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Prosopagnosia: face blindness and its relationship to neurological disorders

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Abstract

This study examines the neurological and neuropathological conditions, and clinical, imaging, and demographic traits linked to prosopagnosia. Out of 475 potential cases, 327 met criteria for probable or definite prosopagnosia. One patient had Niemann-Pick type C and another had a forkhead box G1 gene mutation; ten patients (80% male) had developmental prosopagnosia. Of 317 with acquired prosopagnosia, 228 had degenerative causes, primarily primary prosopagnosia syndrome, Alzheimer's disease dementia, posterior cortical atrophy, and semantic dementia. Non-degenerative cases often involved ischemic and hemorrhagic infarcts. Transient non-degenerative prosopagnosia, linked to hypoxic encephalopathy and migraines, improved over time. Degenerative prosopagnosia patients often showed temporal lobe involvement on PET scans, while non-degenerative patients had right temporal and occipital lobe lesions on MRI. Pathological findings included Alzheimer's, Lewy body disease, and frontotemporal lobar degeneration. Facial recognition loss spans various neurological illnesses.

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INTRODUCTION

Prosopagnosia, also called face blindness, is a cognitive disorder of face perception in which one's ability to recognize familiar faces, including one's face (self-recognition), is impaired. Still, other aspects of visual processing (e.g., object discrimination) and intellectual functioning (e.g., decision-making) are intact. The term was first used to describe a condition known as acquired Prosopagnosia, which occurs after acute brain trauma. However, there is also a congenital or

Figure 1 People with face blindness confront this obstacle

developmental variant of the problem, which is 2.5% prevalent [1]. The fusiform gyrus, which primarily activates in reaction to faces, is the area of the brain commonly associated with Prosopagnosia. The fusiform gyrus's ability to function allows most people to identify faces from comparably complex inanimate objects with more detail. People with Prosopagnosia use the less sensitive object-recognition system to recognize faces. The fusiform gyrus in the right hemisphere is more often activated than the left when identifying a familiar face. It is now unclear if the fusiform gyrus is only used to detect human faces or for highly trained visual stimuli. Patients with Prosopagnosia may usually recognize emotions and facial expressions [2]. The human brain is outfitted with advanced equipment designed to identify faces in tens of milliseconds or less through several calculations. Acquired prosopagnosics, patients with brain lesions who are unable to recognize faces exhibit a stark contrast to this typically efficient process. The functional role and distributed nature of face-sensitive brain areas in the ventral stream, like the lateral part of the inferior occipital gyrus and the fusiform gyrus (fusiform face area [FFA]), have been further defined by the findings from these individuals [3]. Finer-grained functional neurological abnormalities in the processes linked to deficiencies in face recognition have been discovered by brain imaging results from people born with developmental prosopagnosics (deficits in face recognition). In the past 20 years, accumulating these neuropsychological, neuroanatomical, and functional aspects of Prosopagnosia has substantially impacted brain models of face perception. However, very little is known about the characteristics of those patients' facial representations, and even less is known about the brain dynamics and neural computations impacted by prosopagnosia [4].

Types:

Apperceptive

Traditionally, cases of acquired Prosopagnosia involving some of the early mechanisms in the face perception system have been referred to as apperceptive Prosopagnosia. The suitable occipital and temporal brain regions are believed to be crucial in apperceptive Prosopagnosia. When images of various faces are shown, people with this disease cannot distinguish between them or make any meaning of faces [5]. They are unable to identify faces, both known and unknown. Furthermore, apperceptive prosopagnosia subtypes have trouble identifying facial emotions. But, they might be able to identify individuals based on non-facial cues like voice, skin tone, hairdo, or attire. The defective fusiform gyrus is thought to be linked to apperceptive Prosopagnosia [Figure 2]. Studies on developing new face detectors in adults using face-like stimuli (learning to recognize cat faces) show that the lingual gyrus, rather than the fusiform, is where these new detectors are formed [6].

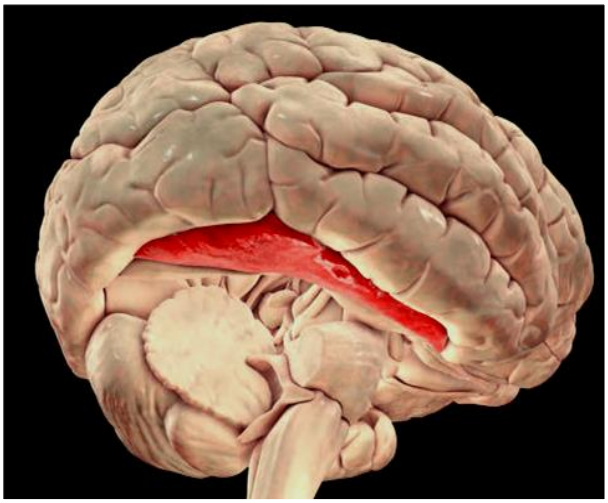

Figure 2 Image of Fusiform Gyrus

Associative

Associative Prosopagnosia is a type of acquired Prosopagnosia that has retained perceptual processes but disrupted linkages between early face perception processes and semantic information that people remember. The suitable anterior temporal regions may have a substantial influence on associative Prosopagnosia. This kind of disease may allow a person to identify between similar and distinct faces in images and estimate the age and gender of a face, demonstrating that they grasp some facial information. However, the person may be unable to identify the individual or provide additional information about them, such as their name, occupation, or last saw date. Associative Prosopagnosia is hypothesized to be caused by decreased function of the parahippocampal gyrus [7].

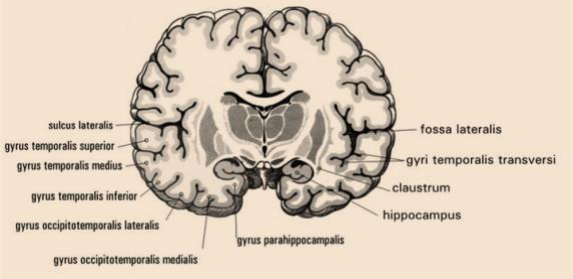

Figure 3 Structural representation of parahippocampal gyrus

Developmental

Congenital Prosopagnosia (CP), also known as developmental Prosopagnosia (DP), is a permanent face-recognition deficit that emerges in early childhood and is not related to acquired brain injury [8]. Even though Prosopagnosia develops early in infancy, many people are unaware of their condition until well into adulthood. Numerous studies employing fMRI and EEG data have revealed functional abnormalities in DP. There have been hypotheses that a hereditary factor causes the sickness. If more than one family member was affected by DP, the term "hereditary prosopagnosia" was established to emphasize the condition's possible genetic basis. Congenital prosopagnosia patients lack the ability, including those of close relatives, yet they may be able to recognize emotions. In ideal settings, emotional and facial expression recognition is frequently intact; nevertheless, in more challenging contexts, some losses may occur [9].

