliable OA lesion database, useful in future investigations.

We chose to focus on optic ataxia because data available in the literature, despite being relatively consistent in defining anatomical correlates, still remain fragmented across different studies. This makes it suitable for testing our cumulative lesion mapping approach.

2.2 Tools and Software Used

The primary tool used in this study is MRICron, an open source software, widely employed for lesion drawing and visualization. It allows to outline lesions on a brain template, potentially enabling a standardized method to reconstruct the lesion distribution from different studies. This method is very limited in accuracy due to its manual nature, but it may provide a starting point for future improvements and advancements, like automated lesion mapping using machine learning.

2.3 Study Design in Pills

For this study we followed a structured workflow:

- 1) Systematic literature review - Selection of relevant studies reporting brain lesions in optic ataxia patients;
- 2) Lesion drawing - Manual reconstruction of lesions from MRI and CT images using MRICron;
- 3) Data analysis - Identification of frequently affected regions.

Further explanations in the 'Methods' section.

2.4 Hypothesis

Our hypothesis is that lesion reconstruction with MRICron, despite its limitations, can provide significant insights about lesion distribution patterns, helping to build a preliminary lesion database for optic ataxia. As already mentioned, with this study we want to explore in depth this new approach and assess its potential for future applications in lesion network mapping. While the identification of functional networks associated with optic ataxia remains a long term goal, this study lays the ground for future research in this direction.

METHODS

3.1 Study Design

In this study, we decided to adopt an hybrid approach, combining both a systematic review of the literature with an experimental reconstruction of brain lesions (Fig. 3.1).

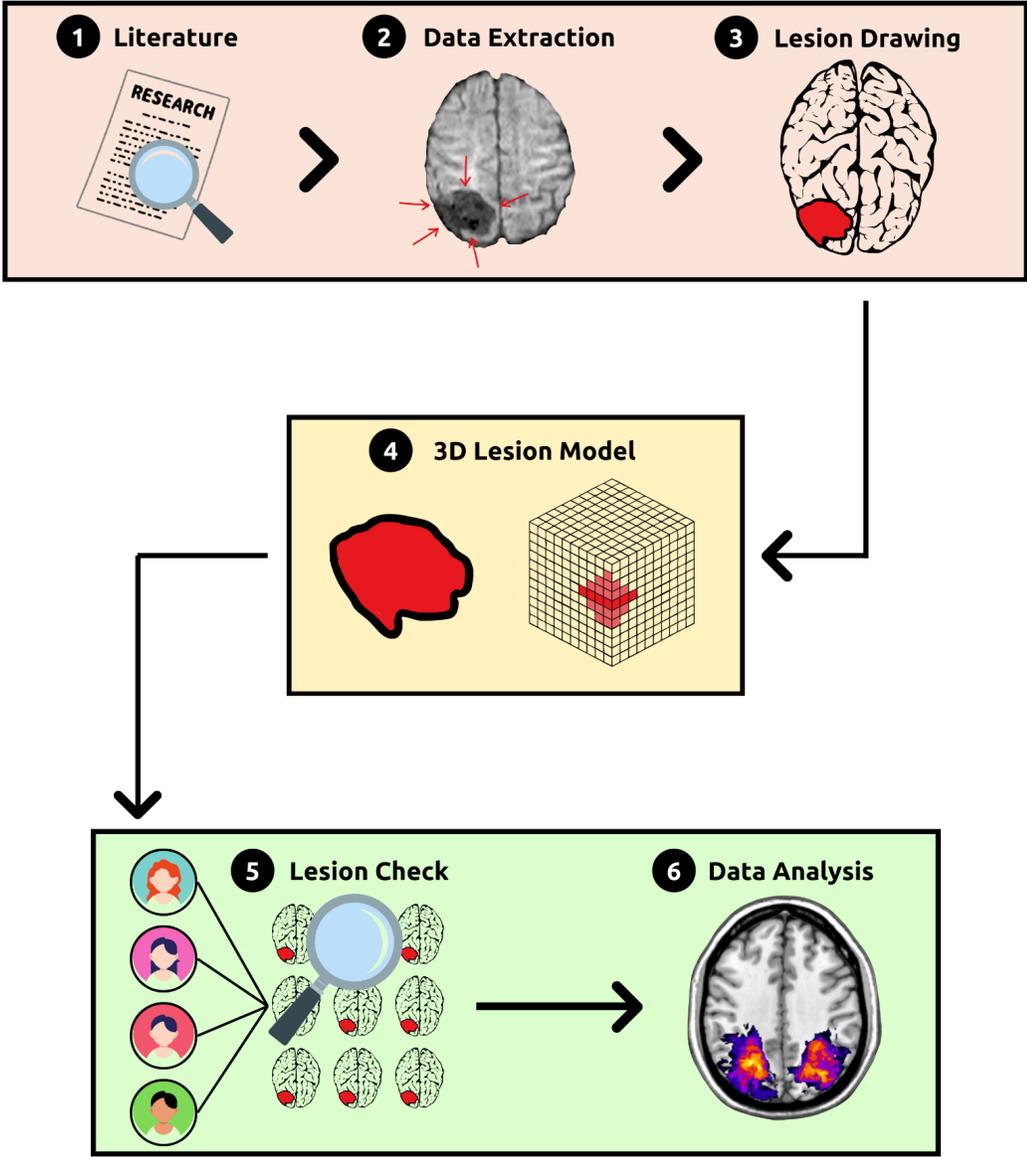


FIGURE 3.1 Study flowchart.

The main goal was to explore the many possibilities and potential applications of MRICron as a tool for manually reconstructing lesions, based on the available neuroimaging data present in previously published studies.

