Lesion network of oculogyric crises maps to brain
dopaminergic transcriptomic signature

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Abstract

Oculogyric crises are acute episodes of sustained, typically upward, conjugate deviation of the eyes. Oculogyric crises usually occur as the result of acute D2-dopamine receptor blockade, but the brain areas causally involved in generating this symptom remain elusive. Here, we used data from 14 previously reported cases of lesion-induced oculogyric crises and employed lesion network mapping to identify their shared connections throughout the brain. This analysis yielded a common network that included basal ganglia, thalamic, and brainstem nuclei, as well as the cerebellum. Comparison of this network with gene expression profiles associated with the dopamine system revealed spatial overlap specifically with the gene coding for dopamine receptor type 2 (DRD2) as defined by a large-scale transcriptomic database of the human brain. Furthermore, spatial overlap with DRD2 and DRD3 gene expression was specific to brain lesions associated with oculogyric crises when contrasted to lesions that led to other movement disorders. Our findings identify a common neural network causally involved in the occurrence of oculogyric crises and provide a pathophysiological link between lesion locations causing this syndrome and its most common pharmacological cause, namely DRD2 blockade.
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Introduction

Oculogyric crises (OGC) describe episodes of sustained, conjugate, typically upward deviations of the eyes that may last between seconds and hours and occur in isolation or as part of a syndrome, most often dystonia \(^{1,2}\). Associated signs may include autonomic disturbances as well as neuropsychiatric symptoms, such as agitation, anxiety, mood disorders, obsessive-compulsive behaviors, and psychotic symptoms \(^{1,2}\). Episodes of OGC were originally described in cases of postencephalitic parkinsonism, but since then a broad range of etiologies has been associated with the manifestation of OGC. These etiologies most commonly include treatment with antidopaminergic medication (specifically targeting dopamine D2 receptors), neurogenetic conditions affecting dopamine pathway metabolism, and brain lesions \(^{1,2}\). While OGC are not life-threatening, they frequently cause distress. Thus, there is a need to characterize and elucidate the pathophysiology of OGC to develop a better understanding of its neural underpinnings.

To date, little is known about the pathophysiological mechanisms subserving OGC. On the one hand, the clinical characteristics of the disorder have prompted authors to propose a key role for vertical gaze-holding mechanisms \(^3\). On the other hand, the etiologies frequently associated with the disorder, especially treatment with antidopaminergic medication that targets dopamine D2 receptors and neurogenetic conditions affecting dopamine pathway metabolism, established a link to the dopaminergic system (for reviews see Barow et al \(^2\) and Slow & Lang \(^1\)). These observations provide some insights to the pathophysiological structure of OGC, but the exact neural architecture underlying this disorder remain unclear. Moreover, the role of brain lesions, another reported - albeit rare - etiology of OGC, is less understood. While it is clear that brain lesions can causally lead to the emergence of OGC, the precise neural networks affected by such lesions and whether they interact with the dopaminergic system to produce the OGC phenotype remain elusive.

‘Lesion network mapping’ constitutes a powerful tool to derive network information from local observations\(^{4,5}\). The method investigates whether brain lesions causally linked to the occurrence of a specific clinical sign or symptom share a common functional brain network in the average healthy human brain. Lesion network mapping has been applied to a wide array of neurological and psychiatric disorders offering valuable insights into their neural mechanisms and informing potential network targets for neuromodulatory treatments\(^{4,6}\).
In the current study, we aimed to uncover the neural circuitry responsible for lesion-induced OGC and identify pathophysiological parallels as reported in other etiologies. To this end, we systematically surveyed the medical literature to identify cases in which brain lesions were associated with the development of OGC and applied lesion network mapping to determine the common functional network underlying these cases. To further explore the role of the dopamine system in OGC pathophysiology, we examined the degree of overlap between our identified OGC lesion network and expression profiles of dopaminergic receptors.

