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REVIEW

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Fluctuations of consciousness, mood, and science: The interhemispheric switch and sticky switch models two decades on

Steven M. Miller[1,2]

[1]Perceptual and Clinical Neuroscience Laboratory, Department of Physiology, Monash Biomedicine Discovery Institute, School of Biomedical Sciences, Monash University, Melbourne, Victoria, Australia

[2]Monash Alfred Psychiatry Research Centre, Central Clinical School, Monash University and Alfred Health, Melbourne, Victoria, Australia

Correspondence
Steven M. Miller, Perceptual and Clinical Neuroscience Laboratory, Department of Physiology, Monash Biomedicine Discovery Institute, School of Biomedical Sciences, Monash University, Melbourne, VIC, Australia.
Email: steven.miller@monash.edu

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Abstract

Science and medicine aim to identify verifiable and replicable truths. However, the paths to such truths are frequently characterized by swinging pendulums of opposing perspectives. This is especially so in human neuroscience and the brain-based clinical sciences, where the target of investigation is the most complex of all biological systems. This article overviews a set of interrelated neuroscientific and clinical hypotheses, models, experiments, and predictions with which I have been involved for the last two decades. Traversing visual neuroscience, consciousness science, genetics, chronobiology, and biological and clinical psychiatry, the work illustrates how developments in science and medicine can occur through a combination of synthesis, serendipity, and experimentation. The article also reflects on doing science with the inimitable John "Jack" Pettigrew, and outlines how Pettigrew and I conceived, proposed, tested, and developed two new scientific models—one on neural mechanisms of binocular rivalry, the other on the pathophysiology of bipolar disorder. I also provide an update on various aspects of our models and data, and describe lessons learned from Pettigrew on how perspectives in science exhibit their own fluctuations, ironically like the very phenomena on which we worked.

KEYWORDS

binocular rivalry, bipolar disorder, bistable oscillator, caloric vestibular stimulation, consciousness, interhemispheric switch, sticky switch

1 | INTRODUCTION

John "Jack" Pettigrew (2/10/43—7/5/19) lived a remarkable life in science (Box 1). The collection of articles and contributors to this special issue illustrates this better than any single description, and conveys the extraordinary breadth and depth of Pettigrew's scientific life. Here I describe just one part of that life. I start by outlining in Sections 2 and 3, the early days of our work together and the ideas that led to our discoveries and proposal of two new models—a mechanistic model of binocular rivalry (BR) and a pathophysiological model of bipolar disorder (BD). In Section 4, I then describe the interhemispheric switch (IHS) model of BR in detail, including our experiments in support of it, clarifications made to it, its further testing, and related research since the model's proposal. Section 5 follows a similar course for the sticky switch model of BD, describing the experiments, further testing of our empirical findings and suggested applications of those findings, further testing of various key aspects of the model, related research since the model's proposal, and clinical translation prospects. In a style befitting of Pettigrew's scientific life, the article is wide-ranging, explores convergent perspectives, is at times opinionated and speculative, but is firmly founded on data.

2 | SYNTHESIS AND SERENDIPITY

In 1996, as a recent medical graduate, I wanted to study the brain to better understand consciousness. I had been fascinated by both consciousness and the philosophy of mind for nearly a decade, taking every opportunity during high school and medical studies to read books on these subjects. While on a visit to Melbourne to consider doing postgraduate study there, I was reading Francis Crick's, "*The Astonishing Hypothesis*" (Crick, 1994), on the emerging discipline of consciousness *science*. Soon after returning to Brisbane and while still contemplating a move South, I had a chance discussion with my University of Queensland (UQ) medical school friend, John McCoombes, who was at the time a training ophthalmologist. We were discussing our medical school lecturers and McCoombes reflected on Jack Pettigrew, who had delivered to us, several undergraduate neurophysiology lectures. McCoombes commented on Pettigrew's renowned contributions to visual neuroscience and his standing as one of Australia's brilliant contemporary scientists. I recalled Pettigrew's lectures being both entertaining and informative, and his use of Bertie the owl to demonstrate the vestibuloocular reflex was a standout memory for us both and no doubt for many of Pettigrew's students.[1] After my discussion with McCoombes, I decided to check whether Pettigrew had a project going that could be relevant to studying consciousness and that would enable me to learn more about the brain. If so, I would stay in Brisbane.

Pettigrew was then Director of the Vision Touch and Hearing Research Centre (VTHRC) at UQ and I made contact. I was offered two projects, with one on oxidative stress that did not intrigue me. The other would turn out to keep me scientifically occupied to the present day. At the time, Pettigrew and his long-time US colleague and friend, Josh Wallman, had been working on the independently alternating eye movements (EM) of a small fish, the sandlance (Pettigrew, Collin, & Ott, 1999; Wallman, Pettigrew, & Fritsches, 1995; see Carter, van Swinderen, Leopold, Collin, & Maier, 2020). They reasoned that the sandlance's unyoked EM must be driven by a neural switch between each side of its divided brain and they wondered whether a hemispheric switch might exist more generally in paired neural structures in the biological world. Pettigrew had also at the time been struck by the views of another long-time US colleague and friend (and former postdoc), V.S. Ramachandran, who had proposed complementary cognitive styles of the two cerebral hemispheres in humans (Ramachandran, 1994). On this view, the left hemisphere is the goal-directed "General," smoothing over discrepancies and advancing no matter the cost, while the right is the discrepancy-seeking "devil's advocate," cautious and more likely to withdraw. Pettigrew could not envisage these opposing styles being active simultaneously and was convinced they would instead alternate. In addition, Pettigrew had a special interest in the clinical psychiatric condition, BD, with which he had been diagnosed in mid-life.[2] In the two poles of this disorder (i.e., mania and depression), he readily identified Ramachandran's opposing hemispheric styles. Pettigrew's interest in BD, and his interactions with Wallman and Ramachandran, thus motivated him to seek a neural switch between left and right hemispheres in humans to help understand the fluctuating mood states of BD.

Intrigued by *this* project, and with Pettigrew's enthusiasm for it clearly evident, I signed up. We began by trying to identify an electroencephalography (EEG) signal of unilateral hemispheric activation. Our plan was to thereafter use such a signal to identify left–right switching of hemispheric activation that correlated with respective manic and depressive (or simply positive and negative) mood states. To elicit the EEG signal we used the same brain stimulation technique—caloric vestibular stimulation (CVS)—that Ramachandran had utilized in arriving at his hemispheric cognitive style proposals (Ramachandran, 1994). CVS involves irrigation of the external ear canal with cold water and at the time it was known from brain-imaging studies that this induced activation in predominantly contralateral cortical and subcortical structures. With Greg Hooper, at the Cognitive Psychophysiology Laboratory of Gina and Laurie Geffen, we spent several months trying this out. However, these initial CVS and EEG experiments would soon give way to a major change in research direction.

