Delusional misidentification syndromes (DMS), such as Capgras and Fregoli, are dramatic, poorly understood and enigmatic. For instance, a 44-year-old man with Capgras syndrome following a traumatic brain injury claimed that substitutes had replaced his wife and five children. An elderly woman who developed reduplicative paramnesia after a stroke clung to a delusion that her house was not her ‘real’ home.

Researchers developed a range of theories to explain these enigmatic syndromes since the original descriptions about 90 years ago. Recent research, however, suggests that DMS might arise from single lesions at unique locations within the neural connections in the brain (the so-called connectome). The finding challenges some long-held beliefs about the underlying pathology. Moreover, the innovative approach used by the researchers might offer new insights into some of the most complex symptoms in psychiatry and neurology as well as ‘normal’ cognition.

‘Delusional misidentifications can occur in patients with neurological diseases,’ said Ryan Darby, Sidney Baer Jr Fellow in Behavioral Neurology and Neuropsychiatry at Beth Israel Deaconess Medical Center, in Boston who led the study. ‘Understanding the neuroanatomy and the mechanism that causes delusional misidentifications is a first step towards developing new therapies.’

### Quick-changes

People with Fregoli syndrome typically believe that a person changes his or her appearance or is in disguise. The name commemorates the performer Leopoldo Fregoli, who found fame as a quick-change artist around the turn of the 20th Century. Fregoli could switch costumes and characters so rapidly that some people claimed that there were several ‘Fregolis’. In 1927, Courbon and Fail reported that a 27-year-old woman believed that two actors whom she often saw at the theatre ‘pursued her closely’ and took the appearance of ‘people she knows or meets’.

People with Capgras syndrome believe that an imposter has replaced a close friend or relative. The French psychiatrists Capgras and Reboul-Lachaux described the condition in 1923 as l’illusion des sosies (the illusion of doubles). There are numerous other DMS (Table 1), which overlap considerably and may evolve into each other. Moreover, delusional misidentifications can involve non-human animals, locations and buildings. Indeed, about 10% of patients have Capgras and Fregoli at the same time and 30% experience delusions about a person and a place.

In addition, several other conditions seem to be related to DMS including: lycanthropy; Ekbom syndrome (people believe they are infested with parasites); delusional hermaphroditism or sexual transformation; a person believing that they are the antichrist.

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**Table 1. Examples of delusional misidentification syndromes**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asomatognosia</td>
<td>The patient repeatedly misidentifies part of their body</td>
</tr>
<tr>
<td>Clonal pluralization</td>
<td>The patient believes that there are multiple physically and psychologically similar copies of themselves</td>
</tr>
<tr>
<td>Delusional companions</td>
<td>The person believes that certain non-living objects possess consciousness, can think and feel emotion</td>
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<tr>
<td>Mirrored-self misidentification</td>
<td>The person believes that the reflection in the mirror is a stranger</td>
</tr>
<tr>
<td>Reduplicative paramnesia</td>
<td>A place or location has been duplicated or relocated</td>
</tr>
<tr>
<td>Reverse Capgras syndrome</td>
<td>The patient believes that they have a new, or rediscovered a pre-existing, identity; often famous figures or someone the patient admired</td>
</tr>
<tr>
<td>Subjective doubles</td>
<td>The patient believes that there are other people who look like them, but with different traits and who lives</td>
</tr>
</tbody>
</table>

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**References**

1. Courbon, J. & Fail, J. (1927). A 27-year-old woman believed that two actors pursued her closely and took the appearance of ‘people she knows or meets’.
2. Courbon, J. & Fail, J. (1927). A 27-year-old woman believed that two actors pursued her closely and took the appearance of ‘people she knows or meets’.
3. Courbon, J. & Fail, J. (1927). A 27-year-old woman believed that two actors pursued her closely and took the appearance of ‘people she knows or meets’.
and asomatognosia.\textsuperscript{1,3} Patients with asomatognosia lose their recognition or awareness of part of their body. So, they might believe that the doctor owns one of their limbs or describe, for example, their arm as ‘a piece of rusty machinery’ or ‘my dead husband’s hand’.

**Relatively common**

DMS seem to be relatively common, at least among some patients. One study estimated that 0.12% of the general population experiences Capgras syndrome. Estimates of the prevalence of DMS among psychiatric inpatients ranges from 1.3% to 4.1%. The rate is especially high in, for example, schizophrenia (15%), Alzheimer’s disease (2–30%) and Lewy body dementia (17%).\textsuperscript{3} Electroconvulsive therapy, certain drugs (eg levodopa, diazepam and disulfiram) and organic disorders – including dementia, head trauma, epilepsy and cerebrovascular disease – might also trigger DMS.\textsuperscript{1,4} Indeed, between 25% and 40% of cases of DMS seem to be associated with organic disorders.\textsuperscript{1} For example, following a large right frontal haemorrhage, an 83-year-old female believed she was hospitalised in a different city and, at times, that she worked at their centre and identified a unique ‘other’.\textsuperscript{2} In other cases, a person may replace a stressful environment – a hospital – with a safe place, such as their place of work.