Following the PRISMA guideline for systematic reviews, relevant papers have been selected. The reconstructed lesions were manually drawn by undergraduate, graduate, and intern students in Psychology, Cognitive Neuroscience, and Neuropsychology programs at the University of Padua. We used MRICron as the main tool (further explanations about this software in the following paragraphs). At the end of the process, three independent raters evaluated each lesion, using Likert scales, trying to assess clarity, anatomical plausibility, and coherence with source images. This design allowed for the creation of a database of reconstructed lesions associated with optic ataxia, as the groundwork for future studies aimed at exploring more in depth the pathology and all its facets.

3.2 Systematic review

The literature review has been conducted following the PRISMA guidelines (<https://www.prisma-statement.org/prisma-2020-flow-diagram>) (Fig. 3.2). The goal was to guarantee transparency and replicability of the process. The literature search was carried out with PubMed, using the following search query: “(optic ataxia [Title/Abstract]) OR (optic ataxic [Title/Abstract])” and 245 studies were identified from 1967 to 2023. Only peer-reviewed studies that included clear neuroimaging images providing enough anatomical detail to allow lesion reconstruction were considered for the evaluation.

Starting from the initial 245 publications identified through the literature search, only 14 were selected. The primary reasons for exclusion were the following:

1. **Lack of MRI T1, MRI T2 or CT scans (87 studies):** these studies did not include essential neuroimaging scans needed for lesion mapping.
2. **Single patient studies (42):** this study focused only on group patients studies, thus single patient studies were eliminated from the pool.

3. **Studies containing only healthy subjects (19):** some studies's participants were healthy subjects. As the aim of study was to analyze brain lesions specific to optic ataxia, those were excluded.
4. **Same patient data in different studies:** after revision of patient demographics, clinical data, and neuroimaging scans, some studies were found to use the same patients. The most comprehensive data was used after the elimination of duplicates.
5. **Non-human studies (6)** were excluded to ensure focus on human subjects, as optic ataxia is a neurological disorder in humans.
6. **Access issues (30)** prevented including studies with unavailable data, ensuring a complete review.
7. **Other languages (5)** were excluded to avoid misinterpretations or biases from translation challenges.
8. **Unclear or Poor-Quality Neuroimaging (17)** studies were excluded because high-quality imaging is essential to accurately assess brain regions involved in optic ataxia.
9. **Unrelated or different pathologies (4):** we included only studies that reported patients with OA following focal lesions (i.e. strokes, tumors, etc) excluding patients with OA due to other pathologies or etiologies (e.g. neurodegenerative pathologies)
10. **Irrelevant participants (7):** studies involving only healthy individuals, children, or conditions unrelated to optic ataxia were excluded to focus solely on patients with optic ataxia.

All studies in our final database had structural neuroimaging data, with both cortical and subcortical representations. As the systematic review was part of an internship program within the University of Padua, people involved in collecting the initial data were substantially different from

those who drew and cross checked the lesions. However, consensus about content was reached every time, before proceeding with the following step.