As mentioned earlier, prior to contacting Pettigrew I had been reading Crick's, "*The Astonishing Hypothesis*" (Crick, 1994). Crick's book discussed BR, a fascinating visual phenomenon that involves fluctuations in perception every few seconds, between two different images that are presented simultaneously, one to each eye (Figure 1a). BR was already considered a phenomenon of some importance to the scientific study of consciousness, given its ability to delineate the "neural correlates of consciousness," a phrase that Crick and Christoph Koch had introduced to the field (and a theoretical and empirical issue to which I would later turn my attention; see Section 4.2).[3] Pettigrew's earliest discoveries had in fact been in the neurophysiology of binocular vision (see Box 1) and soon after I joined his center, he raised with me the intriguing BR findings that were emerging at the time from experiments by Nikos Logothetis, David Sheinberg and David Leopold (reviewed in Logothetis, 1998). These investigators were performing single-neuron electrophysiological studies of BR in alert macaque monkeys and their work was dramatically challenging the prevailing mechanistic paradigm of the phenomenon.

It had been thought until then that BR was mediated by reciprocal inhibition between monocular neurons in the separate ocular dominance columns at an early stage of visual processing (Blake, 1989). However, the new electrophysiological studies showed an absence of any such perception-dependent neural firing in monocular neurons in primary visual cortex (V1). They showed, rather, that while some *binocular* neurons at an early visual processing stage exhibited perception-dependent firing, there was a clear pattern of increasing correlated neural activity when progressing through the visual hierarchy. Only in the highest visual regions in the temporal cortex was there ~90% of neurons whose firing patterns directly tracked the monkey's behaviorally-reported BR perceptual fluctuations. Logothetis, Leopold, and Sheinberg (1996) had also reported new human psychophysical evidence for a late-stage resolution of the visual conflict during BR. Thus, by the late 1990's the pendulum of opinion

regarding high- versus low-level mechanistic interpretations of BR was again swinging, this time toward high, reigniting debates that had a century earlier engaged the likes of Helmholtz, Hering, James, and Sherrington (Blake, 2001).

With the existing goal of identifying a switch between relative hemispheric activation in humans, and with Pettigrew's discussion of the new BR electrophysiological experiments front of mind, I came across three key facts that would conjoin to change the research direction on which Pettigrew and I had embarked. First, Helmholtz, in contrast to Hering (see Blake, 2001), had held the view that BR was primarily a phenomenon of involuntary *attention* (von Helmholtz, 1910/1962). Second, studies of split-brain subjects had shown that each cerebral hemisphere could employ *independent* attentional mechanisms when the corpus callosum was divided (Luck, Hillyard, Mangun, & Gazzaniga, 1989). Third, hemispherectomy studies showed that a *single* cerebral hemisphere could sustain a coherent visual percept (Bogen et al., 1998). The conjunction of these three facts, on the background described above, led me to consider that BR might itself be the sort of switch that Pettigrew and I were seeking!

Excited by my first experience of synthesizing existing concepts and empirical findings into a new hypothesis, I pitched the idea to Pettigrew. I further suggested we use CVS to test it because CVS was known to unilaterally activate structures implicated in attentional processing and to modulate attentional phenomena such as post-stroke neglect (for citations see Miller, 2001). If my hypothesis was correct—that during BR, high-level regions in one hemisphere were relatively more active than similar regions in the other, and that such activation asymmetry switched sides when perception switched—then unilaterally activating those regions with CVS should increase the time spent perceiving that hemisphere's image. The specific hypothesis then was that CVS should change the baseline *predominance* of rivaling images (see Box 2).

Pettigrew did not initially favor the idea or the proposed change in research direction, but he was by nature open-minded and indeed, no stranger himself to proposing bold ideas (see Box 1). After a few weeks of persisting—perhaps pestering—with the idea, Pettigrew yielded to my enthusiasm and arranged for the maintenance staff in the UQ Physiology Department to build us a crude headset with mirrors to elicit BR (Figure 2a). At the Geffen's lab we conducted our first BR experiments, applying CVS to each other after baseline BR data collection, and comparing pre- versus post-stimulation data. To our astonishment and great delight, we readily observed exactly what the hypothesis predicted. Moreover, in looking at the switch rate of each other's BR, we stumbled—entirely serendipitously—upon a finding that would enable us to make a direct link between our new BR mechanistic model and the fluctuating mood states of BD. Pettigrew's BR rate was at least three times slower than mine. On this basis, we further hypothesized that BR is slow in BD. From that first BR pilot experiment started several streams of experimental research that continue to this day.

3 | TWO NEW MODELS

Bolstered by the success of our pilot BR experiments, we moved from using the mirror-based headset to a high-end, user-friendly VisionWorks™ system that had been sent from the US by Wallman to