METHODOLOGY:

SUBJECT:

The terms "prosopagnosia," "facial recognition," "face recognition," "face identification," "person identification," "person recognition," "forgets people," "doesn't remember people," "doesn't remember face," "does not remember faces," and "does not remember people" were all found in the

medical records of every patient that the system identified [10]. Examined all of the patient's medical records that the Intake Centre found to establish if they satisfied the requirements for probable, definite, or no Prosopagnosia [11]. A patient, caretaker, or significant other's subjective complaint of facial recognition loss without objective evidence was called "possible prosopagnosia." Patients whose medical records indicated that they had "no prosopagnosia" or "no facial recognition loss," who described Prosopagnosia that affected a family member rather than themselves, who interpreted their complaint for Prosopagnosia, who used smartphone face recognition, or who had trouble naming faces were not included in our analysis [12]. These included gender, age at the beginning of the neurological disease associated with Prosopagnosia, age at the beginning of Prosopagnosia, documentation of the particular complaint or complaints related to face recognition, age at the time of the neurological examination, formal and informal examination of the loss of facial recognition and performance on testing, and documentation of imaging that was available for review (head CT or MRI and FDG-PET) [13].

Additional clinical data that was extracted included the neurological diagnosis at the time of prosopagnosia onset, as well as other clinical features like auditory delusions, ideomotor limb apraxia, other visual agnosias, homonymous hemianopia, hemineglect, behavioral changes, personality changes, complaint-related ophthalmology evaluations, and neuropathological diagnoses in all deceased subjects who had undergone a brain autopsy. Initially, based on the age at which the loss of face recognition began, the patients were split into two major groups [14]. "Developmental prosopagnosia" was the term used to describe patients who have difficulty recognizing faces at birth or in early childhood. "Acquired prosopagnosia" was the term used to describe those who lost their ability to recognize faces beyond early childhood. Next, based on the neurological diagnosis linked to or established as the cause of the loss of facial recognition, we separated individuals with acquired Prosopagnosia into two subcategories: degenerative and non-degenerative [15].

PROSOPAGNOSIA TESTING

A couple of these patients in our cohort underwent two different kinds of facial recognition tests. The patient was shown the face of a well-known individual in the first test type (informal), and the question was whether the patient recognized the face. The patient did not receive credit if the response was negative. If the response was affirmative, the patient was asked for personal details [16]. Credit was granted if any information was supplied to substantiate the knowledge about the individual; if not, no credit was given. Throughout the study, a variety of various numbers of faces (10–30 faces) and a distinct collection of faces were employed in this test type. In the second test type (formal), the patient was asked to point to the face they recognized from a panel of three, one of which was that of a well-known person. It was clear to the patients that they needed to identify which of the three faces they recognized—not the person's name [17]. Credit is granted if the patient indicates the right or well-known face; credit is denied. After identifying the famous face, the patient was asked if they could identify the individual. Although face naming was not used to diagnose Prosopagnosia, it was crucial to rule out patients who did not have Prosopagnosia but had trouble naming their faces. As mentioned, this test consists of 10 panels with three faces each. Its normative data was obtained from 50 normal controls, with a score of ≤8 being deemed abnormal [18].

Tests of face familiarity

Since the inability of patients to recognize faces is the defining feature of Prosopagnosia, critical diagnostic tests examine their familiarity with faces they have previously seen. Previous face recognition tests might have been less sensitive since the stimuli might have allowed participants to employ other techniques, including memorizing clothes and haircuts, to get around face identification problems. More recent tests have addressed those shortcomings by reducing those unnecessary cues. The Cambridge Face Memory Test (CFMT), which has a high level of internal reliability, is the most widely utilized assessment of familiarity for recently encountered faces [19].

From the test's first version, which only used adult Caucasian faces, the CFMT Chinese, CFMT-Australian, and pediatric variants, CFMT-C and

Table 1 Recommended standards for inclusion and exclusion in the diagnosis of developmental and acquired Prosopagnosia

S. No	Inclusion criteria:	Exclusion criteria
1.	Difficulty recognizing faces in everyday situations (PI20)	Prosopagnosia may be caused by low-level visual impairment.
2.	Impairment of at least two measures of facial familiarity (CFMT).	General visual agnosia
3.	Confirmation of lesion using MRI or CT scan (AP instances only)	Impairment of general memory
4.	-	Neuropsychological conditions linked to difficulties recognizing faces
5.	-	MRI lesion visible (DP instances only)

CFMT-Kids, have all been produced. Because no test participant knows any of the faces they will see on the test beforehand, employing anonymous faces in assessments like the CFMT ensures that all test subjects have the same level of short-term familiarity with the faces they will view. Tests measuring a person's familiarity with well-known faces are also employed. However, they are influenced by age, education level, and cultural background because they rely on the subject's prior exposure to the celebrity. The problem of prosopagnosic subjects losing interest in TV shows and films due to their inability to follow the characters can make matters worse by preventing them from being exposed to more recent superstars [20].

Tests of face perception

Face perception tests, which measure one's capacity to distinguish between faces, are not used to diagnose Prosopagnosia. What they can do is show whether Prosopagnosia is an apperceptive variation (caused by deficient facial structure encoding) or an associative version (caused by intact facial structure encoding). The Glasgow Face Matching Test and the Cambridge Face Perception Test, which require sorting or matching faces based solely on identity with little memory load, have been used to quantify deficits in face perception. For kids, the Dartmouth Face Perception Test is helpful [21].

Exclusionary testing

It is insufficient to demonstrate impaired facial recognition to diagnose Prosopagnosia. Moreover, it must be proven that this isn't the outcome of more common memory and vision problems. Based on acuity and visual field examinations, low-level visual impairments cannot be ruled out as the cause of poor face recognition; in fact, problems recognizing faces are one of the issues reported by patients with macular degeneration [22]. In addition, individuals with Prosopagnosia should be able to identify objects at a "basic" level—that is, recognize that an object is a face, a bicycle, a lamp, etc.—to rule out a more widespread visual agnosia. Some people may have trouble recognizing particular examples of these objects (such as a lamp or bicycle). While this does not rule out a prosopagnosia diagnosis, it does raise questions about how specific the recognition problem in Prosopagnosia is when it comes to faces alone (see the "Face Specificity" section) [23]. This is why complex object identification tests that use premorbid expertise and response time measurements are beneficial. Lastly, deficiencies in face identification recognition might arise with other illnesses, and the diagnostic procedure should consider them. This includes diseases like autism and Turner's syndrome in children, whereas diseases like schizophrenia, Alzheimer's, and Parkinson's have been linked to poor facial recognition in adults. Prosopagnosia should only be diagnosed in situations where one of these other disorders cannot account for poor face recognition. [Table 1] suggests criteria for diagnosing acquired and developmental Prosopagnosia [24].

