Report for the Visual Snow Initiative

KING'S College LONDON

Visual Snow Syndrome

Investigation into the mechanism behind this neurological disorder

Visual Snow research discovery with King's

Visual snow syndrome (VSS) is an under-recognised neurological disorder, for which there is neither a clear understanding of the underlying pathophysiology nor adequate treatment. VSS is characterised by a constant perception of small flickering dots in the entire visual field, associated with a combination of visual symptoms: afterimages, sensitivity to light, entoptic phenomena, and difficulty seeing at night. The criteria for VSS were defined less than 10 years ago thanks to a seminal paper published by Professor Peter Goadsby and was further clinically characterised in a paper by Dr Pueldda, Professor Schankin and Professor Goadsby published in 2020. This long-standing lack of recognition means that very little is currently known about the mechanisms underpinning the development of the disorder, its underlying causes and, most importantly, what valid treatments we can offer patients.

This King's research project – generously funded by the Visual Snow Initiative – proposed to fill this knowledge gap, by using state-of-the-art neuroimaging and neurophysiology, to reach the following aims:

- **To determine biomarkers of cortical connectivity and neuronal metabolism that characterise visual snow syndrome.** By expanding on previous imaging work, this objective focuses on analysing changes in the cortical metabolism (through proton spectroscopy) and functional connectivity of visual areas (through layer-specific functional MRI), thus allowing to infer on the altered mechanisms of sensory processing and visual perception that are at the basis of the disorder.

- **To provide novel insights concerning the neurophysiological changes pertaining to the visual snow brain, and how these differ from migraine biology.** Non-invasive neurophysiology can help disentangle neural networks at the basis of pathological brain function. Little research has been done to investigate this aspect in visual snow syndrome. This objective, reached primarily through the use of advanced electrophysiological techniques (TMS/EEG, high-density EEG, and visual evoked potentials), will allow further investigation of cortical excitability in VSS and enable us to distinguish its neurophysiological fingerprint from that of comorbid migraine biology.

"Targeted research into this syndrome that affects an estimated 2% of the population is still in its infancy. However, leveraging state-of-the-art neuroimaging and neurophysiology technology ensures important progress is being made by Dr Francesca Puledda, in collaboration with the wider neurology, neuropsychiatry, medical physics and clinical imaging colleagues at King's, with clear avenues for future research development, which we would be delighted to discuss with you further.

With our heartfelt thanks again for your investment at King's. We hope you enjoy reading about the latest advances in Dr Puledda's research and we look forward to continuing our partnership."

Professor Peter Goadsby MBBS MD PhD DSc FRACP FRCP.
Director of NIHR Clinical Research Facility & Professor of Neurology

Progress

Since our last report in April 2024, Ms Viviana Santoro, a PhD student, has start working under Dr Puledda and Professor Goadsby's supervision on this research project funded by VSI. The focus of this research is using advanced neurophysiology to untangle the electrical signature of visual snow syndrome in the brain. Dr Puledda and her team have also conducted interim analyses of the collected data, which are showing some very interesting preliminary results.

Neurophysiology of VSS

The main experiment in this study consists of using transcranial magnetic stimulation (TMS) to stimulate different areas of the brain in a non-painful and non-invasive way, and to collect the signal generated by the TMS stimulation through high-density electroencephalography (EEG) – a technique known as TMS/EEG. **Figure 1** shows an example of the response of the brain to the TMS impulse, which is a wave called TMS evoked potential (TEP). By looking at differences in the time in which this potential is generated, as well as its amplitude – between patients with VSS and volunteers without the condition – we can understand multiple aspects of the way different areas of the brain are connected, how they communicate, and how they respond to external signals.

The top part of the Figure shows 'butterfly plots' – these are lots of overlapping lines that represent brain activity from different locations on the head. The blue lines are from healthy volunteers, and the red lines are from VSS patients. The grey bars mark the specific time periods that were focused on in the analysis. The bottom part shows maps of the brain, displaying the strength of these responses in different areas for both groups. These maps were made by averaging the **brain activity over the specific time periods highlighted earlier.**