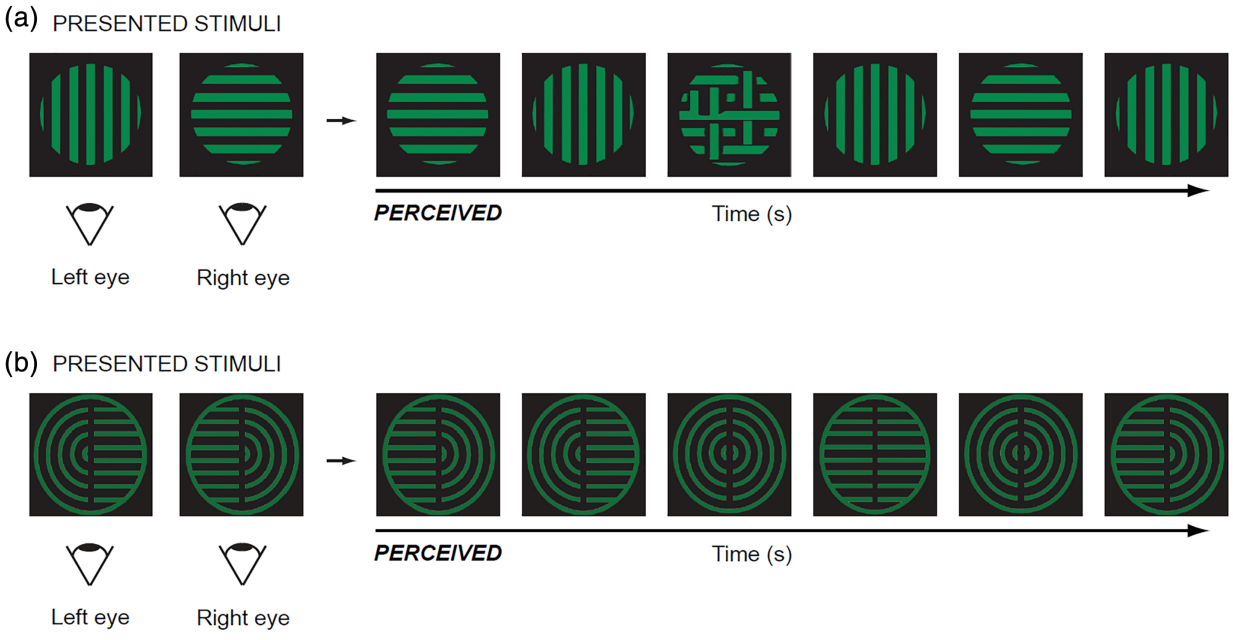

FIGURE 1 BR and coherence rivalry. (a) BR is elicited by presenting incongruous images to each eye, causing the brain to sample each in alternation, every few seconds. There are some perceptual periods in which aspects of each eye's presented image become mixed, but with use of small stimuli these can be minimized (and were always excluded from our calculation of BR rate and predominance). (b) Coherence rivalry involves aspects of each eye's presented image being synthesized (reconstructed) into wholes with which to rival. Perception during coherence rivalry involves periods perceiving each eye's presented (half-field) image and periods perceiving reconstructed whole images. Mixed percepts also occur during coherence rivalry but these are not depicted [Color figure can be viewed at wileyonlinelibrary.com]

Pettigrew's lab. With coding expertise and many collaborative hours contributed by Pettigrew's then postdoc, Guang Bin Liu, we proceeded to formalize our experiments on CVS modulation of BR predominance, utilizing willing VTHRC and UQ staff and students as experimental subjects. These experiments were, to my knowledge, the first application of a brain stimulation technique to the phenomenon of BR, or indeed to any perceptual rivalry type. We collected convincing data in support of what we came to call the IHS model of BR, from both CVS and thereafter transcranial magnetic stimulation (TMS) experiments (Miller et al., 2000; detailed in the next section). Concurrently, we collected BR data in BD and control subjects, and these indeed supported the proposal that BR was slow in BD. Pettigrew and I then set about piecing together how our ideas and findings could explain the fluctuating mood states of BD (explanation of which was, after all, our original intention). The question was: by what mechanism in the brain could human moods shift so extremely, from the exaltation, exuberance and hyperactivity of mania on the one hand, to the despair, anhedonia and hypoactivity of depression on the other? Our efforts to answer this question led to proposal of a new pathophysiological model of BD (Pettigrew & Miller, 1998).

Pettigrew's focus in the conceptual synthesis of our BD pathophysiological model was on: (a) Ramachandran's work on complementary cognitive styles of the left and right cerebral hemispheres (Ramachandran, 1994); (b) the potential role of a subcortical bistable neural oscillator driving the IHS (Marder, 1998; Rowat & Selverston, 1997); and (c) genetically period-coupled oscillators such as those that had been observed in *Drosophila* (Hall & Rosbash, 1988; Kyriacou & Hall, 1980). My focus was on: (a) existing evidence from lesion, inactivation, imaging and EEG studies, as well as repetitive TMS (rTMS) treatment studies, for hemispheric asymmetries of mood and mood disorders (for citations see Pettigrew & Miller, 1998; see also endnote 16) and (b) a little-known existing literature on ultradian rhythms of alternating cerebral activation, evidenced centrally by alternating asymmetries in scalp prefrontal EEG, and peripherally by alternating asymmetries of nasal patency (the nasal cycle). Indeed, the latter literature had already proposed the existence of a ~90-minute IHS in animals and humans (reviewed in Shannahoff-Khalsa, 1993; see also Price & Eccles, 2016), well predating our search. Appealing to all of these sources, we proposed the sticky interhemispheric switch model of BD (or sticky switch model, for short).

There are many elements of our BD pathophysiological model (see Box 3) and some are worth highlighting here. The first is the notion of genetically period-coupled oscillators whereby individual variation in switch rate is proposed to be proportional in switches of different periods. Our model invoked the notion of a short-period (milliseconds) posterior IHS in visual cortex (see Pettigrew, 2001, for details), a longer-period IHS more anteriorly in temporo-parietal regions (i.e., the seconds-long period of BR), and a yet longer and more anterior IHS in prefrontal cortex (i.e., the ~90 min ultradian IHS for mood and positive/negative affect). We proposed that individual variation in the period of the BR IHS would be coupled (i.e., would be proportionate) to periods of other switches in the same individual, such that a slow rate of BR would be associated with a slow visual cortex IHS or a slow prefrontal IHS (and conversely for individuals at the fast end of the distribution). Indeed, genetic coupling of rhythms with vastly different periods—precedent for which existed in *Drosophila* with coupled ultradian and circadian rhythms, as mentioned above (see also endnote 18)—was key to explaining why having a slow BR rate should be associated with BD. To explain this, Pettigrew noted that slow switches are biophysically "sticky" (i.e., prone to being held in one or the other position by extrinsic cortical input to the switch)[4] and therefore, slow prefrontal mood-related switches would get "stuck" in the left hemisphere position (the extreme of which would be mania) or the right-hemisphere position (the extreme of which, depression). This could therefore explain the mood state fluctuations that characterize BD.

Another aspect of the model worth highlighting is its explicitly stated therapeutic prediction. If mania is the result of a "stuck" left hemisphere activation asymmetry, then "unsticking" such asymmetry using left-ear CVS to activate the right hemisphere should restore the asymmetry to normal and thus reduce the signs and symptoms of mania. The converse should also hold for treating depression using right-ear CVS. The current status of evidence for the period-coupling notion and the CVS therapeutic predictions, as well as other aspects of the model such as its genetic defect prediction, is detailed in Section 5.3.

4 | THE IHS MODEL OF BR

4.1 | The experiments

Soon after publishing our initial data on slow BR in BD and our pathophysiological model of BD (Pettigrew & Miller, 1998), we proceeded to publish the data we had obtained in support of the IHS model of BR (Miller et al., 2000). These experiments included our initial study of BR with vertical and horizontal drifting gratings, in which we found that left hemisphere activation (i.e., right-ear CVS) indeed modulated the predominance of one image relative to the other during BR, but that right hemisphere activation (i.e., left-ear CVS) did not. We also published a second experiment, this time with orthogonal oblique stationary gratings, and observed exactly the same findings, suggesting our observations were not an artifact of residual nystagmic EM from the CVS. We reported a third experiment, conducted by Trung Ngo who had joined Pettigrew's lab, showing the same findings once again for viewing of the Necker Cube, thus broadening the IHS model to include ambiguous figure rivalry (Miller et al., 2000). Finally, with colleagues Richard Carson and Stephan Riek, we conducted and reported an experiment conceived by Pettigrew, using the relatively new technique (at the time) of single-pulse TMS (spTMS). Pettigrew also conceived the clever metal-free means of eliciting BR for the spTMS experiments (Figure 2b).