Neuroanatomical suggestions include that the hippocampi of DMS patients become disconnected from other areas that store memory. This means new information is not linked to previous memories, which, in turn, leads to duplication.\textsuperscript{1} Several researchers linked DMS to damage to the right brain, which generates ‘faulty information’. The left hemisphere attempts to interpret this faulty information, which, in turn, leads to DMS. For example, when the injured right hemisphere cannot produce the appropriate emotional response to a patient’s spouse, the left hemisphere concludes there is an impostor.\textsuperscript{3}

Although these explanations seem diverse, they essentially suggest that the functional deficit allows an abnormal perception to go unchallenged by another brain area. This, in turn, leads to DMS.\textsuperscript{3} Now new research suggests that DMS arise from single lesions at unique locations within the connectome.\textsuperscript{3}

**Examining connections**

A new study uses a technique called lesion network mapping, which identifies which brain regions are connected functionally to a lesion. The authors applied the approach to 17 DMS patients either reported in the literature or who presented at their centre and identified a unique pattern of connectivity between the lesions and regions involved in perceiving familiarity and those involved when events do not go as expected (expectation violation).\textsuperscript{2} ‘Despite being located in different parts of the brain, all lesions causing delusional misidentifications had the same pattern of connectivity,’ Dr Darby told *Progress*. ‘The connectivity to regions involved in familiarity and belief evaluation implicates both processes that are thought to be abnormal in these patients. More generally, mapping brain connectivity using this approach may lend insight into the most complex symptoms in psychiatry and neurology.’

The analysis found that the left retrosplenial cortex was most strongly activated by stimuli that are familiar to patients and showed a negative correlation with the locations of all 17 lesions in DMS patients. Sixteen lesions were connected to the right ventral frontal cortex, the region most activated by unexpected or invalid stimuli (expectation violation). Lesions in people with other delusions were not connected to regions involved in familiarity, which explains why DMS are characterised by misidentification. However, lesions in people with other types of delusions were connected to regions activated by expectation violation.\textsuperscript{2}

The findings support suggestions that DMS arise from deficits in brain areas that determine the personal relatedness of objects, theory of mind and retrieval of autobiographical memories. Indeed, the retrosplenial cortex seems to contribute to all these functions. Moreover, the right ventral frontal cortex seems to reorient attention and update our internal mental representations of
the external world. The right dorsal frontal cortex seems to evaluate beliefs and predict error. Our results support the idea that abnormal familiarity and belief evaluation are involved in developing delusional misidentifications,” Dr Darby said.

Previous neurological models suggest that two lesions were needed to account for DMS: one to generate the error and one to allow the delusion to pass unchallenged. Most researchers believed that this ‘two-hit model’ involves a disconnection between visual areas and the amygdala, which seems to integrate emotions, emotional behaviour and motivation. In contrast, the new study found that a single hit in an area that is linked to regions involved in familiarity is enough to generate DMS. ‘We show how DMS can arise with a single lesion connected to two networks as opposed to two separate lesions,’ Dr Darby said. ‘Our model also supports the “prediction error model of delusions”, which proposes that detecting violations of expectation might be an important cognitive process that is impaired in patients who develop delusions. However, we also found that connectivity to regions involved in familiarity explained the specific content of delusional misidentifications, which was not found in lesions causing other delusions.’

Unanswered questions
The pattern of connectivity was consistent across cases of over- and under-familiarity (eg Fregoli and Capgras respectively) as well as misidentifications involving different categories of objects (eg people versus places). This might explain why the same person can develop different DMS. However, as mentioned above, the connections to the left retrosplenial cortex showed negative correlations with the lesion locations, while the right ventral frontal cortex or the anterior insula showed positive correlations. Why one functional deficit showed a negative correlation and another a positive correlation remains unclear. Possibly, regions positively correlated with a lesion location are less active, while negatively correlated regions are more active, following the lesion. In addition, lesion network mapping identifies regions connected functionally to lesion sites. But this does not prove that these regions are dysfunctional.²

In addition, Dr Darby commented that understanding why the different phenotypes (eg Capgras and Fregoli) emerge in the same person is ‘really challenging’. However, while the mechanism to develop each is ‘probably very similar’, environmental factors might influence which delusion develops. ‘One patient in the rehabilitation hospital, an unfamiliar place, she thought she was at work, a familiar place. In contrast, when she arrived home, she thought the home was an unfamiliar replica of her “real” home,’ Dr Darby said. ‘Patients who develop delusions that pets are imposters often, though not exclusively, are socially isolated and don’t have close family or friends to have the delusion about. So, delusions may depend on whether the patient is exposed to familiar or unfamiliar things; they tend to develop a delusion in the opposite direction. Finally, we have a few unpublished observations that there might be a small change that “triggers” the delusion. For instance, photos in a different location on the table might trigger the delusion that the house is a replica instead of the “real” home.’

In addition, future research needs to investigate how DMS resolve, which generally takes several months. ‘We don’t know the exact mechanism for how these delusions resolve,’ Dr Darby said. ‘However, the resolution is likely to involve brain plasticity as the brain remodels itself after the injury. This happens for other symptoms following strokes, like aphasia and weakness.’

Lesion network mapping can also help explain other complex symptoms following focal brain lesions. ‘Our lab has applied lesion network mapping to understanding the neural correlates of lesions causing hallucinations, coma, and abnormal movements like hemichorea, following strokes,’ Dr Darby said. ‘We are in the process of applying this technique to understanding other symptoms and applying a similar technique to understanding symptoms in other neurological disorders like dementia.’

Finally, the findings can help understand human behaviours – including how we discriminate reality – more widely. ‘We show that complex human behaviours, like belief in what is real, probably rely on the interactions between networks of brain regions, not due to one specific brain region,’ Dr Darby concluded. ‘While this is not a new idea, our method shows a striking example of how disrupting the relationship between two networks of brain regions might result in these bizarre beliefs.’

Mark Greener is a freelance medical writer.

References

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