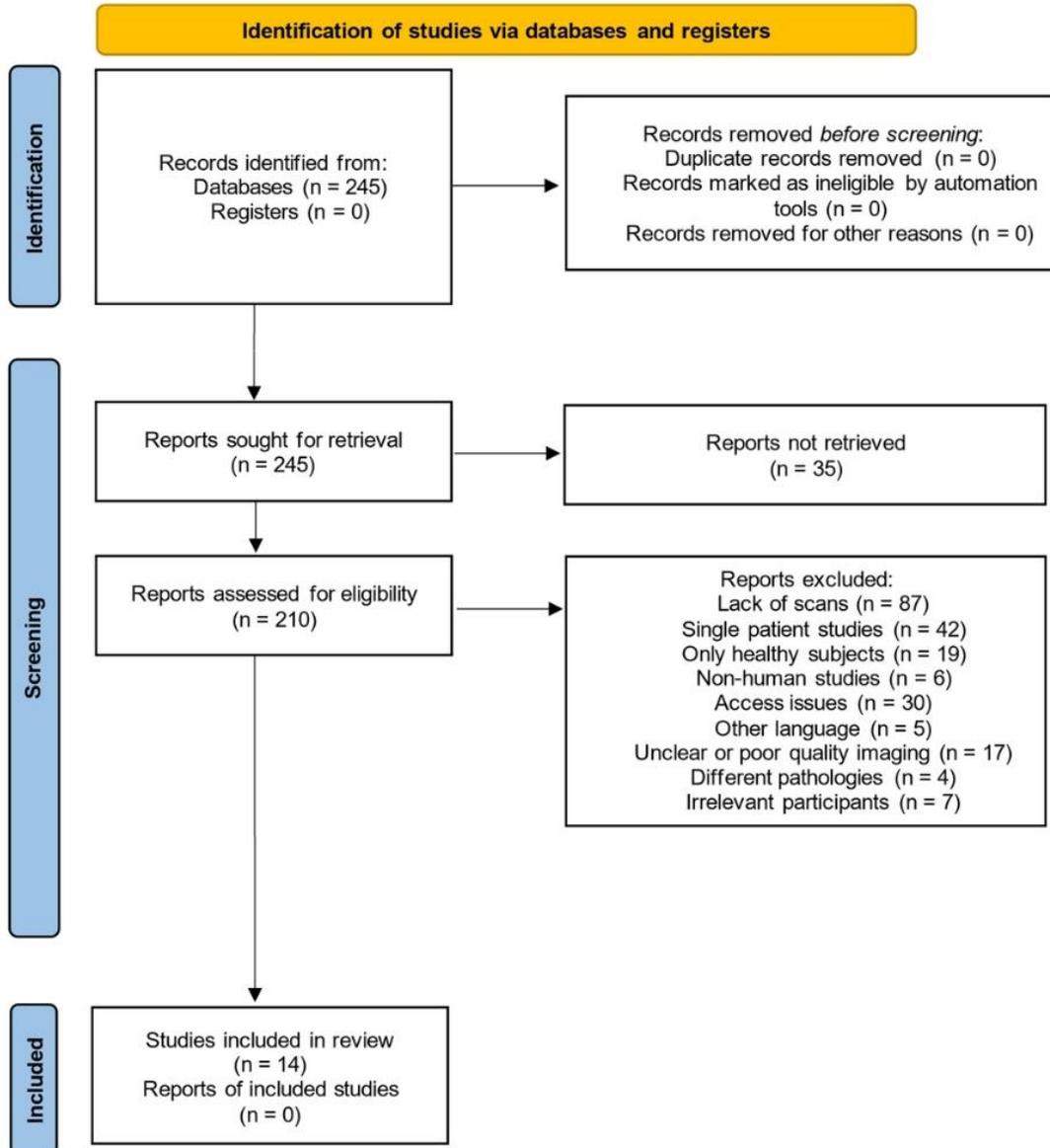


FIGURE 3.2 PRISMA Flow Diagram for Inclusion and Exclusion of Studies on Optic Ataxia Database

3.3 Lesion Mapping and Drawing Process

The lesion mapping process was possible thanks to the imaging software tools MRICron and its new version MRICroGL. Consistency for cross-subject comparison was ensured through the use of a standard brain template, the *MNI 152* (Fig. 3.3).

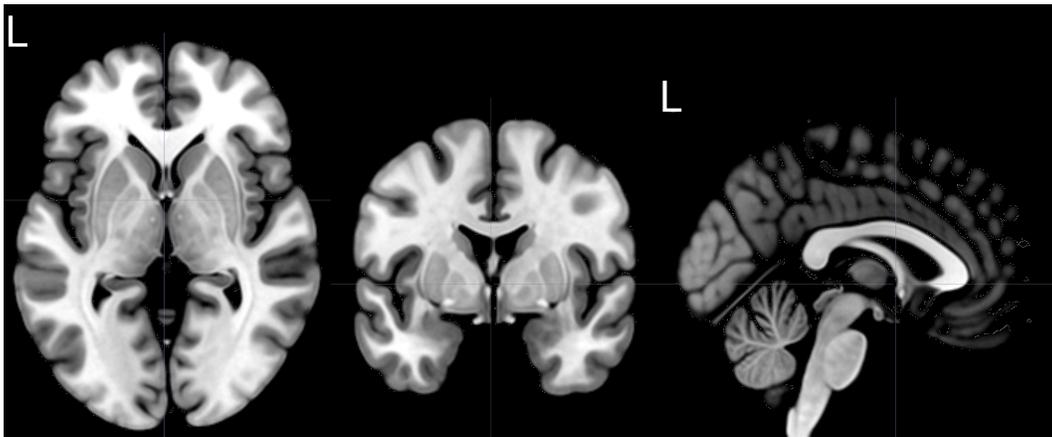


FIGURE 3.3 Montreal Neurological Institute's 152 brain template (from MRICroGL).

Lesions were manually drawn copying on the corresponding axial slice data from the selected studies, including MRI-base templates (sMRI), individual MRI, and CT scans. To approximate the three dimensional extension of the lesion, five additional slices were added above and below the first. With each additional slice the lesion area was progressively reduced, trying to provide a more realistic 3D volume of the 2D image data. Each lesion then underwent axial interpolation to fill the spatial gaps between slices, creating a continuous and coherent lesion. To further improve reliability, reducing individual biases, each lesion was independently evaluated by three raters, using Likert scales on many factors such as anatomical plausibility, lesion boundaries, and overall reconstruction. Low quality or inconsistent ratings were reviewed, discussed among raters, and redrawn when necessary. After this internal review, all files were submitted and checked by project supervisors, for further evaluation. This multi step approach guaranteed the creation of a dataset, with an overall good quality. Right now, this novel approach is not perfect and still has many flaws that decrease both replicability and reliability, but this is just a first step.

3.3.1 Lesion Drawing

The procedure that has been followed to reproduce every lesion is very simple. As Figure 3.4 shows, the first step was the identification of the lesions in the original brain scan, retrieved from the literature database. Each student proceeded to interpret the MRI/CT scan by oneself, trying to manually reproduce each slice on the MNI 152 template. If multiple slices were given by the paper, each one was then drawn on the same template. Finally, an additional slice was added above and below the last one, reducing its area, to provide a 3D-like shape.