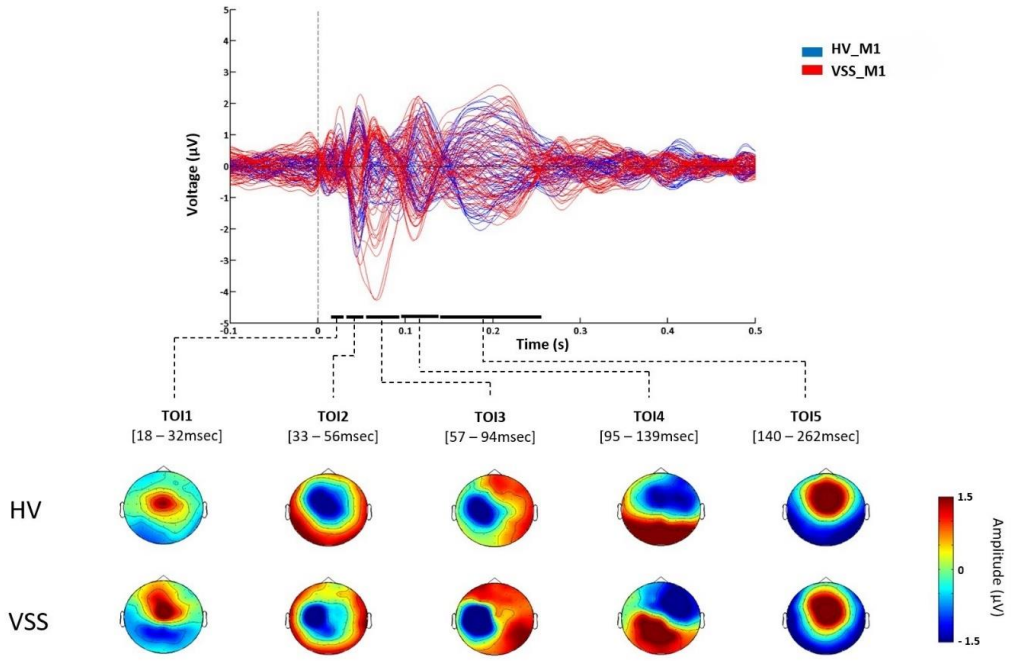
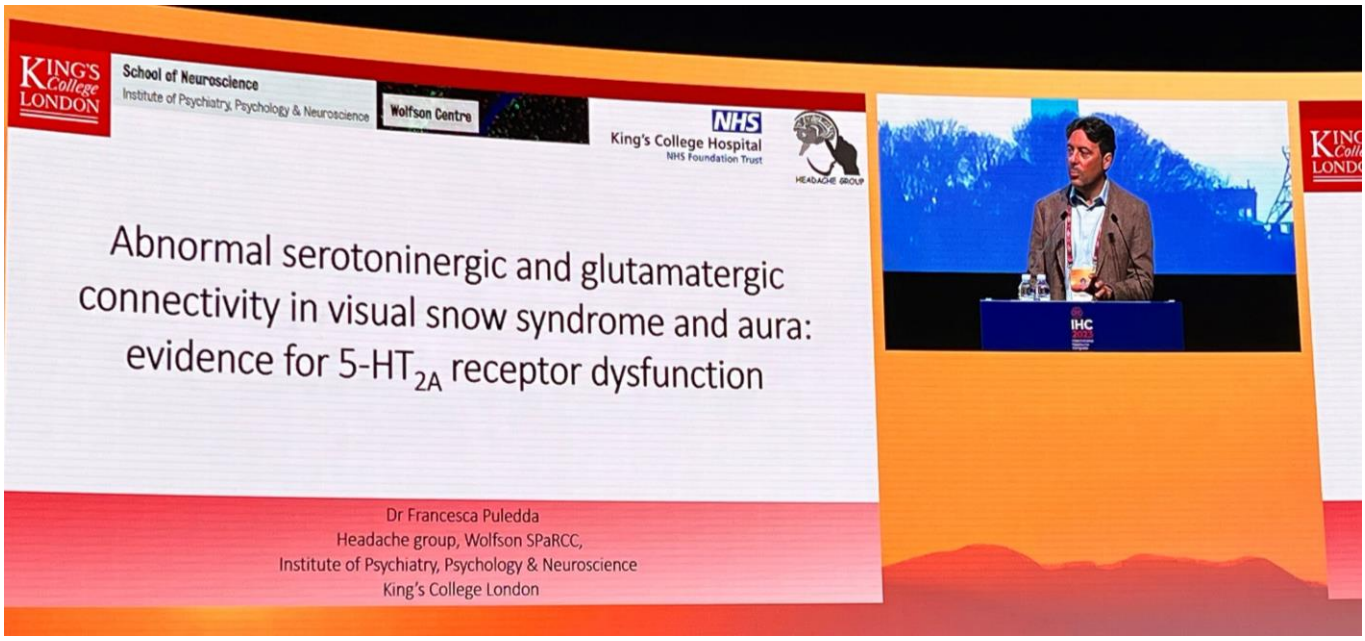


Figure 1: Spatiotemporal profile of TEPs for patients and healthy volunteers over the motor cortex (M1). The top panel shows grand average butterfly plots for healthy volunteers (blue) and patients (red): each line represents TEPs recorded at a single EEG channel; grey bars represent each TOIs used for the analysis. The bottom panel shows the topographical distribution of TEP amplitudes (ʊV) calculated as average over each TOI for healthy volunteers and patients, respectively.