Pettigrew reasoned that unilateral spTMS applied over the temporo-parietal cortex should modulate predominance of BR and that this should occur when the TMS pulse was delivered according to one phase of perceptual switch, but not the other.[5] This was exactly what we observed in the majority of subjects (Miller

BOX 1 Jack Pettigrew's life in science

Jack Pettigrew lived a remarkable life in science (described colorfully and in detail by Mitchell, 2011, and in other articles in this special issue). He contributed to understanding neural mechanisms of binocular vision (reviewed in Bishop & Pettigrew, 1986) and performed, among others, pioneering studies in the pharmacological control of cortical plasticity, auditory physiology and bird navigation, and in the sensory ecology of many Australian species. He was made a Fellow of the Royal Society of London in 1987. He is also known for proposing a controversial hypothesis, based on neuroanatomical organization, that megabats are "flying primates" (Pettigrew, 1986). This proposal caused a storm of intercontinental controversy (see Gibbons, 1992), as molecular data emerged to challenge the hypothesis. Pettigrew refuted the molecular data (Pettigrew & Kirsch, 1995) and arguments over the relative weighting to be apportioned to molecular versus anatomical phenotypic evidence in phylogenetic studies have since appeared elsewhere (Near, 2009). Decades after his proposal, Pettigrew acknowledged that few scientists gave much credence to the flying primate hypothesis, but he considered the issue unsettled: http://www.uq.edu.au/nuq/jack/Update.pdf

From Pettigrew's stories of his lively scientific pursuits, I began to see how science and medicine themselves are subject to swinging pendulums and fluctuations of perspectives and motivations. I therefore learned early in my scientific career that novel hypotheses, such as those Pettigrew and I proposed regarding mechanisms of BR and the pathophysiology of BD, can take many years, indeed decades, to be proven or disproven. I learned further that differing perspectives on the same evidence can lead to entirely orthogonal scientific viewpoints. The irony of that—given BR is fundamentally characterized by fluctuations of perception despite unchanging sensory input—was not lost on either of us.

In a further irony, Pettigrew and I often did not see eye-to-eye as our work progressed. However, our differing scientific and conceptual styles, in my view, played a major part in the successful development of our ideas. The BR phenomenon of coherence rivalry—in which different aspects of each eye's image are combined by the brain into perceptual wholes with which to rival (Figure 1b)—perhaps provides the most appropriate analogy to characterize my intellectual interactions with Pettigrew. We each brought pieces of the scientific puzzle to the table, we usefully synthesized the pieces into meaningful wholes, but we nonetheless tussled in some of our views (though to be sure, we agreed more than we disagreed). For me as a young clinician embarking on scientific training, Pettigrew's infectious enthusiasm, open-mindedness, extraordinary breadth and depth of scientific knowledge, and outstanding capacity for conceptual synthesis provided the most stimulating of intellectual environments.

et al., 2000). While the CVS experiments induced statistically significant modulations of perceptual predominance during rivalry, these effects were mostly subtle and were not able to be noticed by subjects or experimenters until later plotting frequency histograms of interval durations. The TMS experiments, on the other hand, delivered striking (phase-specific) perceptual disruptions, immediately apparent to both subject and experimenter. Interestingly, the spTMS disruption effect was only observed when delivering pulses to the left hemisphere, mirroring the brain stimulation effectiveness asymmetry observed in the CVS experiments. The phase-specific modulation of BR by spTMS was a finding difficult to explain using any of the existing models of BR that assumed symmetrical neural activity between the hemispheres. In addition, by reporting CVS and spTMS modulation effects at high regions of visual and attentional processing, we contributed to the debate regarding high- versus low-level BR mechanisms, favoring the former.

Ngo and I continued experiments with CVS and rivalry, adding to the types of stimuli able to be modulated by the technique. We found Rubin's Face-Vase illusion exhibited the same modulation from left, but not right, hemisphere CVS activation (Ngo, Liu, Tilley, Pettigrew, & Miller, 2008). We also found that for Diaz-Caneja stimuli (Diaz-Caneja, 1928; Ngo, Miller, Liu, & Pettigrew, 2000)—in which aspects of each eye's presented image are combined to create coherent wholes with which to rival ("coherence rivalry"), different from either eye's presented image (Figure 1b)[6]—only the reconstituted coherent percepts were modulated by left, but not right, hemisphere CVS. In contrast, the half-field percepts (which matched the images presented to each eye) were not affected by either left or right hemisphere CVS (Ngo, Liu, Tilley, Pettigrew, & Miller, 2007). To explain those CVS data, Ngo and I postulated that Diaz-Caneja stimuli elicit a process we called "meta-rivalry," in which the two half-field images rival for access to consciousness, the two coherent percepts rival for access to consciousness, and the low-level half-field rivalry itself rivals with the high-level coherence rivalry for access to consciousness (i.e., the inter-level rivalry process being meta-rivalry; Ngo et al., 2007).

In a final large CVS BR experiment, yet to be published but discussed in a comprehensive review (Ngo, Barsdell, Law, & Miller, 2013), Ngo and I set out to examine the reliability of the CVS modulation finding and the issue of which hemisphere selects which percept during BR. This was the only of six separate experiments (other than that for half-field rivalry, as hypothesized) that failed to show statistically significant modulation of BR predominance by CVS (thus also rendering the percept-to-hemisphere selection issue unable to be assessed). The tally, therefore, of experiments showing significant left hemisphere CVS modulation of BR predominance, but not right hemisphere CVS modulation, was five, with one additional