Materials and methods

Literature Review and Case Selection

In April 2022, we carried out a comprehensive literature search to identify brain lesions associated with OGC. Our search strategy incorporated a manual case selection from two exhaustive landmark papers on OGC by Barow et al. and Slow & Lang. In particular, the study by Barow et al. systematically reviewed various etiologies of OGC, including focal brain lesions, up to March 2016. We extracted relevant cases from both studies for our analysis. To increase the search yield of reported cases in the literature, we then extended our search from March 2016 to April 2022 using similar search terms as the ones used by Barow et al. in Pubmed (MEDLINE 1966-2020). The search terms included “oculogyric eye movements”, “oculogyric cris*”, “tonic eye deviation” and “tonic gaze deviation”. Besides limiting the time period of published manuscripts, we did not apply any additional filters. Search results were screened by title and abstract, including only case reports or case series that documented focal brain lesions causing OGC in human patients. We excluded reviews, observational studies, animal studies, in-vitro studies, and commentaries. Similarly, descriptions of functional ocular movement disorders, “seizure-like” movements, cases of ictal eye deviation, diagnosis of paroxysmal tonic upgaze, and dystonic tics were excluded. We also excluded genetic disorders, neurodevelopmental, and neurodegenerative conditions due to their potentially distinct pathophysiological underpinnings, which may not be attributable to a specific causative brain region, even in the presence of a lesion.
We thoroughly reviewed all included case reports and only considered those with documented structural brain lesions in the presence of OGC. Reports with inconclusive patient data were excluded. From the included case reports the following information was extracted: patient characteristics (current age, gender), details about brain lesions (age of brain injuring event, etiology, anatomical localization, modality of visualization) and OGC characteristics (age of OGC symptom onset, latency between brain lesioning event and OGC onset, clinical features, and therapeutic strategy). Further information on the search strategy is provided in Supplementary Figure 1.

**Lesion tracing and lesion network mapping**

Lesion locations were identified from corresponding publication figures and manually traced on a common T1 template in ICBM2009b NLIN Asym (“MNI”) space using ITK-SNAP (www.itksnap.org). The drawn masks were saved in NITI format as binary regions of interest and subsequently entered as seeds into the Lead Connectome Mapper software (www.lead-dbs.org) to run lesions as a seed on a normative functional connectome acquired within the Genomic Superstruct Project. This process seeds functional connectivity from each lesion in each of the 1000 subjects of the functional connectome. Voxel-wise R-values were Fisher-z transformed, averaged across the 1000 subjects and summarized using a one sample t-test. The result was a T-map for each lesion which was thresholded at T>7 and binarized. To generate the final lesion network map (LNM), T-maps were binarized, summed across the 14 lesion cases, and thresholded to highlight clusters of voxels highly connected to all lesions (14/14). Supplementary Figure 2 provides an overview of the individual steps used in the lesion network mapping pipeline and different thresholding of the LNM respectively. Supplementary Figures 3 and 4 demonstrate the robustness of the LNM findings using variable thresholding strategies.

To identify connections differing significantly between OGC lesions and control lesions not associated with OGC, we derived lesion-associated connectivity profiles (T-maps) from the Harvard Lesion Repository (N=1110, Supplementary Table 1). Statistical comparison between the OGC and control maps was then performed using a voxel-wise permutation-based 2-sample t-test implemented within FSL PALM (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM) with 2-tailed testing, family-wise error (FWE) correction, and with and without threshold-free cluster
enhancement (TFCE), controlling for cohorts (Supplementary Table 1). One thousand permutations per test and an \( \alpha<0.05 \) were selected.