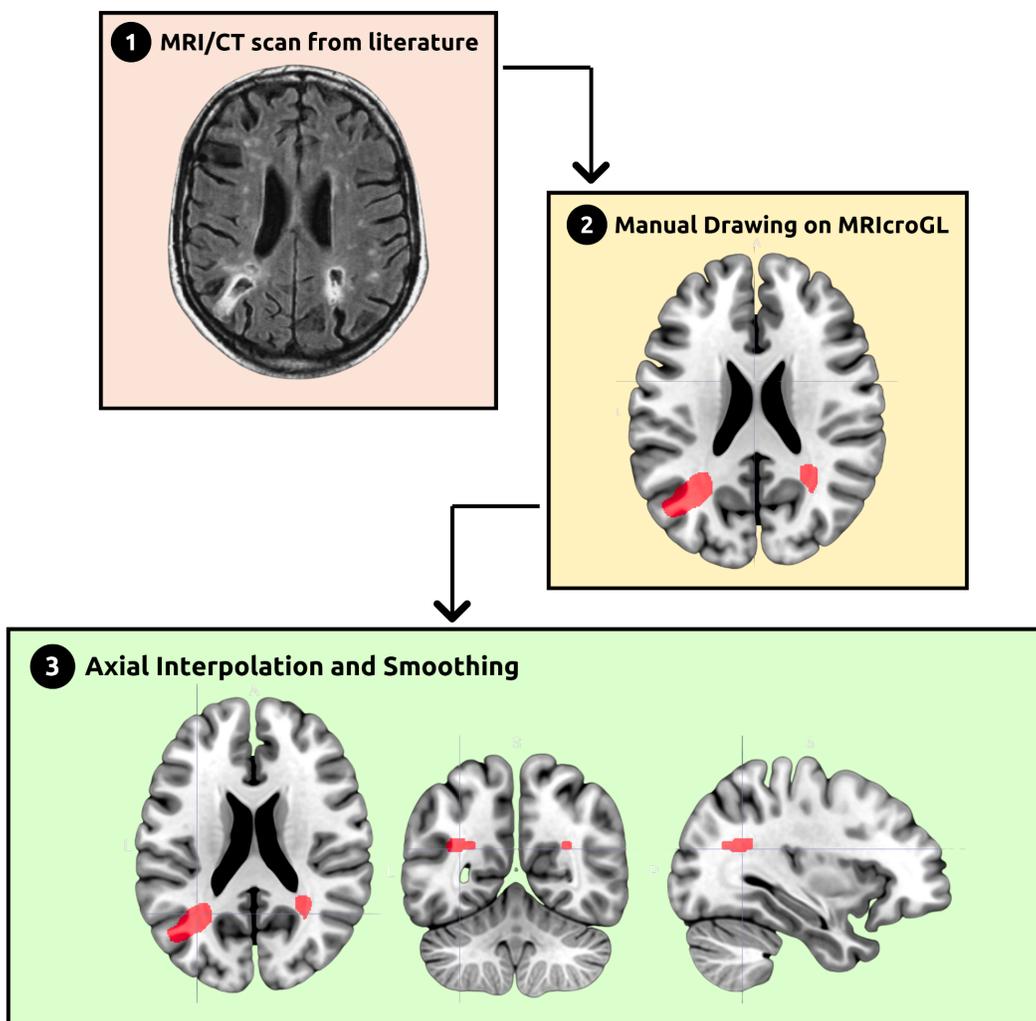


FIGURE 3.4 Lesion drawing procedure

The following step was an interpolation of all slices in the axial plane, and then a refining of the final 3D shape, by applying the ‘smoothing’ function to the whole volume. All this can automatically be done with MRICroGL.

3.3.1 Lesion Evaluation

The lesion evaluation procedure was really simple, but based on a specific structure defined a priori. Three intern students from the Bachelor’s program in Psychology at the University of Padua were involved in the assessment of the lesions dataset. After receiving an appropriate training in MRICron, neuroimaging interpretation, and also brain lesion anatomy, each student independently rated every lesion using a 5 point Likert scale. The key aspects of the evaluation were:

1. Lesion localization accuracy
2. Lesion shape and dimensions
3. 3D continuity of the lesion and feasibility

Every score was then averaged to obtain a “quality score” for each single key aspect analyzed. Lesions receiving an average score above 4.0 were considered sufficiently accurate and reliable, while lesions with a score below this threshold were revised and resubmitted for further evaluation. An example of the scoring process is presented below (see Table 1).

TABLE 1 Example of inter-rater lesion evaluation

	Lesion Localization				Lesion Shape/Dimension				Lesion Continuity			
	<i>M</i>	<i>B</i>	<i>R</i>	<i>avg</i>	<i>M</i>	<i>B</i>	<i>R</i>	<i>avg</i>	<i>M</i>	<i>B</i>	<i>R</i>	<i>avg</i>
Nag. 1	5.0	5.0	3.0	4.3	5.0	5.0	4.0	4.6	3.0	5.0	3.0	3.6
Nag. 2	1.0	1.0	1.0	1.0	1.0	5.0	1.0	2.3	1.0	3.0	1.0	1.6

Nag. 1 = Nagaratnam et al. patient 1, M, B, R = 3 raters. Scores > 4.0 were considered good enough (green), while scores < 4.0 were revised and resubmitted for evaluation (red).

Additionally, we evaluated the process with an inter-rater reliability analysis, using the Intraclass Correlation Coefficient (ICC). The ICC(3, k) was computed with a two-way mixed-effects model, that is appropriate when the same set of raters evaluate each key aspect and the goal is to assess if there is consistency between their scores. The results showed a good amount of agreement across all three dimensions, specifically for “localization”, ICC(3,k) = 0.86 [95% CI: 0.74–0.93]; for “shape”, ICC(3,k) = 0.79 [95% CI: 0.61–0.89]; and for “continuity”, ICC(3,k) = 0.73 [95% CI: 0.52–0.86] (Fig 3.5). These results show high consistency among raters, supporting the method employed.

These findings are relevant, since our protocol is based on manual lesion reconstruction from published scans. We can confirm that such levels of inter-rater agreement, at least show that the criteria and training provided to rater were effective, and probably the resulting dataset is acceptable to further neuroanatomical and statistical analysis.