The preliminary results of the neurophysiology experiment were presented at the Migraine Trust International Symposium in September 2024 and will be sent in abstract form in 2025 to the conferences of the American Academy of Neurology, European Academy of Neurology, and the International Headache Congress.



Dr Puledda's REACT study being shared as one of the highlights of the International Headache Congress.

Biomarkers of sensory processing and visual perception

In parallel with the neurophysiology study, Dr Puledda has been working in the ultra-high-field neuroimaging lab to set up the 7 Tesla magnetic resonance imaging (MRI) experiment. This proved to be a complex task given the highly-experimental nature of 7 Tesla ultra-high-field MRI, which is the highest intensity of MRI that can be used in humans. At King's, it is located in the Advanced MRI Centre based at St Thomas' Hospital, London, part of the wider Guy's & St Thomas' NIHR Imaging Clinical Research Facility (of which Professor Goadsby is Director).

Dr Puledda has now, together with collaborators from the School of Biomedical Engineering & Imaging Sciences based at St Thomas' Hospital, set up the full experiment and collected pilot data prior to the commencement of the study. By expanding on previous imaging work, this project focuses on using laminar fMRI (**Figure 3A**) and magnetic resonance spectroscopy (**Figure 3B**) to study the mechanisms of sensory processing and visual perception that are at the basis of the disorder of VSS in a direct way, and in unprecedented detail.

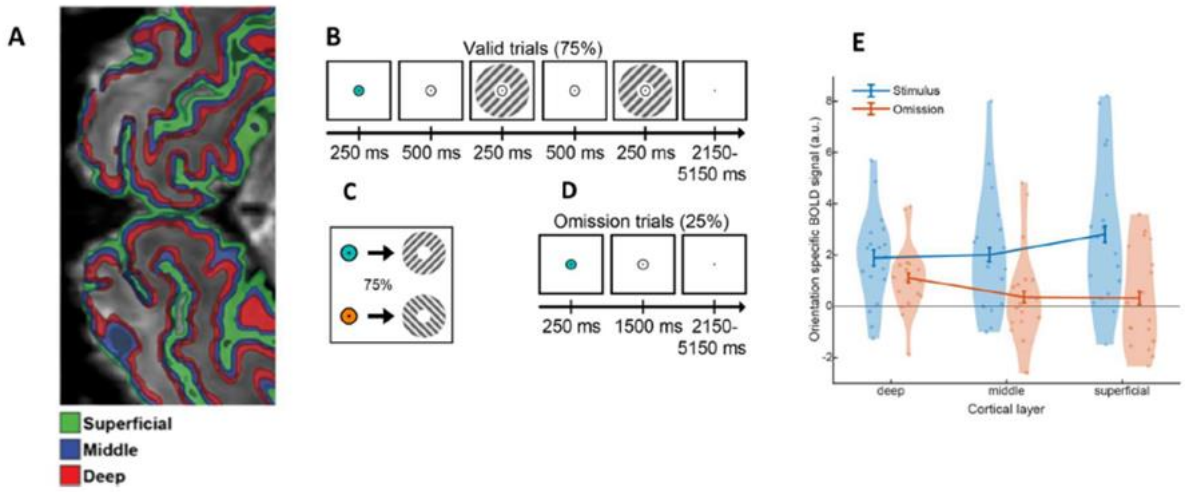
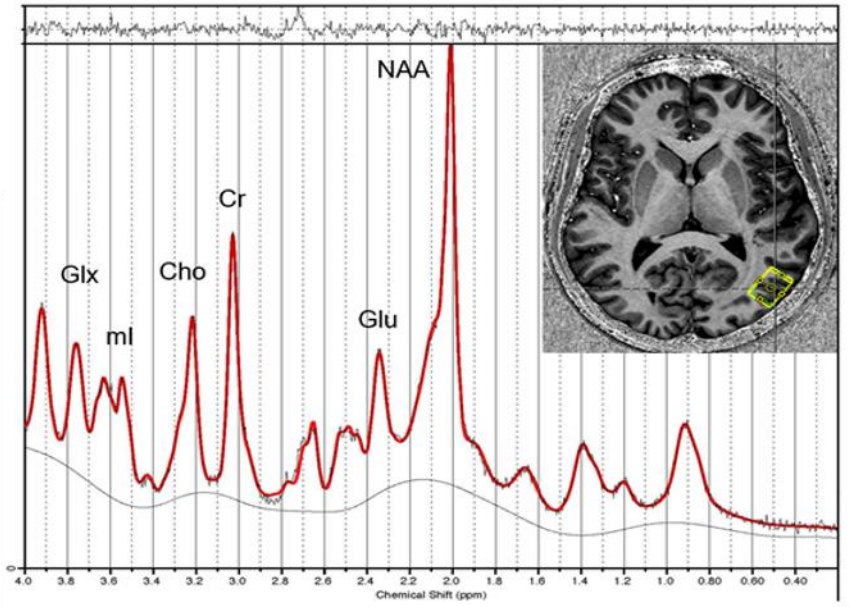


Figure 3: 7T MRI pilot sequences (from LoCUS funding award) and study design.