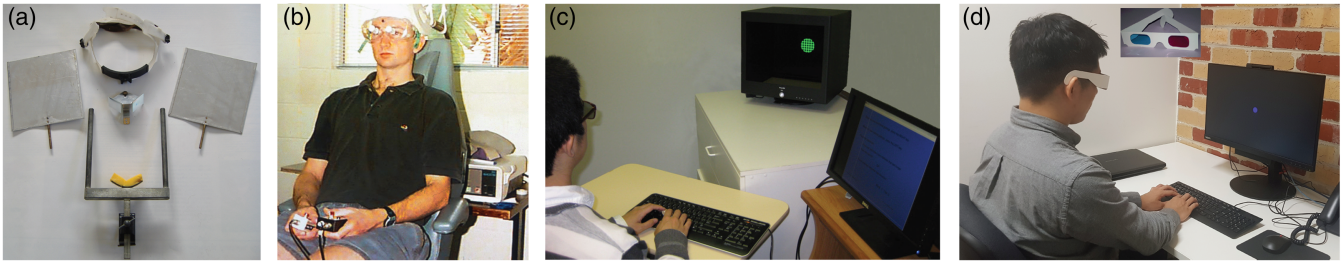

FIGURE 2 Various BR presentation methods. (a) Remnants of the original headset BR set-up with which Pettigrew and I made our initial discoveries. The subject wore the plastic headpiece, from which the mirror-holding plates hung. The subject rested on the chin rest and arms (which are missing from the remnants) connected the rest structure to stimulus-holding plates on either side (stimuli not depicted). The subject moved the arms to position the stimuli in each mirror's field of view and aligned the stimuli to be overlapping so as to induce BR. (b) Pettigrew conceived this novel metal-free BR set-up suitable for our spTMS experiments. Two 2 cm (length) by 1 cm (diameter) translucent plastic tubes were used, each with a 50 diopter lens at the proximal end, that viewed a 1 mm (diameter) grating on translucent paper at the distal end. The subject positioned the tubes on the face-plate of a safety mask, aligning the images, with gratings orthogonal in each eye, to induce BR. The photograph also shows the separate response buttons for each image, with one triggering the spTMS but not the other—the key design element of the experiment. The spTMS paddle was positioned over left temporo-parietal cortex. (c) Soon after making our discoveries with the crude headset device shown in (a), we moved to a variety of computer-based set-ups to collect large BR datasets. These included a VisionWorks™ stimulus presentation system provided by Josh Wallman, then a system put together by Guang Bin Liu using liquid crystal shutter goggles, and thereafter a system using polarization filter glasses and green monochrome stimuli as depicted in the photo. The photograph also depicts the separate computer-based screen instructions (created by Liu) for delivering the BR recording protocol. (d) Our latest work has involved psychophysical validation of an anaglyph BR test method, using inexpensive, foldable cardboard red-blue glasses, that can be readily mailed to existing large psychiatric genetics research cohorts, to facilitate the obtaining of massive sample sizes for genetic endophenotype studies (see text). In (c) and (d) the photographs are taken with the lights on but testing in fact occurs with lights off and with ambient illumination from a small corner lamp [Color figure can be viewed at wileyonlinelibrary.com]

experiment not showing such modulation (half-field rivalry, as hypothesized) and another failing to replicate the five positive experiments.

4.2 | Clarifying the model

Soon after publication of our first two main articles, Pettigrew and I each wrote contributions to a journal special issue on BR. Here too, Randolph Blake (2001) outlined the history of BR research and the swinging pendulum of perspectives in this field, as mentioned in Section 2. Both Pettigrew's and my article discussed our experiments and models, and advanced various aspects therein. Key elements of the IHS model of BR are summarized in Box 1.

Pettigrew's (2001) article outlined why looking at V1 alone to explain BR is misguided and he noted an irony in this regard, given he had spent the prior three decades arguing that V1 had greater capacity for complex analysis and synthesis than previously thought. Pettigrew had a deep understanding of the physiological properties of V1 from his own work on this region and his 2001 article described the many inconsistencies, as he saw them, between V1's properties and those of BR (though he also did not discount V1 entirely from BR processing). He additionally clarified where he considered the BR switch would be located—"in the sub-cortical neuraxis where it straddles the midline and can act as a bistable oscillator acting for both hemispheres" (Pettigrew, 2001; pp. 87). Finally, he outlined his reasons for favoring the existence of such an oscillator, addressed the issue of conflating the visual hemifields and the cerebral hemispheres when thinking about the IHS model, and discussed why he felt that the corpus callosum would not be the site of the switch (in no small part due to his *comparative* neuroscience perspective).[7]

In my article (Miller, 2001), I provided examples (as had Pettigrew) of how existing BR data could be reinterpreted in light of the IHS model, and I also set about refining how to think about the model (and in turn, how best to test it). I distinguished neural activity relevant to the conscious content of each BR state, from neural activity that selected for such content. In so doing, I raised the possibility that the temporo-parietal IHS mediating BR might utilize the independent attentional selection mechanisms in each hemisphere, and thus that an IHS for BR might be synonymous with a process of alternating unihemispheric attentional selection. If so, two possibilities regarding neural mechanisms of visual consciousness during BR emerged. Either visual consciousness during BR is constituted in a unihemispheric fashion (thus mirroring the unihemispheric attentional selection process that selects for its content), or visual consciousness is in fact symmetrical across the hemispheres while it is just the attentional selection for conscious content that alternates in an IHS manner. As well as providing detailed arguments for this proposed refinement of the model, I also provided attention-based explanations for the brain stimulation effectiveness asymmetry evident in the CVS and TMS experiments, discussed links between brainstem regions and attentional processing, and like Pettigrew, discussed the issue of hemifields and hemispheres (I did not discount a role for the corpus callosum, whether or not the subcortical oscillator account was accurate). Finally, I argued that the issue of how to distinguish whether consciousness during BR involved symmetric or asymmetric hemispheric activation was a specific case of a more

general problem for consciousness science, which I termed the correlation/constitution distinction problem. This was a problem about which I would subsequently say much more (Miller, 2007, 2013, 2014, 2015a, 2015b).[8]

4.3 | Further testing the model

Remarkably, in the two decades since Pettigrew and I proposed the IHS model of rivalry, there has been but one attempt to scientifically refute it. Robert O'Shea and Paul Corballis set out to examine BR in the split-brain arguing that its existence would refute the IHS model. Their first report in this regard (O'Shea & Corballis, 2001) appeared in the same BR special issue to which Pettigrew and I had contributed. Their experimental logic was outlined despite the IHS model having specifically predicted that BR would survive sectioning of the corpus callosum (Miller et al., 2000), given we proposed the switch to be driven by a brainstem or subcortical oscillator rather than the callosum. The split-brain experiments conducted by O'Shea and Corballis (2001, 2003, 2005a, 2005b) indeed led them to argue against the IHS model and our responses to their work have been presented in detail elsewhere (Miller, 2001; Ngo et al., 2007; Pettigrew, 2001). Rather than repeating details of that controversy here, it is more informative to reflect on the field's general lack of attempt to refute the IHS model since its proposal (see also Ngo et al., 2013).

Not long after our model was published, Blake and Logothetis (2002) reviewed the evidence for high- and low-level BR models and concluded the phenomenon involves a series of processes at multiple stages of visual processing. Their hybrid model could thus account for the seemingly conflicting data that gave rise to the historical (and continuing) fluctuations of perspectives on the level of BR resolution. While their view is no doubt at least partly accurate, it is also one that may have unintentionally left the field bereft of drive to find a more distinct BR mechanism(s). The electrophysiological data from Logothetis and colleagues—so incompatible as they were with the V1 reciprocal inhibition model of Blake (1989)—did not in themselves explain how switching occurs during BR (though see Section 5.3 for description of the latest striking BR electrophysiological findings from Logothetis and colleagues). The hybrid model had, however, opened the field to new possibilities for BR models. Ours was one such new model, that although did not exclude a role for lower level processing, and rather favored a high-level switching process, was nonetheless a distinct and highly testable mechanistic model (i.e., it was not just another piece of data on the levels issue). In light of an opening up of the field, it is surprising there have been, now two decades on, so few attempts to independently test the IHS model (though a glance at PubMed illustrates that the model has certainly been discussed and appealed to in various articles). In contrast, studies continue to emerge on the levels controversy and there has remained little progress on understanding just how perception switches during BR—on explaining its *fundamental* mechanism(s) (but see Section 5.3). Indeed, it should be noted that Blake and Logothetis (2002) themselves called for a careful look at the IHS model (noting that the model situated BR in the novel context of individual differences, biological rhythms, and mood disorders).