NEUROLOGICAL DIAGNOSIS [25][26]

A board-certified neurologist independently evaluated the medical records to determine the neurological diagnosis for each patient included in the study. This consists of the patient's medical records from their family doctor, neurologist, internist, psychiatrist, and ophthalmologist during

their examination at the Mayo Clinic (which could have lasted years or decades). If the onset of facial recognition loss correlated with a structural lesion (such as an ischemic stroke, brain hemorrhage, or brain tumor) or with a neurological condition that was not thought to be neurodegenerative in origin (such as migraine), the diagnosis was known as an acquired non-degenerative clinical diagnosis. A patient may have two non-degenerative illnesses, such as seizures and a primary brain tumor. The diagnosis was connected to the one that began when the loss of face recognition started. We used published criteria for dementia diagnoses, including posterior cortical atrophy, semantic dementia, dementia with Lewy bodies, Alzheimer's disease dementia (also known as classic, typical, or amnestic Alzheimer's disease), logopenic progressive aphasia, behavioral-variant frontotemporal dementia, Creutzfeldt-Jakob disease, and corticobasal syndrome. For individuals over 60 who exhibit a loss of facial recognition combined with an equally or more pronounced relatively focused loss of episodic memory (i.e., without any additional behavioral or cognitive abnormalities), Primary prosopagnosia syndrome (PPS) was diagnosed in patients with progressive onset and worsening of isolated facial recognition loss over time, or in which facial recognition loss was the most prominent and profound feature, without or with minimal presence of other cognitive or behavioral features. Over the years, I saw minimal change before being diagnosed with hippocampal sclerosis of aging (HSA).

NEUROIMAGING [27][28]

Since the invention of functional imaging, cognitive brain science has undergone a revolutionary transformation. Face study has identified networks of regions that are active during face perception. The posterior area of the superior temporal sulcus, the occipital face region (OFA), and the FFA make up the core face network. Furthermore, an enlarged network includes the anterior temporal face area, inferior frontal gyrus, and precuneus. Faces stimulate both hemispheres, but the right hemisphere is more greatly influenced. The improved structural and functional capabilities of magnetic resonance imaging (MRI) have increased interest in acquired Prosopagnosia. Two noteworthy results from the study of acquired Prosopagnosia were found. First, lesions can be unilateral or bilateral, with the latter more likely to appear on the right. A tiny percentage of prosopagnosic individuals have been observed to have left-sided lesions despite most of them being left-handed; this suggests that their original hemisphere lateralization may have been uncommon. Second, the distinction between anterior temporal damage and occipital temporal damage is useful. Recent functional MRI research has demonstrated that loss of activation of essential components like the FFA and OFA is linked to occipitotemporal injury. On the other hand, the anterior parts may not experience any stimulation.

On the other hand, people with anterior temporal injuries may not activate the FFA and OFA. These observations from contemporary neuroimaging have produced these structural correlates for long-hypothesized functional forms of Prosopagnosia. According to recent research, those with anterior temporal lesions are more likely to have the associative variation of the disorder. In contrast, people with fusiform lesions are more likely to have the apperceptive variety (Figure 4).

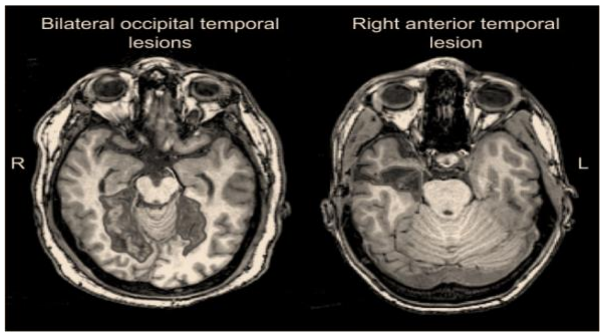

Figure 4 Lesions that result in acquired Prosopagnosia, for instance

NEUROIMAGING GRADINGS

Through the use of 3D stereotactic surface projections from Cortex ID suite images, which normalize activity at each voxel to the pons and Z-score to an age-segmented normative database (GE Healthcare), the individual-level patterns of hypometabolism on FDG-PET were visually reviewed. Eight regions of interest were classified as either absent (Z-score: 0.0 to −2.0) or present (Z-score: −3.0 to −7.0) for the left and right frontal lobes, left and right temporal lobes, left and right parietal lobes, and left and right occipital lobes.

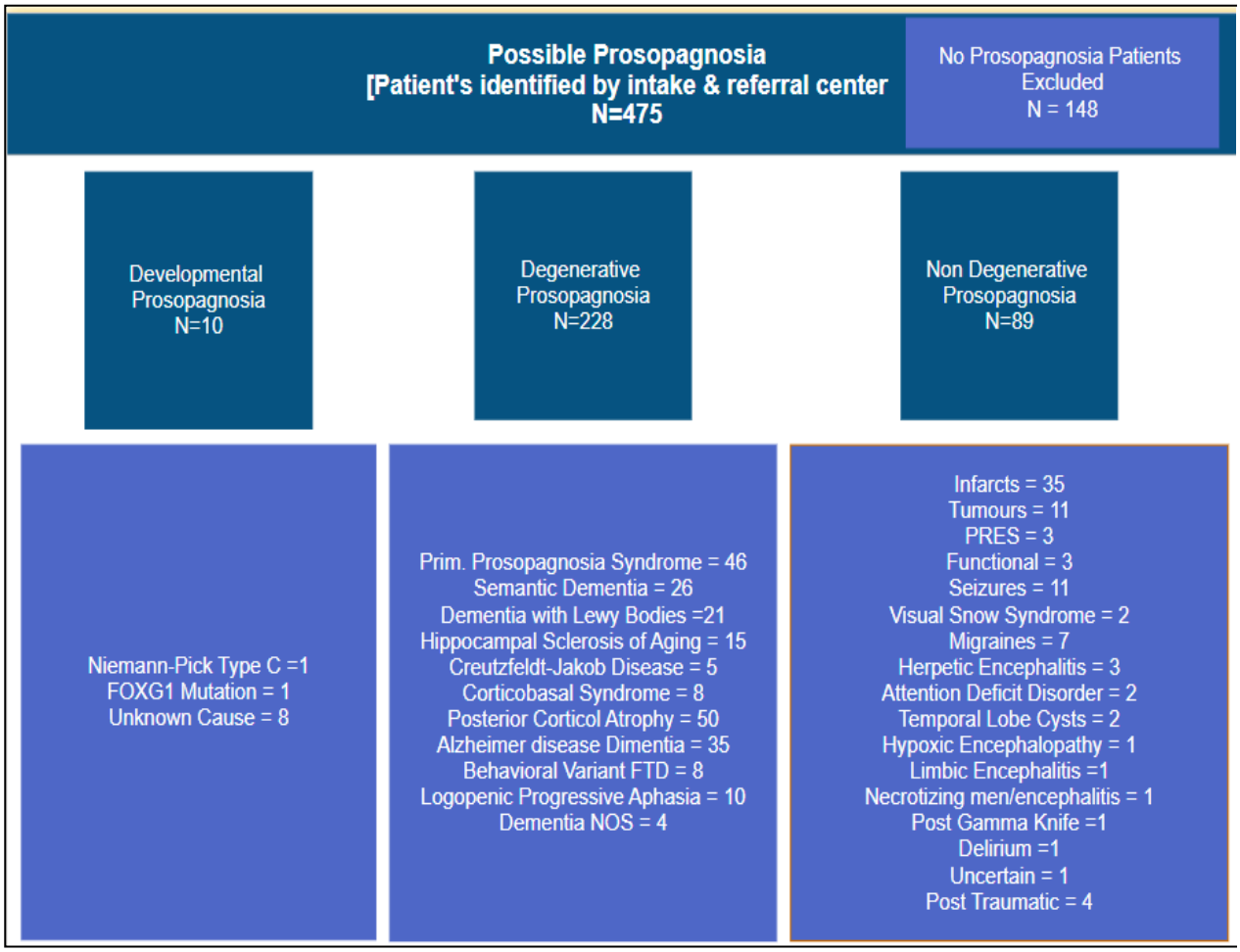

Figure 5 Flowchart of neurological diagnoses and prosopagnosia diagnostic categories