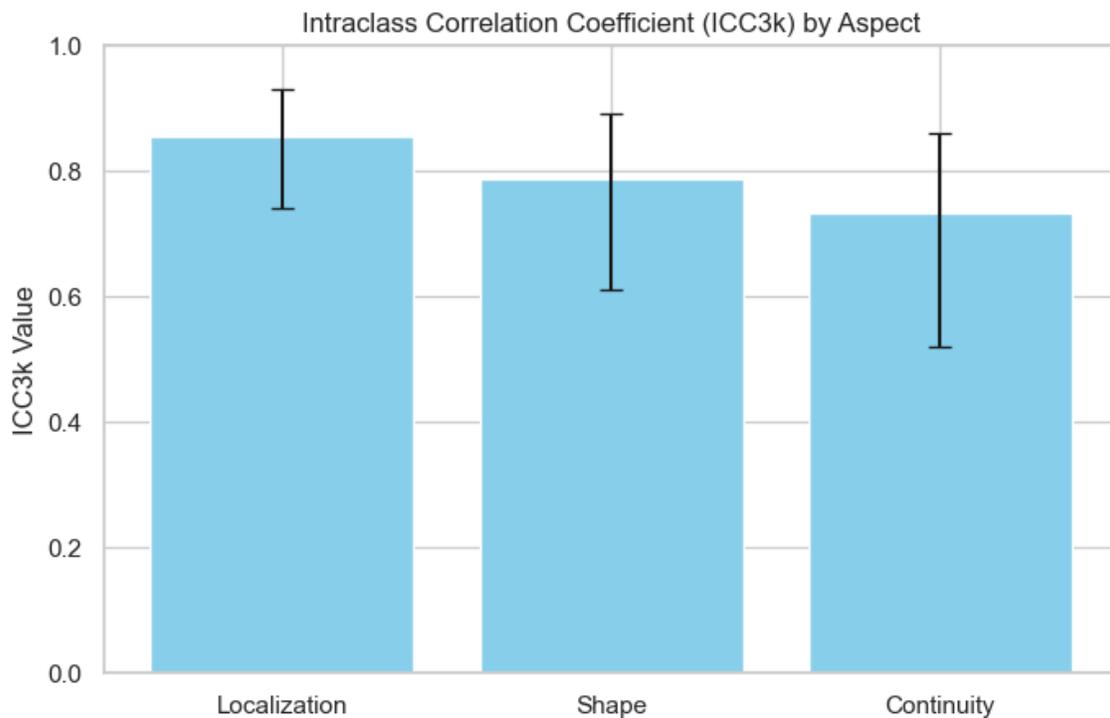


FIGURE 3.5 Intraclass correlation coefficient ICC(3,k)

DATASET DESCRIPTION AND OBSERVATIONS

4.1 Dataset Overview

The dataset used in this review is the result of a systematic literature examination, where group studies describing patients diagnosed with optic ataxia were selected. Fourteen studies were included in the current research, with a total of 66 patients.

TABLE 2 Optic ataxia database

N°	First Author	Journal	Year	Type	N° of Lesions Extracted
58	Nagaratnam N	J Neurol Sci	1997	patients group study	5
64	Blangero A	Cortex	2010	patients group study	7
74	Perenin MT	Brain	1988	patients group study	3
89	Mikula L	J Exp Psychol	2021	patients group study	2*
92	Striemer C	Neuroreport	2007	patients group study	2
97	Himmelbach M	J Cogn Neurosci	2005	patients group study	2
105	Buiatti T	Brain Cogn	2013	patients group study	1 (15 patients overlap)**
107	Karnath HO	Cereb Cortex	2005	patients group study	1 (16 patients overlap)**
113	Gaveau V	Neuropsychologia	2008	patients group study	2*
114	Rossit S	Neuropsychologia	2012	patients group study	1 (7 patients overlap)**
135	Granek JA	PLoS One	2012	patients group study	2*
148	Khan AZ	Nat Neurosci	2005	patients group study	2
203	Blangero A	Vision Res	2011	patients group study	2*
216	Rossetti Y	Neuropsychologia	2005	patients group study	2*

* many patients are present in different studies

** we considered overlap studies as a single patient, drawing only areas including at least 50% of lesions

Out of the total 66 patients, only 28 had individual MRI or CT scans available. The remaining 38 patients were reported in three different group studies, each providing an overlap image. For these manual reconstruction we selected regions showing at least 50% lesion overlap across patients (as visually reported in the original studies). In the end, we obtained a total of 31 lesion files in ‘.voi’ format: 28 from single patients and 3 created from overlay plots studies.

4.2 Demographics and Clinical Details

The patient sample reflects a wide range of individuals with optic ataxia. Even though the primary goal was the lesions reconstruction, we extracted demographic and clinical data, when available. The majority of cases involved adult patients, with ages from 17 to 88 years old. Sex distribution seemed balanced, but specific data weren’t always present.

In terms of lesion laterality, 90% of patients presented unilateral lesions, affecting the right hemisphere in the 58% of cases. The most frequently involved areas, as expected, were the posterior parietal and occipito-parietal regions, generally associated with visuomotor abilities and spatial processing (Andersen et al., 2014). Patients showed clinically relevant symptoms consistent with optic ataxia, including misreaching under visual guidance, impaired hand-eye coordination, and difficulties in grasping or even pointing objects in peripheral field of vision.

4.3 Lesion Topography Observations

Once the lesion drawing and ratings were completed and approved, the following step was the identification of common anatomical regions affected. We overlaid on the MNI 152 brain template all the lesions, to identify possible overlapping damaged regions. At this stage, we did focus on a quantitative lesion overlap map, to understand where the most common damaged areas were. In particular we observed the areas that are frequently involved in optic ataxia, such as the posterior parietal cortex. Specifically, the brain areas associated most frequently with optic ataxia, according to Harvey & Rossit (2011), should be around the lateral and medial parieto-occipital regions, near the parieto-occipital junction and the parieto-occipital sulcus.

DISCUSSION AND CONCLUSION

5.1 Main Findings

One of our goals was to evaluate the use of manual lesion drawing through the use of MRICron and MRICroGL, reconstructing data from previously published neuroimaging data, with a focus on optic ataxia. The project had both a primary and a secondary objective: first to explore a new, low-cost, and time-efficient protocol for 3D lesion mapping, and second to build a lesion dataset related to optic ataxia cases that may be used as a foundation for future investigations.