One particularly unusual aspect of the IHS model's history concerns our spTMS finding described above. While CVS is not a commonly employed brain stimulation technique, TMS has become a widely employed technique and has been used by several researchers to probe BR processing and the role of particular brain regions therein (reviewed in Ngo et al., 2013; see also Sterzer, 2013; Brascamp, Sterzer, Blake, & Knapen, 2018). It is perplexing therefore, that in addition to a lack of attempt to refute the IHS model, there has also been no attempt to independently replicate our striking spTMS finding. Here the issue may be that replicating that finding would place onus on investigators who may not favor the IHS model, to explain the finding without appeal to the model. Indeed, even without conducting further experiments, there have been no alternative explanations offered for our spTMS finding in the literature to date.

Moreover, there have been no brain imaging or EEG studies published with a view to attempting to prove or disprove the IHS model. This is all the more remarkable when considering that, notwithstanding a multitude of proposed computational models of rivalry, there have been few specific mechanistic BR models proposed, and certainly none as readily testable with the methods of modern neuroscience as the IHS model. We have elsewhere outlined the most promising approaches to testing the model, by way of single-unit electrophysiological studies (which would of course be challenging and time-consuming to perform), EEG and magnetoencephalography studies, and functional brain-imaging studies (Miller, 2001; Ngo et al., 2007, 2013). There, we also outlined a range of methodological issues to consider when designing and interpreting such studies (see Box 2). The methodological issues certainly raise complexities, but these are far from insurmountable. Perhaps there is simply a willingness in the field for the model to retain its current perceived status: a curiosity of some interest, but too unlikely to bother testing. Doubters of scientific models, however, are usually driven to demonstrate the falsehood of such models so as to eliminate them. The lack of independent examination of the IHS model of BR therefore remains somewhat of a scientific curiosity in itself. It may be worth remembering Pettigrew's (2001) comments on the decades it took for his V1 binocular disparity detection proposals to be accepted, as well as his still unresolved controversy over megabat evolution (see Box 1). No doubt, time will tell on the IHS model's fate.[9,10]

4.4 | Related research

Comparative evidence was a key piece of the puzzle leading Pettigrew and I to propose that an IHS mechanism mediated BR. As mentioned, Wallman and Pettigrew (and Pettigrew's doctoral student at the time, Kerstin Fritsches) had observed and reported independent EM of the sandlance (Wallman et al., 1995) that suggested the existence of an IHS, with similar EM patterns also observed in the chameleon (Pettigrew et al., 1999; see Carter et al., 2020). Wallman and Pettigrew considered IHS mechanisms should be widespread in the biological world and indeed the list of identified IHS phenomena

continues to grow. For example, IHS mechanisms exist also in birdsong production, rodent suprachiasmatic nucleus, marine mammal and avian sleep, and in humans in the form of the nasal cycle (which is also observed in other species), ultradian rhythms of prefrontal activation, sleep, and as we would hold, perceptual rivalry (reviewed in Miller, Ngo, & van Swinderen, 2012; Ngo et al., 2013; and discussed below in this section and in Section 5.4). In 2010, the first comparative evidence for an IHS driving perceptual rivalry was reported, in the miniature brain of *Drosophila*.

Tang and Juuosola (2010) elicited switching behavior in *Drosophila* in response to incongruent dichoptic (separate eye) visual stimulation of the sort that induces BR in humans, nonhuman primates and cats. The fly responds to such stimuli by exhibiting behavioral orientation shifts that alternate, providing clear evidence that the fly's brain is rivaling. Others had previously demonstrated such rivalry-like switching behavior in flies (see Carter et al., 2020; Miller et al., 2012), but remarkably, Tang and Juusola (2010) showed that local field potentials (LFPs) measured either side of the midline in the fly's optic lobe preceded changes in direction of such orienting behavior in an IHS manner (Figure 3.). This comparative evidence for a visual rivalry IHS was first brought to my attention by Ngo and on its basis, he and I joined forces with *Drosophila* researcher, Bruno van Swinderen, publishing an article outlining in detail the relevance of Tang and Juusola's (2010) finding to human rivalry, the IHS model, the sticky switch model, and the genetics of BR and BD (Miller et al., 2012). In that article, we discussed notions of attention, suppression, and switching in humans and flies, and presented a potential research program that we argued could capitalize on the powerful genetic and molecular investigative capacity afforded by the *Drosophila* model. The article also enabled expression of ideas concerning evolutionary aspects of interhemispheric switching, my contributions to which were influenced by discussions I'd had with Pettigrew during early development of our models.

A particularly interesting related research area concerns IHS electrophysiological activity during sleep. Sleep has provided comparative evidence for IHS mechanisms including alternating unihemispheric slow wave sleep in aquatic mammals and avians (for reviews and citations see Dell et al., 2016; Lyamin, Manger, Ridgway, Mukhametov, & Siegel, 2008; Manger & Siegel, 2020; Miller et al., 2012; Ngo et al., 2013; Rattenborg et al., 2016). There have also been reports of IHS electrophysiological signals during human sleep (Imbach et al., 2012[11]; Tamaki, Bang, Watanabe, & Sasaki, 2016) and IHS activity might be implied from other human sleep data. For example, in an intracranial recording study of human sleep, local (regional) slow wave activity has been identified with varying degrees of concordance across the midline, with highest concordance in prefrontal regions and lowest in the posterior cingulate cortex (PCC; Nir et al., 2011). The poor concordance in slow wave activity between left and right PCC regions may be reflective of an IHS during human sleep, that is moreover, locked to single-unit activity.[12] A type of IHS during human sleep was also recently demonstrated by way of the first night (or night watch) effect. Interhemispheric asymmetry of electrophysiological activity reflecting sleep depth was observed in the default mode network (DMN) during the first night's sleep in a new environment, with the less asleep hemisphere also showing increased vigilance to deviant stimuli (Tamaki et al., 2016[13]). Although the function of the PCC is not fully understood, during awake states it is a key hub of the DMN and it is relevant to both attentional and emotional salience processing (Leech & Sharp, 2014). I would speculate that, if IHS sleep activity in the PCC has an awake IHS counterpart, with oscillations perhaps also locked to single-unit activity, this may yield important clues to mechanisms underlying fluctuations in attention and consciousness (including rivalry), and mood. At the very least, the evidence for existing IHS phenomena—both comparative and human—should render the IHS model of BR less unlikely than many in the field might choose to believe.[14,15]