**Expression profiles of genes coding for dopamine receptors**

OGC frequently occur in the context of pharmacotherapy, particularly in association with D2-receptor antagonist treatment\(^2\). To test whether the brain network linked to lesions causing OGC overlapped with the expression profile of genes coding for dopamine receptors (DRD1-5), we generated receptor subtype-specific gene expression maps using transcriptomic expression data from the Allen Human Brain Atlas (AHBA)\(^10\). These maps provided voxel-wise insights into the extent of expression of each dopamine receptor subtype across the brain. Spatial correlations between the unthresholded OGC-LNM and each of the generated gene expression profiles were calculated (see Supplementary Figure 5 for thresholded results). To establish the significance of the calculated correlation strengths (Fisher z-transformed Pearson’s coefficient) and evaluate the sensitivity of each dopamine receptor subtype in contrast to every other expression profile available in the AHBA, we subsequently correlated the identified OGC-LNM with each of the other 29,133 expression maps included in the AHBA to estimate the null distribution. In addition, we calculated spatial similarities (Fisher-z scored) between each lesion-specific connectivity map in our OGC series and the dopamine receptor expression profiles and compared the resulting correlation coefficients to the correlation strength resulting from correlating dopamine gene expression maps with all lesion-specific connectivity maps of the Harvard Lesion Repository \((N = 1110)\)\(^5,6\). This analysis sought to evaluate the specificity of dopamine receptor expression profiles regarding OGC lesions. Similarity indices were compared between OGC and non-OGC cohort using a two-sample t-test. Finally, we validated the findings derived from transcriptomic profiles using previously published reference maps of D1- and D2-receptor PET tracer images (D3-D5 PET tracers have not yet been utilized in human studies, which is why our analysis was limited to D1 and D2 receptors)\(^11\).

**Results**

The systematic review identified 14 cases with new-onset OGC due to brain lesions. The mean age at OGC onset was 24.9 years \((\pm 18.7 \text{ standard deviation (SD)}, \text{ range 1-59y})\). The majority of
OGC cases co-occurred with dystonia (n = 8), but patients also presented with other symptoms including weakness (n = 5), neuropsychiatric signs (n = 4), and headaches (n=1) (Supplementary Table 2 features a complete list of patient demographics and characteristics). Lesions causative of OGC were documented in different parts of the basal ganglia, including the internal (GPI) and external (GPe) segments of the pallidum, the caudate nucleus, the putamen, and the substantia nigra, but also involved the red nucleus and other subcortical brain areas (Figure 1). Lesion etiologies were variable and mostly associated with autoimmune, toxic, and infectious causes.

Lesion network mapping revealed that all 14 cases causing OGC were part of a common brain network (Figure 2), which comprised the caudate nucleus, the GPi and GPe, thalamic nuclei (e.g., medial dorsal, lateral posterior, ventral lateral, ventral anterior), the pulvinar, as well as the subthalamic nucleus and mesencephalic nuclei, the red nucleus, and the rostral interstitial nucleus of medial longitudinal fasciculus. Furthermore, the network encompassed the anterior cingulate cortex, the superior temporal gyrus, the insula, the parahippocampal gyrus, and parts of the cerebellum (detailed information provided in Supplementary Table 2). Anticorrelated regions within the common network largely encompassed the occipital lobe and ventral visual stream, as well as a smaller cluster in the middle frontal gyrus. Specificity of findings was evaluated using a single combined analysis in PALM comparing connectivity from control lesions in the Harvard Lesion Repository (N=1110) to the OGC lesion cohort. FWE-corrected results with and without threshold-free cluster enhancement (TFCE) are featured in Figure 2B. The spatial distribution of significant voxels in the TFCE map matched the profile identified in the OGC-LNM; a more stringent voxel-wise analysis revealed peak intensities within the striatum, pallidum, midbrain, and cerebellum; adjustment of the t-threshold (T>5 to T>12) did not alter results (Supplementary Figure 4). To evaluate the robustness of the generated LNM we further performed permutation-based (randomized sign-flipping) one-sample t-tests using PALM (Figure 2B) and leave-one-out cross-validation (Supplementary Figure 6), which did not alter the spatial distribution of peak intensities and remained consistent when compared to the original OGC-LNM.

Next, we examined the relationship between the OGC-LNM and DRD gene expression profiles. Given the high occurrence of OGC in cases treated with D2-receptor blockers, we specifically assessed the spatial correlation between the OGC-LNM and DRD2 gene expression profiles, including the other DRD gene expression profiles as controls. This analysis revealed a spatial
similarity between the OGC-LNM and the DRD2 gene expression profile that was significantly higher than expected by chance based on the null-model (derived from all other genes in the AHBA; \( P = 0.035 \), Figure 3A). Critically, the same analysis was not significant for DRD1, DRD3, DRD4, and DRD5 (Figure 3A), suggesting some degree of specificity of the spatial similarity between DRD2 gene expression profile and the OGC-LNM (see also Supplementary Figure 5 for results based on thresholded LNMs).