Table 2 Characteristics of the entire cohort with Prosopagnosia

Demographic and clinical characteristics	*N* = 327
Female	184 (54.8%)
Years at the median (range) age of neurologic disease onset	63 (0–90)
Years of prosopagnosia onset at median (range) age	66 (0–92)
Years of the baseline neurological examination's median (range) age	68 (7–92)
How many people have acquired Prosopagnosia (%)	327 (97.0%)
Quantity experiencing visual hallucinations (%)	37 (11.0%)
Number of delusional people (%)	14 (4.2%)
Ideomotor limb apraxia count (%)	26 (7.7%)
The percentage of people with other agnosias	82 (24.4%)
Haemoplegic number (%)	52 (15.5%)
Total number of cases of neglect (%)	19 (5.7%)
Number of alterations in behavior (%)	69 (20.5%)
Number of personality shifts (%)	77 (22.9%)
Number of ophthalmologic examination completions (%)	83 (24.7%)
Number of autopsies finished (%)	13 (3.9%)
Number of available imaging modalities (CT, MRI, FDG-PET) (%)	331 (98.5%)
The total number of completed head MRIs that can be reviewed	309 (92.0%)
Quantity of completed head FDG-PET available for examination	127 (37.8%)

The patients' structural head MRI scan sequences that showed any structural lesion(s) in the same eight areas of interest were those with non-degenerative diagnoses [29].

STATISTICAL ANALYSES

The statistical analyses were conducted using GraphPad Prism version 9.2.0, with a significance level of $P < 0.05$. The Chi-square test was utilized to look at sex ratios and binary variables between the degenerative and non-degenerative groups. In contrast, the Mann-Whitney test assessed continuous factors like age at onset [30].

RESULTS AND DISCUSSION:

SUBJECT:

A total of 475 patients were identified as potentially having Prosopagnosia by the Mayo Intake and Referral Centre (Figure 5). One hundred forty-eight of them were disqualified. Thirty-five patients were excluded because they did not report any loss of facial recognition and had passed standard objective testing for facial recognition with normal findings, indicating that they did not exhibit Prosopagnosia. Ninety-two patients were excluded because their clinical notes stated that they did not have Prosopagnosia. Due to their inability to use the smartphone's face recognition feature, five patients were eliminated. Because the patient's mother, wife, and grandson all had Prosopagnosia, according to the medical records, yet the condition did not apply to the patient, three cases were disqualified. Because the term prosopagnosia was misused, three patients were removed (i.e., Prosopagnosia was used instead of agraphesthesia for one patient and astereognosis for two patients). Thirteen individuals were removed due to anomia, a problem naming faces, even though there was no objective proof of face recognition difficulties (i.e., performance on formal face recognition testing was within normal limits). The study's inclusion criteria were satisfied by the remaining 327 patients. Table 2 displays the clinical and demographic details of these 327 patients. The percentage of females was higher than that of males (45%), at 55%. The cohort's prosopagnosia onset age ranged from 0 to 92, with a median of 66 years. While a quarter of the patients showed other visual agnosias, three used speech or scent for recognition, and other clinical characteristics were found at a lower frequency. Formal ophthalmologic evaluations were performed on 25% of the patient population. Over 90% of the patients had at least one head MRI scan accessible for assessment. All patients had undergone at least one neuroimaging modality (CT, MRI, FDG-PET). Our institute performed brain autopsies on thirteen people, the findings of which are now public.

DEVELOPMENTAL PROSOPAGNOSIA

Ten individuals with developmental Prosopagnosia (Figure 5) out of the 327 patients who met the inclusion criteria were male (80.0%). This cohort's median age at which prosopagnosia onset occurred was 0 years (range: 0–0 years). It was assumed that everyone had Prosopagnosia from birth. Two of the ten patients who underwent testing satisfied the requirements for certain Prosopagnosia. One patient with developmental Prosopagnosia did not become aware of his disability until he entered a university. One patient in this group, out of ten, was diagnosed with Niemann-Pick type C disease, while the other patient had a mutation in the FOXG1 gene. On a head MRI scan performed at the age of two, the latter patient showed signs of delayed myelination and cortical blindness. Prosopagnosia was also diagnosed in the father of a different case.

It was determined that the remaining 317 patients had acquired Prosopagnosia. Of the 317 patients, 225 (70.6%) satisfied the requirements for Prosopagnosia that is certain, and 92 (29.4%) met the criteria for Prosopagnosia that is likely. Of these, 182 (55.8%) had a median age of onset of 67 years (range: 7–92 years) and were female. Table 3 describes particular symptoms of loss of facial recognition.

PROSOPAGNOSIA DUE TO NEURODEGENERATIVE DISEASE

A degenerative diagnosis was made in 228 of the 327 patients with acquired Prosopagnosia. Three degenerative diagnoses accounted for more than 10% of the neurodegenerative aetiologies: posterior cortical atrophy, Parkinson's disease dementia, and Alzheimer's disease dementia. These diagnoses were the most common cases. Figure 5 depicts an additional, less typical diagnosis. The median age at which

Table 3 Examples of particular face blindness problems and the corresponding diagnoses

Face blindness description by patient or spouse	Associated diagnosis
Shopping in different locations to avoid coming across anyone he might know; he does not recognize people he has not seen in his hometown in a long time.	Attention deficit disorder
Having trouble identifying familiar faces, such as her students' families and extended family.	Epilepsy with focal partial seizures
Sometimes, she saw that certain TV personalities or family members seemed like "cubism."	Medically intractable epilepsy
Needs to identify persons using their voices and sense of smell.	Post-herpetic encephalitis
Face recognition was a challenge following the stroke but has since improved.	Right posterior cerebral artery ischaemic infarct
He looked in the mirror and could not recognize himself.	Right posterior cerebral artery ischaemic infarct
I was unable to identify my wife's face in the supermarket.	Traumatic brain injury
He was a rowing team coach who went through a phase of not being able to identify his team.	Visual migraines
Husband claims that unless a person's name is recalled, she has problems recognizing them.	Alzheimer's disease, dementia
Fails to identify her spouse and, believing him to be an intruder, calls the police.	Alzheimer's disease, dementia
Sporadically, I have trouble identifying persons, particularly upon awakening.	Alzheimer's disease, dementia
Having trouble identifying her family, particularly her grandchildren	Corticobasal syndrome
Did not recognise her daughter's face.	Dementia with Lewy bodies
Sometimes, he had trouble recognizing his wife.	Hippocampal sclerosis of aging
Did not recognize his son-in-law and granddaughter when they paid him an unexpected visit.	Hippocampal sclerosis of aging
Recognition issues with his grandchildren and regular visitors.	Logopenic progressive aphasia
He has trouble identifying his daughters and can only do so by hearing their voices.	Posterior cortical atrophy

Prosopagnosia begins occurring was 82 years in patients with HSA, 20 years older than semantic dementia patients, whose median age at onset was 62 years. Lewy body dementia patients (71.4%) had the highest frequency of visual hallucinations, while patients with corticobasal syndrome (100%) had the highest frequency of limb apraxia. In patients with posterior cortical atrophy, other visual agnosias were most common (73.5%), while in patients with behavioral-variant frontotemporal dementia, behavioral and personality abnormalities were more common (100% for both). Prosopagnosia in patients with degenerative Prosopagnosia was either stable or will eventually get worse. Eight patients may have had the prosopagnosia-like Capgras syndrome. Six of these eight individuals had Lewy body dementia, one had posterior cortical atrophy, and one had dementia associated with Alzheimer's disease.