This manual reconstruction method, despite its intrinsic limitations in precision, proved to be a valuable exploratory tool for visualizing lesions when volumetric data are not available from source literature. Also, high levels of inter-rater general agreement on accuracy suggest potential reliability of the method. Additionally, lesion overlap observations suggest a non-random distribution of brain lesions, with the majority of them converging into parieto-occipital lobes.

These findings seem to be consistent with the most recent literature on optic ataxia. This cumulative approach to lesion mapping, even with many limitations, may provide meaningful insights about the structural foundations of neuropsychological syndromes.

5.2 Interpretation of Results

To quantitatively assess the distribution of brain lesions, we used a MRICron feature that allowed us to overlay our overlap onto the Automated Anatomical Labeling atlas (AAL). This allowed us to find the frequencies of brain damage in specific cortical and subcortical areas.

At this stage, our main focus was to highlight the most consistently damaged regions, comparing them with the latest literature available. This approach is in alignment with the exploratory and cumulative goal of this study. In the next page a comprehensive view of the overlap is available.

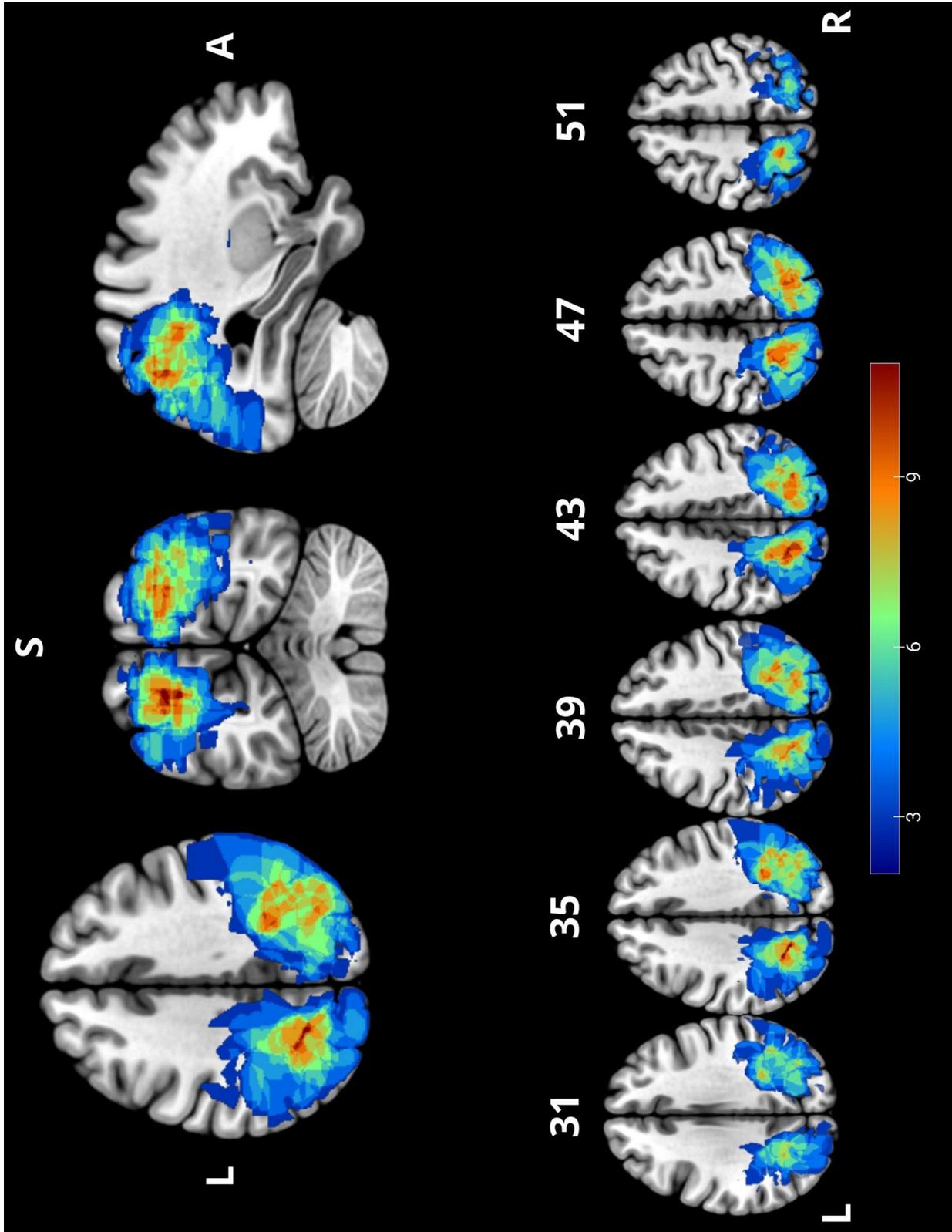


FIGURE 5.1 Lesions overlap map, displayed on the MNI152 template.

Lesion overlap analysis showed a consistent involvement of bilateral occipital and parietal regions, including left and right cuneus, superior and middle occipital gyri, superior and inferior parietal lobules, angular gyrus, and precuneus. This bilateral distribution supports the view that optic ataxia isn't only related to the functionality of a single region, but instead it's caused by a disruption of a broader network, most likely the dorsal visual stream, crucial in mediating visuomotor skills (Milner A. D., 2006).

The middle and superior occipital gyri damage, together with the cuneus, may suggest an important role of occipital areas damage, which can compromise early visual processing, affecting also the integration of spatial information.