To further evaluate the specificity of dopaminergic receptors in OGC, we analyzed the congruence between dopamine gene expression profiles and the connectivity patterns originating both from individual OGC lesions and a set of 1110 control lesions related to movement disorders and psychiatric diseases, sourced from the Harvard Lesion Repository (Figure 3B and Supplementary Figure 7). This analysis yielded a significant correlation between OGC lesion connectivity and the gene expression maps of DRD2 and DRD3. In contrast, no significant relationship was observed for DRD1,4, and 5, indicating a specific role of DRD2 and DRD3 receptors in the pathophysiology of OGC, distinguishing it from other lesion syndromes.

In a final analysis we utilized PET receptor maps for dopamine D1 and D2 receptors as curated by Markello et al.\(^{11} \) to corroborate our findings derived from transcriptomic data. Comparison of lesion-specific OGC maps with these PET imaging data sets revealed a significantly lower spatial correlation with the D1 receptor maps in contrast to three of the four assessed D2 receptor maps (Figure 4). The consistency observed between the transcriptomic patterns and the PET-based imaging substantiate our study’s findings, underscoring DRD2/D2 involvement in OGC.

### Discussion

This study provides insights into the neural underpinnings and pathophysiology of OGC. Our results show that lesions causative of OGC map to a common brain network and establish a significant overlap between this network and the transcriptomic expression profile of DRD2. Specificity of this overlap was demonstrated from both angles, i.e., contrasting this pairing with other genes and other lesions, each from a large database. Lastly, the conclusions drawn from transcriptomic profiles were corroborated through analysis of D1- and D2-receptor PET tracer images.
By examining 14 rare cases of brain lesions causative of OGC identified in the literature, we were able to map a common network involved in the pathophysiology OGC. This network encompassed critical nodes in the brainstem, mesencephalon, basal ganglia (caudate nucleus, globus pallidum pars interna and externa and substantia nigra), thalamus, and cerebellum. These regions are known to play a significant role in motor behaviors, including the control of conjugate eye movements\textsuperscript{3,13,14}. Importantly, the network comprised central effectors of vertical gaze-holding, which have been implicated in the pathophysiology of OGC and are suggested to cause the characteristic upward deviation of the eyes during ongoing crisis. These effectors are located in mesencephalic areas and include the rostral interstitial nucleus of the medial longitudinal fasciculus and the interstitial nucleus of Cajal (Figure 2). Further pontine and cerebellar nodes were also identified as part of the OGC lesion-network (see Supplementary Table 3), many of which have well-established roles in the maintenance of high-fidelity performance in vertical oculomotor control\textsuperscript{3,15}. The fact that all 14 cases with brain lesions identified in our study connect to this network, further supports its pathophysiological involvement in OGC.

The lesion network identified from cases with OGC also encompassed hierarchically higher brain regions, such as the thalamus and the basal ganglia. Thalamic nuclei, including the mediodorsal nucleus and the pulvinar, are key nuclei of visuomotor control and responsible for the regulation of perceptual stability of visual imagery\textsuperscript{16}. Moreover, the pulvinar has been proposed to act as an integrator of signals that mediate voluntary and reflexive oculomotor control\textsuperscript{17}. The thalamus does not send direct output to mesencephalic effectors of vertical gaze-holding, but achieves its effects through striatal and cortical projections, including connections to the caudate nucleus, the putamen, the cingulate cortex and the superior temporal gyrus, which are also part of the OGC network described here\textsuperscript{16,19}. In contrast, the basal ganglia project to the superior colliculus directly through efferents from the substantia nigra pars reticulata (SNr), which receives input from the striatum, the GPe, and the subthalamic nucleus as part of the direct and indirect pathway. Taken together, the lesion network results presented here reveal a clear connectivity blueprint of brain areas that mediate oculomotor control\textsuperscript{13} and establish their relevance in the occurrence of OGC. Lesion network mapping also identified anticorrelated regions within the shared network, predominantly within the occipital lobe and the ventral visual stream (Figure 2). The interpretation of negative correlations seen in fMRI remains a matter of
debate. However, drawing parallels from dystonia research, where negative correlations were associated with hyperactivity and disinhibition in the somatosensory cortex during motor tasks, a similar mechanism may be inferred for OGC. Here, the increased activity in the visual cortex during OGC episodes may represent an analogous response, namely a state of hyperactivity as the brain attempts to process and adapt to the aberrant visual inputs caused by involuntary eye movements. This may suggest that the visual cortex is actively engaged, and potentially overcompensating, in an effort to maintain visual perception during OGC.