PROSOPAGNOSIA DUE TO NON-DEGENERATIVE DISEASE

The diagnosis for eighty-nine patients was non-degenerative (Figure 5). Infarcts (both ischemic and hemorrhagic) were the most common non-degenerative diagnoses, followed by disorders associated with epilepsy seizures and primary brain tumors. Two patients, one presenting with infarcts and the other with convulsions, were diagnosed with mitochondrial encephalopathy with lactic acidosis and strokes. Less often diagnosed non-degenerative conditions included

Table 4 Clinical descriptions of Prosopagnosia related to migraines

Patient	Summary
1	A forty-three-year-old man who has had HA since he was seven years old, as well as h/o from radiation-induced meningioma, cerebellar astrocytoma excision, and RoRx ten years prior, presented with acute visual abnormalities along with persistent, incapacitating headaches. It was discovered that the man also had Prosopagnosia and simultagnosia. An MRI revealed a recent stroke to the right occipital lobe, given a SMART syndrome diagnosis. The Prosopagnosia remained but became better with time.
2	A 52-year-old woman who had radiation-induced meningioma 35 years prior and had undergone h/o cerebellar astrocytoma excision presented with acute onset vision abnormalities along with headaches. He was discovered to have Prosopagnosia, oculomotor apraxia, optic ataxia, and simultagnosia. A gyriform increase of the right occipital lobe was observed on MRI. Following treatment, the augmentation improved, but the Prosopagnosia persisted.
3	A sixty-nine-year-old man who had experienced two identical episodes two and seven years earlier appeared with abrupt onset prosopagnosia and topographagnosia once more. There were no language or speech issues at the time. The spells don't give him headaches. The Prosopagnosia subsided when the about three-hour spells ended. The patient has normal levels of blood thinners for heart disease. Head CT scans have detected no lesions or strokes. Identified as potentially having migrainous auras.
4	A male aged fifty-seven has a history of headaches since infancy. During adolescence, headaches become more intense and connected to visual auras. Stated that he had an odd headache in his 20s that caused him to lose his ability to recognize individuals momentarily. After a few hours, the Prosopagnosia and headache both disappeared.
5	A 49-year-old man with a history of attention deficit hyperactivity disorder and classic migraines came in for treatment of anxiety and recurrent vertigo. Claimed to have experienced intermittent facial blindness most of his life.
6	A twenty-four-year-old woman arrived for treatment of migraines that she had started ten years prior. Her phonophobia, photophobia, osmophobia, and nausea are linked to headaches. She has spells of facial blindness due to her headaches. These episodes, along with her headaches, currently happen every day. An MRI head scan shows a little thalamic lesion, but nothing else is seen.

Prosopagnosia associated with migraines. (For a medical summary of presenting features, see Table 4.) Following radiation therapy, two patients with migraine-associated Prosopagnosia were identified with stroke-like migraine attacks (SMART) syndrome. Following a catastrophic brain injury, Prosopagnosia was experienced by five patients right away. Three female patients with somatization/functional dysfunction and ages of onset of 42, 54, and 60 years old were diagnosed with non-degenerative Prosopagnosia. Prosopagnosia was reported to have started acutely in all three patients, except one patient (age 42) who reported that it started right after giving birth. Three individuals had been diagnosed with post-herpetic encephalitis, three with posterior reversible encephalopathy syndrome (PRES), and one in which Capgras was thought to be imitating Prosopagnosia. Attention deficit disorder and visual snow syndrome were seen in two of the individuals. A patient with visual snow syndrome said that, at times, it seemed like they were seeing through bubble wrap and that their vision was like "snow on a black and white television." These two patients similarly experienced problems with visual motion, and ophthalmologic consultations for each of them confirmed the diagnosis.

According to some infarct patients, Prosopagnosia got better with time. However, it didn't always go away. Prosopagnosia caused by migraines was temporary and went away entirely in a few hours for patients with the condition, including one with SMART syndrome. However, Prosopagnosia did recur frequently. Similarly, three PRES patients reported experiencing transient Prosopagnosia

that resolved entirely over a few days to weeks, including one who experienced delirium from hypernatremia and drug overdose, one who experienced an infarct, and one who experienced hypoxic encephalopathy following ventricular fibrillation arrest.

A COMPARISON BETWEEN NON-DEGENERATIVE AND DEGENERATIVE DISEASES

Table 5 displays the clinical and demographic features contrasting the non-degenerative and degenerative groups. In comparison to the non-degenerative diagnoses, the group with degenerative diagnoses had a considerably higher frequency of definitive Prosopagnosia ($P < 0.0001$). In the degenerative group, there were significant differences in the median age at the onset of neurological diagnosis, Prosopagnosia, and neurological examination ($P < 0.0001$). Homonymous hemianopsia was present in 19 patients (8.1%) with a degenerative diagnosis and 34 patients (37.3%) with a non-degenerative diagnosis; 21 of the 34 patients had bleeding or ischemic infarcts ($P < 0.0001$). While the number of patients who received ophthalmologic examination was more prevalent in the non-degenerative group ($P = 0.04$), behavioral and personality changes were more common in the degenerative group ($P < 0.0001$).

The number of patients who underwent FDG-PET scans and had a degenerative diagnosis that explained their Prosopagnosia was 117. Figure 6 displays representative 3D stereotactic-surface projections from the Cortex ID suite for the various degenerative diagnoses. The majority of patients (n = 81) with a non-degenerative diagnosis had a head MRI that could be reviewed; the other patients' MRI reports contained no images. Figure 6 displays representative structural anomalies in the patients who do not have degenerative diagnoses. All but five individuals (7.7%) who underwent structural head imaging (MRI or CT scan) and showed a lesion, out of the 89 patients with non-degenerative Prosopagnosia, had a lesion involving the right temporal or right occipital lobe.

OPHTHALMOLOGIC FINDINGS:

At our institution, an ophthalmologic evaluation was performed on eighty-three patients, four of whom had developmental Prosopagnosia and the other 79 of whom had acquired Prosopagnosia (32 non-degenerative and 47 degenerative). Of the four, ocular atrophy was present in one with developing Prosopagnosia. Among patients with acquired Prosopagnosia, cataracts were found in 27 (35.4%), glaucoma in 12 (13.9%), and macular degeneration in 6 (7.6%) cases. There were ten patients with various visual problems, such as melanoma-associated retinopathy, subconjunctival hemorrhage, chorioretinopathy, Fuchs' endothelial dystrophy, and two each with scleritis, retinal detachment, and vitreous detachment.