A) Laminar fMRI protocol: based on functional differences in cortical layers between feedforward and feedback transmission (A), an experiment causing a feedback driven expectation cue (B, C, D) causes preferential actitation of deep layers (E), and can be used to reflect feedback from higher-order cortical regions (Aitken et al. 2020).



B) 1H-MRS: Preliminary data of spectrum collected from V5. Acquisition time of 11" with 3" calibration, provides reliable quantification of GABA (quantified in LC model), Glu and Gln.

Direct impact for understanding Visual Snow Syndrome

Although the analyses shown above are preliminary and represent only a limited part of the larger experiment, they have already highlighted expected changes in the activity of the cortex (the outermost part of the brain) in VSS. It is hoped that future analyses will confirm these findings and allow the mapping of these changes over the areas of the cortex where they are occurring in a far more detailed way.

Further, starting the novel neuroimaging experiment at ultra-high-field will allow the collection of neuroimaging data with an incredibly high level of spatial detail and will enable us to confirm such neurotransmitter changes directly. In fact, this protocol has been set up in order to allow the direct measures of both GABA and glutamate – the main excitatory neurotransmitter in the brain – within different regions of the visual cortex.

Finally, as you are already aware, Dr Puledda has been working directly with Professor Schankin and Professor Goadsby on setting up a pharmacological study to investigate the effects of ketanserin – a serotoninergic inhibitor – on

VSS symptoms. The rationale for this study stems directly from the results of her paper published in *Annals of Neurology*, a high impact neuroscience and neurology journal. This study has received great interest and has highlighted the importance of the glutamatergic and serotoninergic 5HT2A systems in the pathophysiology of VSS.

Together, the results of these different methodologies are paving the way towards the translation of disease mechanisms into future pharmacological and neuromodulation treatments for visual snow syndrome, which are currently lacking.

Contributing to a wider body of work on neurological disorders

Advancing research into chronic pain and migraine, Dr Puledda was recently published as lead author of the first guidelines of the International Headache Society for the acute and preventive treatment of migraine. The landmark publication of these global practice recommendations will improve migraine management around the world.

Further, Professor Goadsby has published research that found that the headache drug, atogepant, can be used as a preventive measure in people overusing acute migraine medications like triptans, ergots and simple analgesics – and is an effective means of decreasing migraine days in adults with chronic migraine.

Looking forward

In parallel to the neurophysiology study – and preparing imminent applications for VSS research funding to the Royal Society, Wellcome Trust, and UKRI – Dr Puledda is setting up a treatment experiment to study the potential use of virtual reality to treat VSS. This stems from anecdotal reports that patients have shared with her (and also through the VSI team) that observing an external reproduction of static, such as in a video or with an Oculus device, can improve their symptoms, albeit temporarily. Dr Puledda has recently teamed up with the Neuropsychiatry team here at King's and plans to include this experiment as part of the ongoing TMS/EEG investigations.

Through your generous investment, we have already been able to discover important aspects of VSS and continue investigating its unknown biology, as well as making King's College London one of the leading centres for visual snow research worldwide. We look forward to having conversations about ways we can continue to partner on essential VSS research and make more strides towards improving the quality of life for people with this disorder, together.

Thank you from Dr Francesca Puledda

I would like to express my heartfelt gratitude to the Visual Snow Initiative community for the generous support of my study. Your contribution has been instrumental in allowing me to pursue critical research in the field of VSS, and I am deeply appreciative of your commitment to advancing scientific knowledge as well as to help patients with this debilitating condition.

With your help, we are not just making significant strides in understanding VSS, but we are also contributing to the general scientific and clinical interest in this condition, which is finally becoming recognised by healthcare professionals from all over the world. This would not be possible without the backing of people like yourselves, who believe in the importance of scientific discovery and innovation and understand how changes in patients' lives must go through the difficult – and sometimes lengthy – steps of rigorous research.

Thank you once again for your invaluable support. I look forward to sharing future outcomes of this important work and demonstrating the impact your generosity has made.