OGC most commonly occur due to pharmacological dopaminergic blockade. Therefore, we explored whether the distribution pattern of expression of genes coding for dopamine receptors shared spatial properties with the OGC lesion network. This analysis revealed a spatial relationship between regions implicated in OGC and brain areas expressing DRD2. This finding is in line with existing models of OGC pathophysiology which assumed a functional disturbance of dopaminergic neurotransmission, specifically involving D2 receptors. However, DRD2 neurotransmission exerts wide effects on behavior and is involved in the pathophysiology of several neurological and psychiatric disorders. In particular, there has been an association with movement disorders, namely dystonia and chorea, symptoms that were comorbid in our patient population and may have emerged owing to effects on the network mitigating D2-receptor effects. We therefore examined the specificity of DRD2 involvement in OGC by comparing the similarity between the expression maps of dopaminergic receptors (DRD1-5) with all individual OGC lesion maps contrasted to the maps of 1100 cases of other lesion-induced neurological and psychiatric syndromes. This analysis verified the overlap of DRD2 transcriptomic signature with OGC cases compared to other lesion syndromes. In addition, the analysis implicated DRD3-receptors, which belong to the D2-like receptor group. Given the evidence supporting DRD3-receptor involvement in emotional, motivational, and cognitive aspects of behavior, the overlap might help explain the range of neuropsychiatric symptoms that typically occur in the context of OGC, including anxiety, sudden changes in mood, and even psychotic symptoms. Interestingly, one previous study associated DRD3 gene polymorphism with oculomotor performance in schizophrenic adults and healthy controls, however, these findings have not been further substantiated.

One limitation of this study is the small number of cases (reports) that were collected retrospectively. While the very rare occurrence of lesion-induced OGC precludes the possibility...
of a larger targeted study, it is important to note that results were robust and could be replicated consistently using permutation-based strategies (Figure 2B) and leave-one-out cross-validation (Supplementary Figure 6). Second, many of the included lesion cases featured etiologies other than ischemic stroke, which complicated the clear delineation of lesion borders. Importantly, in certain instances, such as autoimmune disorders, we cannot exclude that the neurological dysfunction contributing to OGC might extend beyond the identified lesion areas. Nevertheless, since all selected lesions identified common shared substrates and were robust to permutation analysis and cross-validation, we feel confident that our results reflect a core neural network underlying the emergence of OGC in the selected cases. Additionally, lesions were manually traced in 2D slices and used as seed for functional connectivity estimation following previous reports\cite{4}. However, it was previously shown that 2D slices provide a good approximation of the connectivity profile of the full 3D lesions\cite{4,28}. Finally, functional connectivity was estimated based on an average normative human brain connectome. The use of patient-specific connectivity is impossible since the lesion alters the functional connectome of the patient and no sensible BOLD signal can be extracted from lesioned brain tissue. Instead, the current method probes connectivity in the average human brain and has been successfully used in previous reports that had a similar aim in different contexts\cite{4,6,6,29,30}.

Our study demonstrates the utility of combining lesion network mapping with transcriptomic receptor gene expression to shed light on the pathophysiological underpinnings of disorders such as OGC. This approach has facilitated a more nuanced understanding of the relationship between specific receptor distributions and lesion-induced network disruptions. The methodology employed here could be adapted for further research to explore a range of neurological and psychiatric conditions, providing additional insights into their pathophysiological mechanisms and shape therapeutic interventions. The herein presented approach could contribute to a more comprehensive understanding of brain network dysfunction, moving beyond anatomical mapping to a richer synthesis of molecular and network-level insights.
Data availability

Lesion tracings and lesion network map are available from the corresponding author upon reasonable request. All code used to analyze the datasets is available within Lead-DBS-/Connectome software (https://github.com/leaddbs/). Transcriptomic distribution maps are incorporated and publicly available in Lead-DBS software.