PATHOLOGICAL FINDINGS:

In the hospital, brain autopsies were performed on thirteen patients with degenerative Prosopagnosia (Table 6). Frontotemporal lobar degeneration (FTLD) with TAR DNA binding protein 42 (TDP-43) inclusions (n = 8) together with hippocampal sclerosis (n = 5/8), FTLD-tau (n = 4), and mixed high likelihood Alzheimer's disease and Lewy body disease (n = 4) were the most frequent histological findings. The FTLD-TDP-43 type C pathology was seen in three PPS patients. Pick's disease, globular glial tauopathy, and diffuse argyrophilic grain disease were among the other diseases. Anterior medial temporal lobe regions, including the fusiform gyrus, showed marked to severe shrinkage in all cases of FTLD disease (Figure 7).

NEUROIMAGING GRADINGS

Three groups of FDG-PET data are presented for the 117 individuals with degenerative diagnoses (Figure 8). Three illnesses that were thought to be on the spectrum for Alzheimer's disease made up Group 1, and four diseases that were supposed to be on the spectrum for frontotemporal dementia made up Group 2. The remaining diagnoses made up Group 3. Bilateral temporal lobe hypometabolism was the most prominent finding in Group 1 diagnosis, with bilateral occipital and parietal lobe involvement following. The logopedic progressive aphasia group exhibited decreased participation on the right side compared to the other two groups. The majority of bilateral temporal lobe hypometabolism was seen in Group 2 diagnosis. Only those diagnosed with behavioral-variant frontotemporal dementia showed involvement of the frontal lobes.

Table 5 Features of individuals with acquired Prosopagnosia both with and without a diagnosis of degeneration

Characteristics	Degenerative (*N* = 228)	Non-degenerative (*N* = 89)	*P*-value
Probable: definite Prosopagnosia	25:211	71:19	<0.0001
Female sex	134 (56.6%)	48 (53.8%)	0.6161
Median age of disease onset (range), years	66 (24–90)	61 (9–89)	<0.0001
Median age at the beginning of Prosopagnosia, years	69 (39–92)	61 (12–89)	<0.0001
The median age at neurological assessment is years.	71.5 (26–92)	62 (12–89)	<0.0001
Number with visual hallucinations (%)	29 (11.9%)	9 (9.9%)	0.7007
Number with delusions (%)	13 (5.1%)	2 (2.2%)	0.2559
Number of individuals with ideomotor limb apraxia (%)	25 (10.2%)	4 (4.4%)	0.0982
Number with visual agnosia (%)[a]	49 (20.9%)	20 (22.0%)	0.5053
Number of patients with homonomous hemianopia (%)	20 (8.0%)	34 (37.3%)	<0.0001
Number with neglect (%)	12 (5.1%)	6 (6.6%)	0.5783
Number with behavioral changes (%)	66 (28.1%)	4 (4.4%)	<0.0001
Number with personality changes (%)	73 (31.1%)	5 (5.5%)	<0.0001
Number completing ophthalmologic examinations (%)	49 (20.9%)	30 (33.0%)	0.0181
Number completing autopsy (%)	13 (5.5%)	3 (3.3%)	0.1570

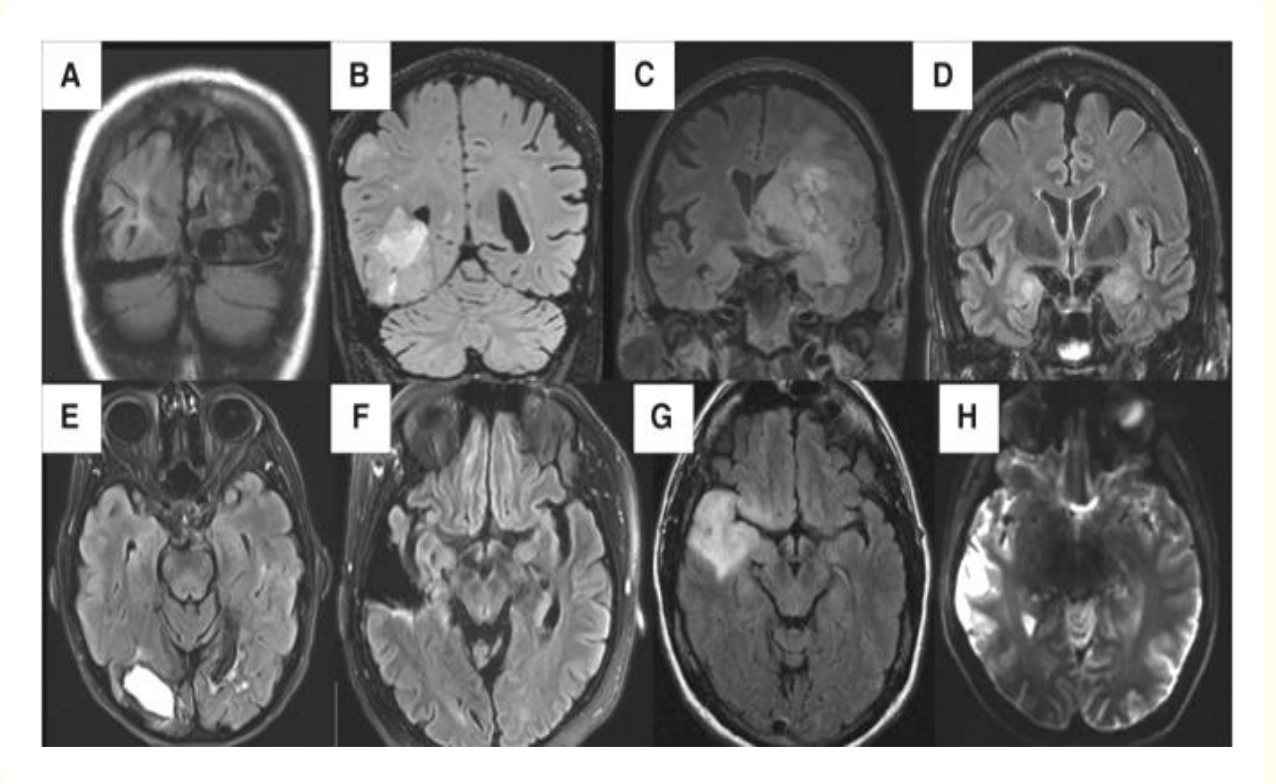

Figure 6 MRI scans showing structural abnormalities in individuals not diagnosed with dementia

Table 6 Thirteen examples of neurodegenerative Prosopagnosia with pathological diagnosis