These findings seem to support prior hypotheses about the topography of optic ataxia brain damage, suggesting that the cumulative lesion mapping approach is consistent in capturing neuroanatomical patterns. In the following section we are going to critically discuss the theoretical and methodological contributions of this study, considering both strengths and limitations.

TABLE 3 MRICron's descriptives output (peak: lesion files overlapping)

Index	Name	numVox	numVoxNotZero	fracNotZero	peak	min	mean	meanNotZero
45	Cuneus_L 5011	12133	9668	0.797	8	0	1.993	2.501
46	Cuneus_R 5012	11323	8031	0.709	8	0	1.953	2.753
49	Occipital_Sup_L 5101	10791	10609	0.983	11	0	3.247	3.303
50	Occipital_Sup_R 5102	11149	10370	0.930	10	0	3.518	3.782
51	Occipital_Mid_L 5201	25989	25207	0.970	11	0	2.988	3.080
52	Occipital_Mid_R 5202	16512	16256	0.984	10	0	3.723	3.782
59	Parietal_Sup_L 6101	16519	10446	0.632	11	0	2.779	4.395
60	Parietal_Sup_R 6102	17554	9488	0.541	9	0	1.499	2.773
61	Parietal_Inf_L 6201	19447	18595	0.956	11	0	2.842	2.972
62	Parietal_Inf_R 6202	10763	10478	0.974	9	0	2.800	2.876
65	Angular_L 6221	9313	8690	0.933	10	0	2.996	3.211
66	Angular_R 6222	14009	13876	0.991	10	0	4.811	4.858
67	Precuneus_L 6301	28358	17600	0.621	11	0	1.522	2.452
68	Precuneus_R 6302	26083	12511	0.480	9	0	1.448	3.019

5.3 Methodological Considerations and Limitations

This method presents several methodological considerations that must be acknowledged, including both positive and negative aspects.

First, the manual nature of lesion drawing, using softwares such as MRICron and MRICroGL, introduces a certain degree of subjectivity. Despite the drawer training and the Likert scale assessment, the accuracy of reconstructions heavily depends on the original MRI and CT scans quality. However, using the Intraclass Correlation Coefficient, we observed substantial agreement between raters. This at least supports the general reliability of the dataset.

Second, source data pose many limitations. In many studies information derives from overlay plots, while in others from very low resolution single slice scans, sometimes also lacking precise anatomical indicators. Relying on reconstructions from 2D to 3D inevitably decreases spatial precision and may hide patterns of cortical and subcortical involvement.

Third, limitations concerning selection criteria of included cases. We included only group studies, which may introduce a selection bias toward more well documented cases. In addition, clinical data weren't always available across patients, making it difficult to correlate lesion patterns with symptom severity and behavioral outcomes. However, the study demonstrates that a manual, time saving, and low cost mapping approach can provide reliable and relevant insights, especially in rare or under-represented conditions. This protocol can be easily replicated and refined in future research and it might be used as a method to explore novel hypotheses in lesion symptom mapping, serving as a foundational tool for pilot studies and also database construction.

5.4 Future Directions

The nature of this study opens up many paths for methodological refinement and future research. First of all, the optimization of the lesion reconstruction protocol is crucial. Manual tracing is both reliable and limited, and with the rise of artificial intelligence and machine learning,

it would be interesting to employ an automated or AI assisted approach. A model trained on neuroimaging data could assist in a more precise lesion drawing, also increasing reproducibility. With the use of large language models (LLM) it would be possible to facilitate the extraction of relevant data from the literature, improving speed and objectivity of the process.

Another important step is the expansion of the dataset, including new cases of optic ataxia as well as related syndromes (e.g. Balint's syndrome). On top of that, incorporating detailed clinical variables (e.g. laterality of impairment, visuo-attentive overload), would make it possible to analyse correlations between lesion location and functional impairment.

A promising future direction is related to the investigation of white matter disconnections. Recent progress in connectomics may provide new insights on the functional architecture of optic ataxia, revealing novel brain networks disruptions. This perspective would significantly refine our understanding of the syndrome, while also aligning with current trends in cognitive neurosciences.

