What the “man in the moon” can tell us about the future of our brains

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Taeko Sasai-Sakuma and her coauthors from Professor Inoue's research group at the Tokyo Medical University, recently published a study (1), which is a timely addition to ongoing research for biomarkers of neurodegeneration in idiopathic RBD (iRBD) (2,3).

Idiopathic RBD is the most specific sign of prodromal Parkinson’s disease, and is now considered an early stage synucleinopathy by itself (4). However, the length of time until conversion to fully manifest alpha synuclein disease is of concern and has stimulated research into biomarkers that could potentially indicate immediacy of conversion, or progression, to other clinical and daytime manifestations of fully manifest alpha synuclein disease (5-7). In contrast, trying to identify more specific endpoints of conversion has not been a major focus in research.

In this context, the study presented by Sasai-Sakuma and coworkers is of particular interest. They present a novel test, based on a compact series of 10 pictures that facilitate pareidolias used for the first time in patients with iRBD. For their study, published earlier this year (1), they investigated a large cohort of 202 untreated patients with iRBD recruited from the outpatient clinic of Japanese Somnology Center Neuropsychiatric Research Institute over less than 2.5 years, and compared them to a healthy control group. Apart from the pareidolia test (administered in an abbreviated and ready-to-use validated 10-picture version (8), the participants underwent a series of other tests and full polysomnography.

The authors showed that a much larger proportion of patients with iRBD exhibited at least one more pareidolic response than controls, and that a larger number of ambiguous pictures evoked pareidolic responses in patients compared with controls. This suggests that pareidolic responses are elicited more easily in patients with iRBD.

Interestingly, the authors also found that iRBD patients with pareidolic responses (compared to those without) had different REM sleep microstructure with higher amounts of REM without atonia (RWA), lower cognitive function (Addenbrook's scores, scores of verbal fluency, language and visuospatial perception) and were older. Specifically, pareidolic responses were shown to be associated more intimately with cognitive decline than other variables related to iRBD, and suggest that iRBD patients with pareidolia belong to a subgroup close to clinical Lewy body disease.

In addition, iRBD patients with pareidolic responses had lower sleep efficiency and more wake after sleep onset. It is of course not possible to disentangle from a cross sectional study whether decreased sleep integrity heightened the susceptibility for pareidolic responses, or whether pareidolic responses and disturbed sleep integrity indicate more advanced neurodegeneration. Future studies might seek to investigate the effect of sleep deprivation on pareidolia, namely, if marked sleep restriction or sleep fragmentation induce more pareidolic responses even in healthy subjects.

Nevertheless, the rate of pareidolic responses of the
iRBD patients is lower than in those with manifest Lewy body disease who experience day- and nighttime symptoms, in line with the observation that iRBD heralds Lewy body disease or indicates early stage dementia with Lewy bodies (DLB) (9,10). The results of this study also correspond with the fact that REM behavioral events (11), REM without atonia (RWA), increase over time in patients with iRBD (12), even in patients with still isolated RWA (13-15).

Sasai-Sakuma et al. discuss whether the more severe motor dysregulation of REM sleep in iRBD patients with pareidolia could indicate a more widespread neuropathological involvement (potentially cholinergic) in this subgroup. Such an interpretation is in line with previous experimental findings that the onset and current distribution of the neurodegenerative process is responsible for the predominance of symptoms in iRBD (16,17).

Although the iRBD patients in this study had no complaints of delusions, hallucinations or fluctuations in cognition, the ACE-R was lower. It is notable that previous studies have reported decreased performance of otherwise cognitively intact iRBD patients in decision-making under ambiguity (18,19) and it has been discussed if this could potentially predict PD or Lewy body disease (18).

Regarding iRBD, different endpoints have been used for follow-up and conversion studies in patients with initial iRBD, e.g., Parkinson Disease, DLB, multiple system atrophy, or mild cognitive impairment (MCI)/dementia. It is considered that Lewy body disease includes both DLB and Parkinson Disease dementia (PDD) (20,21), and the Mayo Clinic has reported a strong association of RBD with synucleinopathies, specifically DLB, PDD and PD (20).

Findings from the present study by Sasai-Sakuma suggest that pareidolia, therefore, might help to identify earlier a subgroup within iRBD, and may predict Lewy body disease. In this sense, pareidolia may be a more specific biomarker than others to predict DLB or PDD.

Therefore, the pareidolia test in patients with iRBD could be useful as prognostic biomarker of potential conversion into DLB (or PDD).

**Pareidolia in other contexts**

Pareidolias are defined as complex visual illusions (22). While they were initially thought to be a surrogate marker of visual hallucinations, they are now seen as a susceptibility marker of those (1,22). Pareidolias were observed in DLB patients both with and without visual hallucinations (22). The Pareidolia test was developed by Uchiyama et al. (22), and was shown to discriminate very well between DLB and Alzheimer's disease.

The interaction between pareidolias and visual hallucinations in DLB is still debated. Cholinergic insufficiency has been suggested to be the common neural background (23). In non-demented PD, pareidolia was reported in all patients with visual hallucinations, and in part of those without (24).