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Competing interests

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University Press. CG was supported by the VolkswagenStiftung (Freigeist), received honoraria for educational activities from the Movement Disorder Society and holds the Wolf Chair for Neurodevelopmental Psychiatry, a joint Hospital-University Named Chair between the University of Toronto, UHN, and the UHN Foundation. MDF has intellectual property on the use of brain connectivity imaging to analyze lesions and guide brain stimulation and is a consultant for Magnus Medical, Soterix, Abbott, and Boston Scientific. MDF was supported by grants from the NIH (R01MH113929, R21MH126271, R56AG069086, R21NS123813, R01NS127892), the Kaye Family Research Endowment, the Ellison / Baszucki Family Foundation, and the Manley Family. BA-F, CN and DK have nothing to declare.

Supplementary material

Supplementary material is available at Brain online.

References


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**Figure Legends:**

**Figure 1** Spatial distribution of brain lesions causative of oculogyric crisis. Fourteen literature-based cases with heterogeneous lesion distribution across the brain were identified using strict inclusion criteria. Binary lesion masks were overlaid on a BigBrain template which has been warped to MNI space. Cases #8, #9, #12 and #13 featured multifocal lesion sites and were traced on two levels.

**Figure 2** Validation of the OGC lesion network map. (A) Detailed depiction of the original (n=14) LNM and relationship to cortical, thalamic, and brainstem nuclei. (B) (Top row) OGC lesion network map derived from a clinical cohort of 11 patients. (Second row) Permutation (n=5000) -based one-sample t-test map generated using FSL-PALM. (Third row) Specificity maps using threshold free cluster enhancement (TFCE) were obtained using a voxel-wise permutation-based 2-sample t-test performed within FSL PALM (1000 permutations) and controlling for group. Connectivity maps are displayed at an FWE-corrected level of $P < 0.05$. (Bottom row) Specificity maps were obtained using a voxel-wise permutation-based 2-sample t test performed within FSL PALM (1000 permutations) and controlling for group. Connectivity maps are displayed at FWE-corrected level of $P < 0.05$. ACC, anterior cingulate cortex; INC, interstitial nucleus of Cajal; riMLF, Rostral interstitial nucleus of medial longitudinal fasciculus; RN, red nucleus.

**Figure 3** Relationship between dopamine receptor gene expression profiles, PET densities, and the identified oculogyric crisis lesion network. (A) The OGC-LNM from the current study was compared to expression profiles of genes coding for the five dopamine receptor subtypes (DRD1-5) as well as to all other 29,133 gene expression maps included in the AHBA (distribution plots). The OGC-LNM was significantly more similar to the DRD2 gene.
expression map as compared to the null-model established by all other genes. The DRD2 gene expression profile is depicted in green. All other DRDs gene expression profiles are depicted in blue. The OGC-LNM (14/14) is featured in magenta with a green outline of DRD2 overlaid on the template brain. DRDs gene expression maps were thresholded to a z-score > ±2SD from the corresponding mean expression value for visualization purposes. (B) Spatial correlation of DRDs expression distribution with connectivity profiles seeding from individual OGC lesions and all other lesions from Harvard repository. Only spatial correlation with DRD2 and DRD3 revealed statistically significant differences when compared to spatial correlation with lesion-specific non-OGC maps. Boxplots represent median and interquartile distribution of the spatial correlation (FzR) between DRDs and OGC lesion maps on the left and between DRDs and non-OGC lesion maps on the right.

**Figure 4** Comparison of lesion-specific OGC maps with dopamine receptor densities as derived from PET imaging. Analogous to our transcriptomic findings, PET analysis revealed a significantly lower spatial correlation of the OGC-LNM with the D1 receptor PET map as compared to three of the four assessed D2 receptor PET maps.
Figure 2
169x72 mm (DPI)
Figure 3

144x193 mm (DPI)
Dopamine Receptors

Figure 4

152x107 mm (DPI)