REFERENCES

- Andersen, R. A., Andersen, K. N., Hwang, E. J., & Hauschild, M. (2014). Optic ataxia: from Balint's syndrome to the parietal reach region. *Neuron*, *81*(5), 967–983. <https://doi.org/10.1016/j.neuron.2014.02.025>
- Blangero, A., Khan, A., Rode, G., Rossetti, Y., & Pisella, L. (2011). Dissociation between intentional and automatic remapping: different levels of inter-hemispheric transfer. *Vision research*, *51*(8), 932–939. <https://doi.org/10.1016/j.visres.2011.01.012>
- Blangero, A., Ota, H., Rossetti, Y., Fujii, T., Ohtake, H., Tabuchi, M., Vighetto, A., Yamadori, A., Vindras, P., & Pisella, L. (2010). Systematic retinotopic reaching error vectors in unilateral optic ataxia. *Cortex; a journal devoted to the study of the nervous system and behavior*, *46*(1), 77–93. <https://doi.org/10.1016/j.cortex.2009.02.015>
- Buiatti, T., Skrap, M., & Shallice, T. (2013). Reaching a moveable visual target: dissociations in brain tumour patients. *Brain and cognition*, *82*(1), 6–17. <https://doi.org/10.1016/j.bandc.2013.02.004>
- Cogan D. G. (1965). Ophthalmic manifestations of bilateral non-occipital cerebral lesions. *The British journal of ophthalmology*, *49*(6), 281–297. <https://doi.org/10.1136/bjo.49.6.281>
- Erol, A. & Hunyadi, B. (2022). *Tensors for Data Processing*. Academic Press. <https://doi.org/10.1016/B978-0-12-824447-0.00018-2>
- Gaveau, V., Pélisson, D., Blangero, A., Urquizar, C., Prablanc, C., Vighetto, A., & Pisella, L. (2008). Saccade control and eye-hand coordination in optic ataxia. *Neuropsychologia*, *46*(2), 475–486. <https://doi.org/10.1016/j.neuropsychologia.2007.08.028>
- Granek, J. A., Pisella, L., Blangero, A., Rossetti, Y., & Sergio, L. E. (2012). The role of the caudal superior parietal lobule in updating hand location in peripheral vision: further evidence from optic ataxia. *PloS one*, *7*(10), e46619. <https://doi.org/10.1371/journal.pone.0046619>
- Harvey, M., & Rossit, S. (2012). Visuospatial neglect in action. *Neuropsychologia*, *50*(6), 1018–1028. <https://doi.org/10.1016/j.neuropsychologia.2011.09.030>
- Himmelbach, M., & Karnath, H. O. (2005). Dorsal and ventral stream interaction: contributions from optic ataxia. *Journal of cognitive neuroscience*, *17*(4), 632–640. <https://doi.org/10.1162/0898929053467514>
- Joutsa, J., Corp, D. T., & Fox, M. D. (2022). Lesion network mapping for symptom localization: recent developments and future directions. *Current opinion in neurology*, *35*(4), 453–459. <https://doi.org/10.1097/WCO.0000000000001085>
- Karnath, H. O., & Perenin, M. T. (2005). Cortical control of visually guided reaching: evidence from patients with optic ataxia. *Cerebral cortex (New York, N.Y. : 1991)*, *15*(10), 1561–1569. <https://doi.org/10.1093/cercor/bhi034>
- Karnath, H. O., Sperber, C., & Rorden, C. (2018). Mapping human brain lesions and their functional consequences. *NeuroImage*, *165*, 180–189. <https://doi.org/10.1016/j.neuroimage.2017.10.028>

- Khan, A. Z., Pisella, L., Vighetto, A., Cotton, F., Luauté, J., Boisson, D., Salemme, R., Crawford, J. D., & Rossetti, Y. (2005). Optic ataxia errors depend on remapped, not viewed, target location. *Nature neuroscience*, 8(4), 418–420. <https://doi.org/10.1038/nn1425>
- Mikula, L., Blohm, G., Koun, É., Khan, A. Z., & Pisella, L. (2021). Movement drift in optic ataxia reveals deficits in hand state estimation in oculocentric coordinates. *Journal of experimental psychology. Human perception and performance*, 47(5), 635–647. <https://doi.org/10.1037/xhp0000901>
- Milner A. D. (2017). How do the two visual streams interact with each other?. *Experimental brain research*, 235(5), 1297–1308. <https://doi.org/10.1007/s00221-017-4917-4>
- Moore, M. J., Demeyere, N., Rorden, C., & Mattingley, J. B. (2024). Lesion mapping in neuropsychological research: A practical and conceptual guide. *Cortex; a journal devoted to the study of the nervous system and behavior*, 170, 38–52. <https://doi.org/10.1016/j.cortex.2023.10.001>
- Nabizadeh, F., & Aarabi, M. H. (2023). Functional and structural lesion network mapping in neurological and psychiatric disorders: a systematic review. *Frontiers in neurology*, 14, 1100067. <https://doi.org/10.3389/fneur.2023.1100067>
- Nagaratnam, N., Grice, D., & Kalouche, H. (1998). Optic ataxia following unilateral stroke. *Journal of the neurological sciences*, 155(2), 204–207. [https://doi.org/10.1016/s0022-510x\(97\)00301-8](https://doi.org/10.1016/s0022-510x(97)00301-8)
- Perenin, M. T., & Vighetto, A. (1988). Optic ataxia: a specific disruption in visuomotor mechanisms. I. Different aspects of the deficit in reaching for objects. *Brain : a journal of neurology*, 111 (Pt 3), 643–674. <https://doi.org/10.1093/brain/111.3.643>
- Pisella, L., Rossetti, Y., & Rode, G. (2017). Optic ataxia in Bálint-Holmes syndrome. *Annals of physical and rehabilitation medicine*, 60(3), 148–154. <https://doi.org/10.1016/j.rehab.2016.01.003>
- Rossetti, Y., Revol, P., McIntosh, R., Pisella, L., Rode, G., Danckert, J., Tilikete, C., Dijkerman, H. C., Boisson, D., Vighetto, A., Michel, F., & Milner, A. D. (2005). Visually guided reaching: bilateral posterior parietal lesions cause a switch from fast visuomotor to slow cognitive control. *Neuropsychologia*, 43(2), 162–177. <https://doi.org/10.1016/j.neuropsychologia.2004.11.004>
- Rossetti, Y., McIntosh, R. D., Malhotra, P., Butler, S. H., Muir, K., & Harvey, M. (2012). Attention in action: evidence from on-line corrections in left visual neglect. *Neuropsychologia*, 50(6), 1124–1135. <https://doi.org/10.1016/j.neuropsychologia.2011.10.004>
- Schindler, I., Rice, N. J., McIntosh, R. D., Rossetti, Y., Vighetto, A., & Milner, A. D. (2004). Automatic avoidance of obstacles is a dorsal stream function: evidence from optic ataxia. *Nature neuroscience*, 7(7), 779–784. <https://doi.org/10.1038/nn1273>
- Striener, C., Blangero, A., Rossetti, Y., Boisson, D., Rode, G., Vighetto, A., Pisella, L., & Danckert, J. (2007). Deficits in peripheral visual attention in patients with optic ataxia. *Neuroreport*, 18(11), 1171–1175. <https://doi.org/10.1097/WNR.0b013e32820049bd>