PROJECT TITLE: Elucidating the pathophysiological signature of visual snow

PRINCIPAL INVESTIGATORS:

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Associate Professor Fielding is a Research Fellow and Co-Director of the Ocular Motor Research Unit at the Van Cleef Centre, Monash University. She is an experimental neuropsychologist broadly interested in using the ocular motor system as a means of investigating neurocognitive processes in human disease states. She has previously been supported by an NHMRC Research Fellowship (2007-2010) at the University of Melbourne, and held a tenured academic position at Monash University in the School of Psychological Sciences from 2011 to 2017.

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Professor White is a clinical neuro-ophthalmologist and Co-Director of the Ocular Motor Research Unit at the Van Cleef Centre, Monash University. With an interest in disorders of ocular motility, he has been involved in clinical and research oculomotor studies for over 30 years, establishing the first academic neuro-ophthalmology unit and oculomotor laboratory in Australia, at the University of Melbourne, Royal Melbourne Hospital site (2001-2017), before moving to the current position.

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Professor McKendrick is Head of the Department of Optometry & Vision Sciences at the University of Melbourne (since 2014). Her research is broadly encapsulated under the umbrella of human visual neuroscience, with particular interests in healthy aging, migraine and glaucoma. She has previously been supported by an ARC Future Fellowship (2009-2013) and an NHMRC Australian Clinical Research Fellowship (2000-2003), at University of Western Australia.

LOCATION OF RESEARCH: The Alfred Centre, Melbourne, Victoria, AUSTRALIA

and

Department of Optometry & Vision Sciences, The University of Melbourne, Parkville, Victoria, AUSTRALIA

PROPOSITIONS

1. Visual snow (VS) is a disorder of sensory processing, likely a failure to screen multimodal sensory input to unimodal cortex (i.e. visual cortex). As the response of that cortex is unimodal, intrusion of extraneous afferents will manifest as visual phenomena.
2. VS is part of a broader range of disorders of sensory processing that might include, auditory, vestibular and somatosensory dysfunction.
3. By evaluating physiological deficits in VS in conjunction with neuroimaging investigations, we will be better able to:
    a. develop measurable physiological parameters that might help clarify the underlying pathophysiology of the disorder.
    b. Identify, recommend and evaluate the efficacy of therapeutic interventions.

OVERVIEW:

Although health care providers often see patients who report 'visual snow' (VS), the condition is poorly understood, historically misdiagnosed as either psychogenic or migraine with aura, or otherwise attributed to hallucinogen persisting perception disorder. This often creates undue stress on sufferers, precipitating endless and unnecessary investigations and further opinions. However, there is increasing evidence that VS has a biological basis, and that it may arise from similar pathophysiological mechanisms as migraine [2]. As proposed for migraine, it may be that VS is a consequence of aberrant cortical excitation or hyperexcitability [3]. Unfortunately, VS commonly co-occurs with migraine, confounding our understanding of its underlying pathophysiology. If we can more fully understand the specific features of VS, as distinct from comorbid migraine, we may then be in a position to develop diagnostic tools and effective treatment strategies for this significantly understudied condition.

RESEARCH PLAN:

This research aims to further our understanding of VS, by disambiguating the neurobiological signatures of migraine and VS using psychophysical, ocular motor, electrophysiological and imaging techniques. The research will explore differences between individuals with VS both with and without migraine, and individuals with migraine both with and without aura. This is key to exploring the unique contributions of VS, migraine and aura to the clinical and pathophysiological picture.

SPECIFIC STUDY AIMS:

1. To fully characterise visual perceptual and attentional (ocular motor) deficits associated with VS, eliminating the confound of comorbid migraine by contrasting performance in groups of individuals with:
    a. VS, with and without migraine,
    b. migraine and no VS, with and without aura.
2. To ascertain and dissociate the neural and neurochemical substrates of identified deficits across these groups using neuroimaging and visual electrophysiological techniques.

Participants (20 in each group as a minimum):

- individuals with VS, with migraine
- individuals with VS, without migraine
- migraineurs without VS, with aura
- migraineurs without VS, without aura
- neurologically healthy controls

Inclusion criteria for individuals with VS: With reference to recently proposed diagnostic criteria [24]: 1) dynamic, continuous VS for more than 3 months, 2) at least two additional visual symptoms of palinopsia, entoptic phenomena, photophobia or nyctalopia; and 3) symptoms not better explained by any other disorder or intake of psychotropic drugs.