5 | SLOW BR IN BD AND THE STICKY SWITCH MODEL OF BD

5.1 | The experiments

In our first publication, Pettigrew and I presented both our initial findings on slow BR in BD compared with controls, and the various elements of the sticky switch model (Pettigrew & Miller, 1998). That first study used high-strength rivalry gratings (i.e., drifting and of high spatial frequency; Figure 4a). The follow-up study (with additional involvement of Bruce Gynther, Philip Mitchell, Karen Heslop, Laurie Geffen, Ngo and Liu; Miller et al., 2003) added to this dataset with further BD and control subjects viewing high-strength gratings, and BD and control subjects viewing lower strength gratings (i.e., stationary and of lower spatial frequency; Figure 4a). The higher strength stimuli appeared to better separate the BD from control groups when comparing data from our two studies. Miller et al. (2003) also examined BR rate in schizophrenia and major depression (notably using the less effective lower-strength stimuli; Figure 4a). We reported that while BR rate was significantly slower in BD than controls, this was not the case for patients with schizophrenia or major depression, at least on a group basis (however there were clearly some subjects in these groups, and indeed in the control group, who exhibited slow BR). Miller et al. (2003) also found that neither medication nor clinical state appeared to modulate BR rate, though we were cautious about these findings because such effects ultimately require assessment of BR rate before and after medication or state changes.

An important element of the sticky switch model was that an individual's BR rate would be under genetic control. It was already known that BR rate varied widely between healthy individuals but was reliable within an individual on re-testing (Aafjes, Heuting, & Visser, 1966; Enoksson, 1963; George, 1936; Mull, Armstrong, & Telfer, 1956). We confirmed those findings and added to them by reporting that BR rate was also reliable in BD subjects. At the time of our initial publication, we had also collected a small pilot dataset of BR rates in monozygotic and dizygotic twins and we appealed to those data in proposing genetic control of BR rate. The pilot twin

BOX 2 Key elements of the IHS model of BR

- There is wide-ranging comparative and human evidence for the existence of IHS phenomena.
- BR has been considered an involuntary attentional phenomenon; attentional function can occur independently in each hemisphere in split-brain subjects; a single cerebral hemisphere can sustain a coherent visual percept in hemispherectomy subjects.
- BR may therefore be mediated by an IHS.
- On this view of BR (and of other rivalry types, such as the Necker cube), one hemisphere selects one image representation (or perspective in the case of the Necker cube), the other selects the other image representation, and perceptual alternations reflect a process of alternating relative hemispheric activation (interhemispheric switching).
- Low-level visual regions are not entirely excluded from BR processing, but the fundamental BR mechanism is an IHS occurring at high levels of visual processing.
- The corpus callosum does not drive the IHS; rather a subcortical or brainstem bistable oscillator does so; because of this, BR was predicted to survive sectioning of the callosum (as has been shown to be the case); the callosum may nonetheless play some role in IHS processing.
- On an IHS model of BR it is critical to not conflate visual hemifields and cerebral hemispheres; while there is a clear hemisphere and hemifield link at low levels of visual processing, this is not where IHS processing is proposed to occur; at high levels of visual processing, such as inferotemporal cortex, single-units have large bilateral receptive fields, suggesting the low-level hemisphere-hemifield link is no longer relevant at these later stages; hence the hemisphere-hemifield link is not relevant to the IHS model.
- A distinction can be made between visual consciousness during BR being asymmetrical in IHS fashion and/or attentional selection for access to visual consciousness during BR being asymmetrical in IHS fashion.
- On either IHS model interpretation however, unilaterally activating or disrupting high-level regions in one cerebral hemisphere should alter the relative time spent perceiving that hemisphere's image representation (i.e., should alter BR predominance); this has been shown to be the case using two brain stimulation techniques (CVS and spTMS).
- There is, however, a brain stimulation effectiveness asymmetry evident in both CVS and spTMS experimental data (i.e., activating the left hemisphere with CVS and disrupting the left hemisphere with spTMS induced predominance modulation, while similar effects were not observed for the same interventions targeting the right hemisphere); there are several possible explanations for this effectiveness asymmetry and these include reference to known hemispheric asymmetries observed in BR imaging studies and known hemispheric asymmetries of attentional processing and spatial representation (detailed in Miller, 2001; see also Brascamp, Sterzer, et al., 2018).
- Further testing of the IHS model with imaging or electrophysiological studies should avoid: (a) using stimuli that are likely to lateralize (e.g., faces), (b) averaging signals across subjects, and (c) averaging signals for both directions of perceptual switch; rather analyses should be done on an individual subject basis and separately for each direction of perceptual switch; analyses should examine for signals consistent not only with a straightforward IHS model, but also the more complex attention-based interpretation of the model in which the right hemisphere selects *both* representations while the left hemisphere selects only one (see Miller, 2001); the IHS model does not propose there to be asymmetric activity across the entire hemisphere; rather regions of interest in imaging studies seeking to identify IHS signals should include those that may correlate with perception during BR and those that may select for perceptual content.

data had been collected with Nick Martin and Margie Wright at the Queensland Institute of Medical Research (now QIMR-Berghofer Medical Research Institute) and had emerged following a chance meeting between Pettigrew and Martin in a supermarket queue. A decade later we published a dataset of 722 twins, confirming genetic contribution to individual variation in BR rate (Miller et al., 2010; Figure 4c,d). That study also represented the first report of genetic contribution to any postretinal visual processing phenomenon, to our knowledge. It additionally confirmed, in a large dataset, the high retest reliability of BR rate, both between blocks within a test session and between test sessions on separate days (Figure 4e,f).

Genetic modeling of our twin data suggested that around 50% of the variation in BR rate could be accounted for by genetic factors (Figure 4d). This was important not only because our BD model entailed the notion of genetically period-coupled oscillators and a specific genetic defect prediction, but also because BD is a heritable condition (Johansson, Kuja-Halkola, Cannon, Hultman, & Hedman, 2019) and biomarkers for heritable conditions can potentially be used as endophenotypes (i.e., markers of genetic predisposition to a disorder, even prior to the disorder manifesting; Gottesman & Gould, 2003; Hasler, Drevets, Gould, Gottesman, & Manji, 2006; Kendler & Neale, 2010; Leboyer et al., 1998). High retest reliability also supported the notion of using slow BR as an endophenotype for