In a discussion on the phenomenological similarities between visual hallucinations and pareidolic responses, Sasai-Sakuma et al. suggest that among common underlying mechanisms visuoperceptual and attentional deficits play a role in both phenomena. Pareidolias have also been located between hallucinations and visual misperceptions (25). Uchiyama has suggested that the pareidolia test is simply a test of visuoperceptual function itself, rather than a measure of pathological processes associated with visual hallucinations. This is based on the fact that there was a negative correlation between the number of illusory responses in the pareidolia test and scores on face recognition test in DLB patients treated with donepezil (22). With FDG PET it was found that the number of pareidolic illusions correlated with bilateral temporal, parental and occipital cortex hypometabolism (24).

**What is pareidolia and where else is it useful?**

Despite these significant findings described above, the pareidolia story is not limited to neurodegeneration; it has other chapters and a long history. The term pareidolia stems from ancient Greek (παρα εἴδολον) phantom image, or παρα εἴδειν (to look alongside) and is used to describe the fact that subjects find meaningful objects or faces in pictures, which only show neutral, non-object content. The “man in the moon”, induced by the lunar surface structure, is often referenced as a classical pareidolia existent since ancient times, although different cultures and observer positions see different faces or figures. Apart from its use in the context of Lewy body disease, it has been suggested that pareidolias do not, *per se*, reflect a pathologic sign, but instead a well-wired brain or even reflect creativity (26).

Historically, the pareidolias evoked by looking at the random patterns of the Rorschach ink plots have been promoted as a “psychological X-ray” able to “unlock the hidden secrets of the human unconscious” (26). In more recent times, the ability to recognize shapes and figures in
Rorschach plots has been viewed as more indicative of the observer's creativity (26). More recently, the potential of the human brain to create pareidolic responses has been target of research and other applications.

Pareidolia, defined as external stimuli triggering perception of non-existent entities, is thought to reflect “erroneous matches between internal representations and sensory inputs” (27). An fMRI study has shown that the right fusiform face area is involved not only in processing real faces, but also in illusory face perception in pareidolia (27). Magnetoencephalography has also identified early activation in the ventral fusiform cortex in pareidolia, similarly timed and located to those evoked by real faces (28). The authors interpret their findings that face perception evoked by remotely face-like looking objects is an innate faculty to rapidly detect and spot faces (and not dependent on cognitive phenomena which would appear later). The findings that non-facial objects can be recognized as faces is therefore considered to be due to the human brain being “hard-wired to detect the presence of a face as quickly as possible” (28).

A precondition of pareidolia is the “ambiguous” character of the object that evokes a pareidolic response. To induce perception of a face, the picture is thought to require a configuration and properties that remotely resemble those of a face (28).

More recently, fractal analysis of the historical Rorschach ink plots has demonstrated that the ability of each plot pattern to induce a sizable number of pareidolic responses is related to certain fractal characteristics that occur on the edges of the plots (26). Based on the results of their fractal analysis study, Taylor et al. suggest that future developments could try to better define certain pattern characteristics that stimulate pareidolic responses, for instance for camouflage design or artificial vision (26).

In neuroimaging, assigning to a certain image pattern a pareidolic interpretation has been used to improve recognition of specific patterns indicative of a particular disease (29) e.g., by defining characteristic patterns for specific diseases such as the Penguin sign or Mickey Mouse sign in PSP, the Panda sign in Wilson Disease, the eye-of-the-tiger sign (Hallervorden-Spatz-Syndrome or PKAN) (29), or the absence of the swallow tail sign, indicating loss of dorsolateral nigral hyperintensity in patients with iRBD (30). Finally, gender differences are notable in pareidolia, with healthy women being able to recognize non-facial images as faces earlier and more numerously than healthy men (31,32).

Therefore, besides pareidolia now being investigated as a promising new biomarker of neurodegeneration, the history pareidolia has seen multiple other interpretations, ranging from manifestation of the subconscious to expression of a simply well-wired brain (27), or expression of creativity (26), and as a support to pattern recognition and memorization. To make this distinction between creativity and pathology correctly, Sasai-Sakuma and coworkers state that clinicians need to distinguish carefully between conviction or reminiscence. So if a participant says, “it looks like” the clinician should ask whether they mean that it actually is, or only looks like. To count as pareidolia in this test, the subject should have the conviction or belief of reality.

Conclusion and outlook

Here, Sasai-Sakuma and coworkers present a new application for a test, which is quick and easy to perform, inexpensive, and uncomplicated to analyze (1). In patients with iRBD, the pareidolia test is a ready-to-use application and a new, possibly more specific biomarker for Lewy body disease and PDD.

Based on the fact that iRBD diagnosed by polysomnography is by far the most specific prodromal sign of an evolving underlying synuclein disease (33), or even an indication of ongoing α-synuclein disease (4), patients with iRBD are a potentially important target population to study in upcoming trials, not only with substances to alleviate symptoms of RBD (34), but also with potentially disease—modifying or neuroprotective substances. In addition, the long gap between the onset of iRBD and conversion to neurodegeneration (up to several decades) creates a need to identify subsets of patients who are going to convert in the near future, or who will convert to a more specific endpoint.

While certain clinical tests, like olfactory function, color discrimination and certain video-PSG and imaging tests have already indicated their potential for predict conversion (5-7,11,14,35,36), the present study from Taeko Sasai-Sakuma and the group around Professor Inoue at the Japan Somnology Center represents not only another fast and convenient test as a biomarker of potential neurodegeneration in RBD, but also has the potential to indicate a more specific pathologic profile and clinical endpoint.

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Footnote

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