Inclusion/screening criteria for all participants: A full ophthalmic assessment will be conducted to establish normal visual acuity (Snellen chart, acuity 6/12 or better in at least one eye), normal retinal anatomy and function (dilated fundus slit lamp examination), and normal full-field electroretinography in accordance with the International Society for Clinical Electrophysiology of Vision standards [25].

Exclusion criteria for individuals with VS: Any history of neurological disease, other than migraine, or demonstrable abnormal neurological signs.

Exclusion criteria for controls: History of migraine with or without aura, history of visual or neurological condition, intake of medication known to affect visual and cognitive function.

PLANNED TASKS:

Visual perception tasks: a series of studies will be conducted that assess perceptual responses to visual noise. Based on our own results and previous literature, we hypothesise that these tests will reveal differences in the profile of visual perception anomalies as a function of symptomatology (VS, aura, migraine headache).

Visual attention (ocular motor) tasks: a series of studies will be conducted that assess attentional control of eye movements. We hypothesise for each of these tasks that hyperexcitability will underlie the performance of all individuals, but that we will reveal differences in the profile of deficit as a function of symptomatology (VS, aura, migraine headache).

Magnetic Resonance Imaging tasks: a series of studies will be conducted that assess neurochemical and neuro-activation profiles using magnetic resonance imaging techniques. We hypothesise that these studies will reveal differences in the neurochemical, activation and association profiles as a function of symptomatology (VS, aura, migraine headache)

Electrophysiology tasks: a series of studies will be conducted that assess visual electrophysiology markers of performance. We hypothesise that we will reveal differences in the profile of potentiation and habituation as a function of symptomatology (VS, aura, migraine headache)

BUDGET ITEMS (AUD$) subject to project scope and term:

Personnel (level and term of funding subject to funds available)	**Level A3 – A1 (PhD) Post Doc** • includes on-costs (excludes overheads: 28% faculty, 32% central)	2018 - $110,000 2019 - $118,000 2020 - $126,000 2021 - $130,000
	Research Assistant (Hons) • includes on-costs (excludes overheads: 28% faculty, 32% central)	2018 - $86,000 2019 - $89,000 2020 - $92,000 2021 - $95,000
	PhD student stipend	2018 - $27,500 2019 - $28,500 2020 - $29,500 2021 - $30,500
	PhD student stipend top-up	$10,000 pa
Ophthalmological examinations	100 'sessions' (includes individuals excluded as unsuitable) @ $240 per session	$24,000
Electrophysiology studies	100 participants @ $200 each	$20,000
MRI sessions	100 participants x 2 x 1 hour imaging sessions @ $700 each	$140,000
Participant transport	**All studies**: 100 participants @ $60 each x 4	$24,000
	Behavioural and electrophysiological studies only: 100 participants @ $60 each x 2	$12,000

'OPTIMAL' BUDGET (AUD$):

Fully funded behavioural and electrophysiological studies only:

- **Research Personnel, Level A Post Doc:** 4 years = $484,000 (excludes overheads)
- **Ophthalmological examinations:** 100 sessions will be required (including excluded individuals) @ $240 per session = $24,000.
- **Participant transport:** 100 participants @ $60 each x 2 = $12,000.
- **Electrophysiology studies: $20,000**

Total - $530,000

Fully funded all studies:

- **Research Fellow, Level A (Post Doc):** 4 years = $484,000 (excludes overheads)
- **Research assistant:** 4 years = $362,000 (excludes overheads)
- **MRI sessions:** 100 participants x 2 x 1 hour imaging sessions @ $700 each = $140,000
- **Ophthalmological examinations:** 100 sessions will be required (including excluded individuals) @ $240 per session = $24,000.
- **Participant transport:** 100 participants @ $60 each x 4 = $24,000.
- **Electrophysiology studies: $20,000**

Total - $1,054,000

Issues

1. More common disease than previously identified
2. Poorly characterised
    a. Clinically – still some uncertainty re spectrum of complaints occurring with greater than chance frequency
    b. Physiologically
    c. Structurally – imaging
3. Without full understanding of pathophysiology, it is difficult to postulate what therapeutic interventions might work
4. Without measurable abnormalities, it is difficult to assess therapeutic responses
5. What is the relationship to migraine, HPPD, PPPD and other sensory disorders without explanation, including tinnitus, migratory paraesthesia etc