Case	Age at death	Clinical Diagnosis	Alzheimer Disease	FTLD-tau
1	85	Alzheimer's disease, dementia	A3B3C3	-
2	80	Behavioral variant FTD	-	Diffuse AGD
3	61	Behavioral variant FTD	-	-
4	89	Dementia with Lewy bodies	-	-
5	84	Logopenic progressive aphasia	A3B3C3	-
6	68	Posterior cortical atrophy	A3B3C3	-
7	74	Posterior cortical atrophy	A3B3C3	-
8	86	Primary prosopagnosia syndrome	-	Diffuse AGD
9	73	Primary prosopagnosia syndrome	-	-
10	61	Primary prosopagnosia syndrome	-	-
11	81	Primary prosopagnosia syndrome		-
12	71	Semantic dementia	-	Pick's disease
13	61	Semantic dementia	-	Globular glial tauopathy

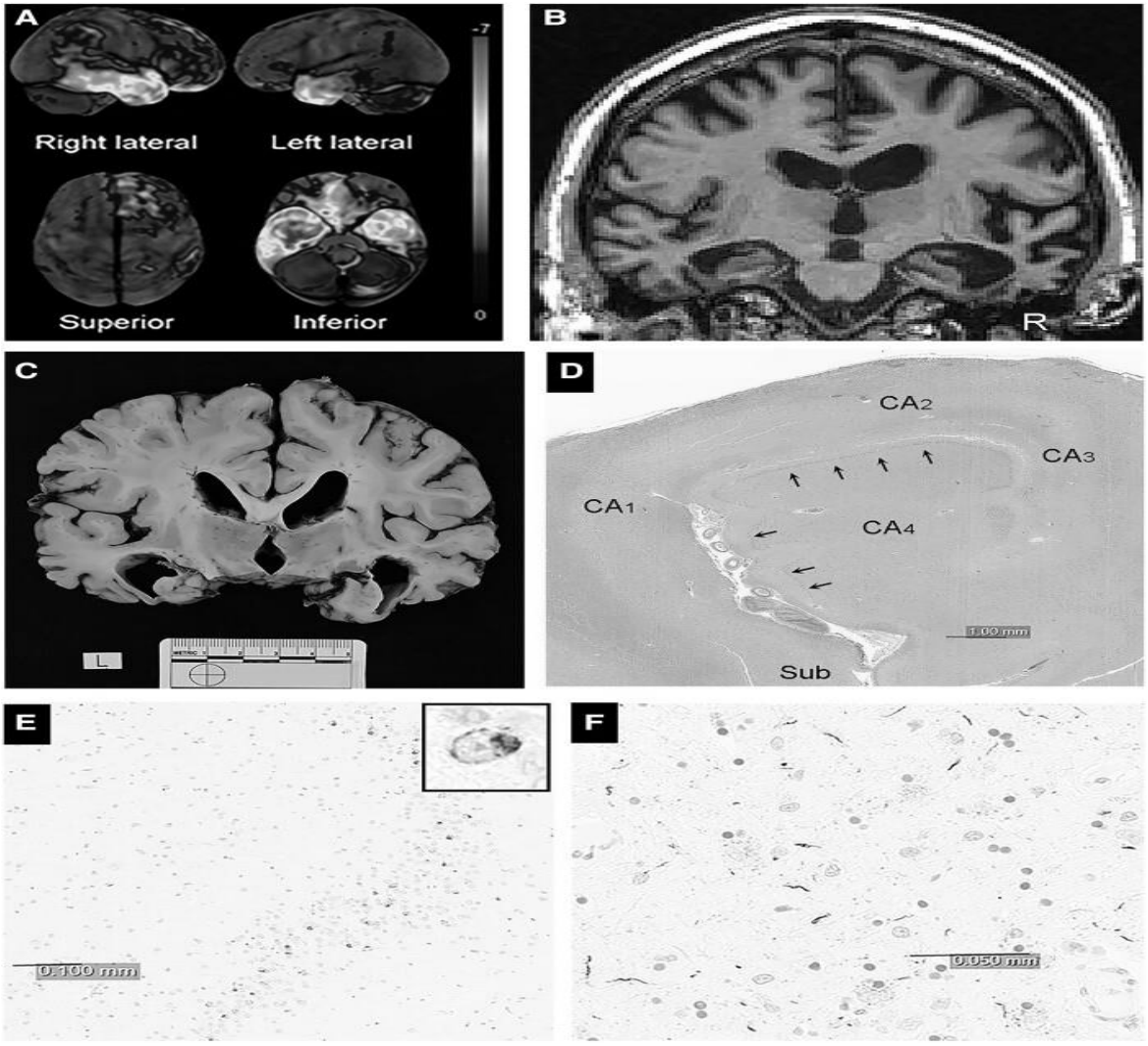

Figure 7 A patient with PPS had gross and histological abnormalities, head MRI, and FDG-PET

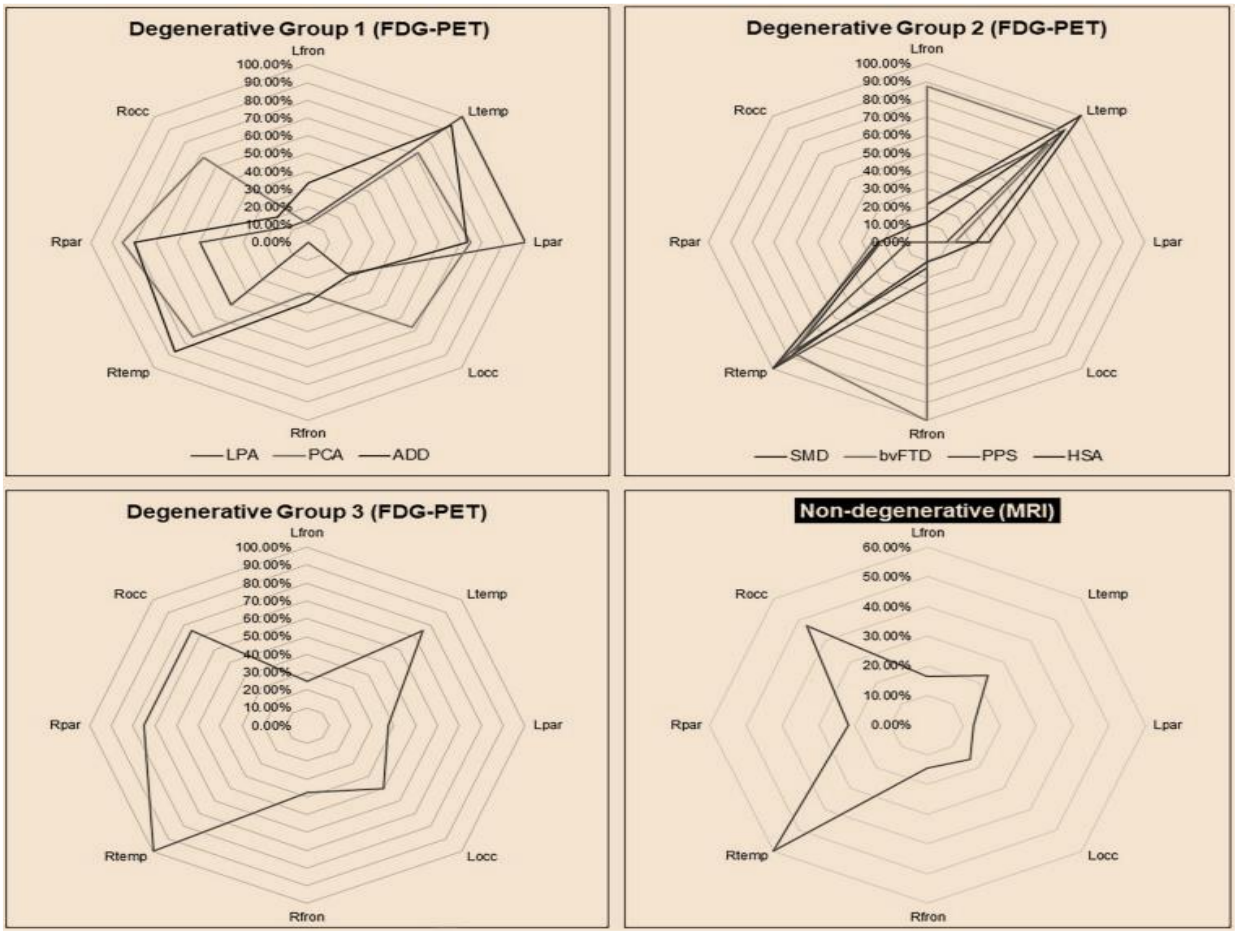

Figure 8 Radar maps displaying the location of lesions and regional hypometabolism

Though small sample sizes hampered Group 3's findings, they indicated participation mainly on the right, particularly the right temporal region, followed by the suitable parietal and occipital areas.

The 81 patients with a non-degenerative diagnosis had their MRI results summarised as a single group (Figure 8). We discovered a startling asymmetry in the right temporal lobe's participation and the occipital lobe's involvement. The right temporal lobe (50%) and right occipital lobe (68%) showed the highest frequency of lesions in patients with tumors and epilepsy (75%).

DISCUSSION:

We discovered numerous distinct neurological causes of Prosopagnosia in our extensive case series of 327 people, most of whom developed the condition later in life. However, we also uncovered patients whose Prosopagnosia started at birth. We saw certain prosopagnosia patients identifying people by speech or scent, among other non-visual cues. Several degenerative and non-degenerative aetiologies were found, most of which mainly affected the right anterior medial temporal and/or right occipital lobes. We noted that Prosopagnosia is not always a lifelong symptom and that it sometimes gets better or goes away over time when related to specific non-degenerative aetiologies. We found that degenerative Prosopagnosia is linked to various underlying diseases, the most prevalent of which is FTLD.

Degenerative illness was the most frequently diagnosed category. In this group, Prosopagnosia often occurs as a co-occurring symptom alongside a variety of additional indications and symptoms that are essential components of the disease. One of the main characteristics of semantic dementia is the associative form of Prosopagnosia, particularly in cases where the right anterior temporal lobe is impacted.

In contrast to the other neurological disorders in this group, PPS and HSA affect the fusiform gyrus and other anterior medial temporal lobes. There aren't many more symptoms in PPS and HSA. Prosopagnosia is the primary, most noticeable complaint in PPS and, in some instances, the only finding and complaint. Similar cases have been reported in the literature, yet progressive Prosopagnosia and primary progressive Prosopagnosia have been among the diagnostic labels given. Unlike PPS, episodic memory loss is typically the most noticeable presenting symptom in HSA and can exist for years before Prosopagnosia develops. Patients with HSA usually begin their lives older than those with PPS.

It is not generally agreed upon that patients with trouble perceiving faces in the context of other visual and cognitive dysfunctions that may impact face perception should be diagnosed with apperceptive Prosopagnosia. This makes the diagnosis of Prosopagnosia in neurodegenerative diseases somewhat contentious. Diagnosing associative Prosopagnosia in patients with semantic dementia and suitable temporal and frontal temporal dementia is another topic of contemporary discussion.

A curious finding in our degenerative cohort was the challenge of distinguishing between Prosopagnosia and Capgras syndrome, particularly in patients with dementia who also had Lewy bodies. A delusional misidentification symptom known as caps syndrome is the conviction that an imposter has replaced a person. It is, therefore, challenging to distinguish Capgras syndrome from Prosopagnosia in individuals with dementia with Lewy bodies because of its high correlation with dementia associated with Lewy illness. We advise against diagnosing Prosopagnosia and strongly advise formal facial recognition testing to ascertain whether one or both symptoms are present, given the established link between dementia with Lewy bodies and Capgras syndrome.

This discovery will significantly impact the preoperative planning for the excision of lesions affecting the right occipital lobe, the right anterior temporal lobe, lesions in the fusiform gyrus, and even lesions in deep subcortical regions in the right hemisphere. According to our research, infarcts were primarily found in the right occipital lobe. Still, seizure-related Prosopagnosia and tumors were mainly linked to the involvement of the right anterior medial temporal lobe, including the fusiform gyrus. The correlation between Prosopagnosia and migraines, as well as the fact that Prosopagnosia can be temporary and resolve over time, were two of the most intriguing findings in the individuals with a non-degenerative diagnosis.

The MRI head and FDG-PET scans are two commonly used neuroimaging examinations in clinical practice. The anterior medial temporal and occipital lobes are significantly correlated with Prosopagnosia, according to the results of both neuroimaging analyses. As these are degenerative diseases, it is unsurprising that we discovered involvement in these regions in both hemispheres. One would predict that more brain regions would be affected as the disease progressed from inception to the evaluation. Additionally, we discovered localized patterns of hypometabolism on FDG-PET, which corroborate the clinical diagnoses of semantic dementia, behaviorally variant frontotemporal dementia, and posterior cortical atrophy.

Our study's strength is the cohort size, which allows us to generalize the results to patients with Prosopagnosia and other neurological diseases. The significant number of people who finished brain imaging is another asset. One drawback of the study is its retrospective nature. Not every patient finished an objective, standardized prosopagnosia measure and several tests with unknown sensitivity and specificity. Another disadvantage of the study was the lack of testing to ascertain if those with definite Prosopagnosia also had apperceptive or associative Prosopagnosia. We cannot rule out the chance that the diagnoses do not apply to other cohorts due to the small sample size of individuals who underwent pathological investigation.

CONCLUSION:

Numerous neurological conditions, such as focal brain lesions, non-degenerative non-lesion conditions including migraine and epilepsy, neurodegenerative diseases with a range of underlying neuropathologies, and even functional disorders, can cause or result in Prosopagnosia. It can also be acquired later in life. It might also be temporary or get better with time. This symptom

is primarily caused by involvement in the right anterior medial temporal and occipital lobes. In patients with degenerative Prosopagnosia, combined Alzheimer's and Lewy body disease pathology, as well as frontotemporal lobar degeneration with hippocampal sclerosis, were the most frequent pathological findings. Across a broad spectrum of acquired degenerative and non-degenerative neurological illnesses, we found that facial recognition loss occurs in this significant case series of individuals with Prosopagnosia, most typically in males with developmental Prosopagnosia. A critical region is the fusiform gyrus, which connects the right temporal and occipital lobes. Several distinct disorders bring on degenerative Prosopagnosia.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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