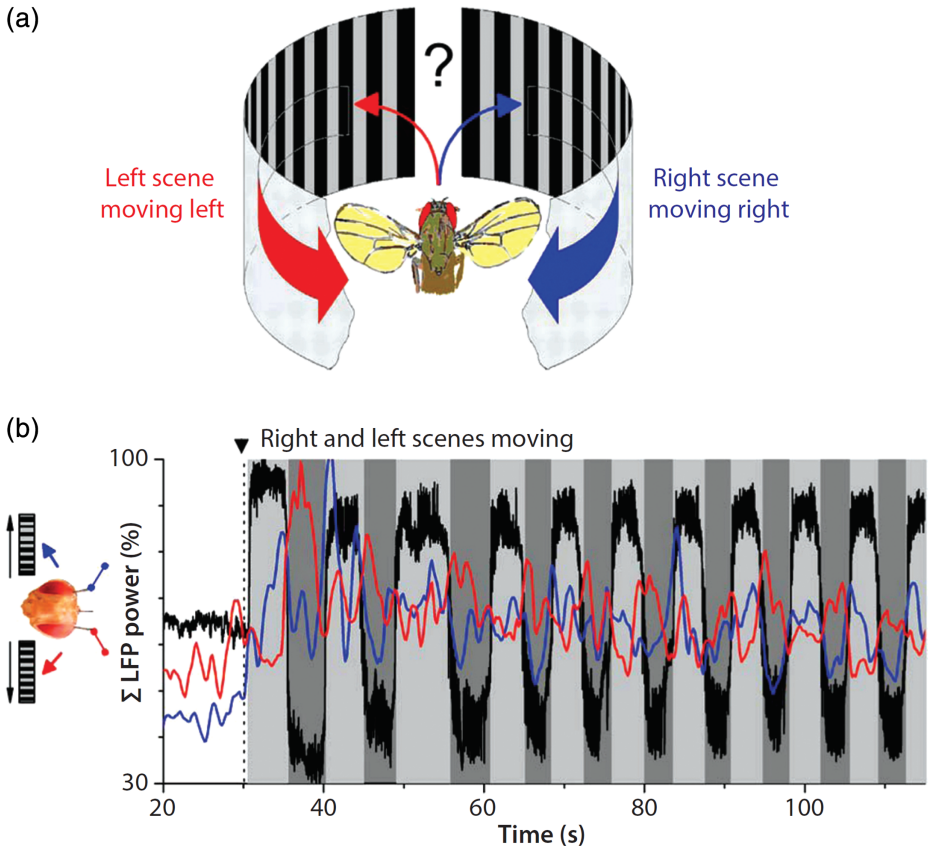

FIGURE 3 Rivalry in *Drosophila* and its IHS electrophysiological basis. (a) A fly presented with dichoptic visual stimulation in a tethered flight set-up displays rivalry-like orienting behavioral switches between the left and right competing stimuli, which are measured using a torque meter (not shown). Bilateral electrophysiological recordings from the fly's optic lobes (b) revealed unilateral local field potential (LFP) activity preceded the switch toward the same side (while LFP activity on the opposite side was inhibited), and that this unilateral LFP activity exhibited left-right (interhemispheric) alternations in accordance with the fly's switching behavior. Figure reprinted from Tang and Juusola (2010) and caption from Ngo et al. (2013) [Color figure can be viewed at wileyonlinelibrary.com]

BD, as did the indication in our data that neither clinical state nor medication affected BR rate and that some first-degree relatives of BD probands exhibited the slow BR trait (Miller et al., 2003). Pettigrew and I discussed the proposal to utilize BR rate as an endophenotype for BD in our first article (Pettigrew & Miller, 1998) and Ngo and I, and colleagues, later did so in a more focused manner (Ngo, Mitchell, Martin, & Miller, 2011). This proposal remains a goal that Martin and I are continuing to pursue (as outlined in the next section).

5.2 | Further testing the empirical finding of slow BR in BD, the endophenotype proposal and the genetics of BR

Pettigrew and I reported our finding of slow BR rate in BD and developed it into a pathophysiological model of BD by combining the conceptual elements outlined earlier with our concurrently new IHS model of BR. Key elements of the sticky switch model of BD are summarized in Box 3. As with all new models, several or even all proposed elements may turn out to be wrong. Should that in fact be the case, however, there would remain the empirical data to be explained in some other way. As mentioned earlier, there have been no alternative explanations offered for the CVS and TMS brain stimulation data. If the IHS model is wrong, those data will remain in need of explanation and while a field may choose to pass over new models for testing, doing the same for the empirical data is less defensible.

As with the CVS and TMS data, it is possible that the finding of slow BR in BD is accurate (indeed this is now established; see below) but that our explanations for it may not be. For example, one alternative explanation is that the slow BR trait may simply reflect abnormal EM profiles in BD subjects. In line with this rationale, a study of healthy subjects reported that individual variation in BR rate correlated with saccadic EM profiles (Hancock, Gareze, Findlay, & Andrews, 2012). Because of that report, and potential EM-based alternative explanations, Phillip Law—who joined my lab as a PhD student in 2012—along with Ngo and I and colleagues including Caroline Gurvich, examined BR rates and EM profiles in healthy and BD subjects. In two articles, we reported no relationship between BR rates and EM profiles in either healthy or BD subjects, thus excluding EM explanations for slow BR in BD (Law et al., 2015; Law, Gurvich, Ngo, & Miller, 2017).

The finding of slow BR in BD has now been independently replicated at multiple sites worldwide. In addition to our report in an Australian population, slow BR in BD compared with controls was observed in Japanese (Nagamine, Yoshino, Miyazaki, Takahashi, & Nomura, 2009), New Zealand (Vierck et al., 2013), and Chinese (Zhu et al., 2013) populations. The findings in independent studies regarding effects of clinical state on BR rate have been mixed, however, with some studies supporting an apparent lack of effect of state (e.g., Vierck et al., 2013) and others pointing toward a slowing

of BR rate with depressive state (Jia et al., 2015; Zhu et al., 2013). Medications commonly used to treat BD and depression do not appear to modulate BR rate in independent studies, though some medication and other pharmacological effects have been reported (Carter & Pettigrew, 2003; Mentch, Spiegel, Ricciardi, & Robertson, 2019; Nagamine, Yoshino, Miyazaki, Takahashi, & Nomura, 2008; van Loon et al., 2013). Moreover, in BD subjects there were reportedly no links between BR rate and performance on tests measuring visual processing, visual and spatial memory, sustained attention, general motor speed, and IQ (Vierck et al., 2013). An important issue for the clinical BR literature concerns the specificity of slow BR to BD. While our study in 2003 was suggestive that BR is not slow in schizophrenia or major depression, other data since then have challenged this notion, and pointed toward a general slowing of BR rate across psychiatric disorders (Jia et al., 2015; Xiao et al., 2019; Ye, Zhu, Zhou, He, & Wang, 2019). While the finding of slow BR in BD is consistent across our and independent studies, the inconsistencies in specificity findings raise issues concerning the use of differing BR test protocols (discussed below).

Our most recent work, in addition to the EM studies described above, has been to focus on BR presentation methods that will facilitate progression of the proposal to use BR rate as an endophenotype in BD genetic studies and as a potentially useful clinical biomarker. While very large consortium genome-wide association studies (GWAS) have identified genes predisposing to BD (e.g., Stahl et al., 2019), the genetic basis of BD—as for all psychiatric disorders—remains poorly understood. Nonetheless, there has been remarkable progress in discovering the underlying genetic causes of complex disorders, with improved biological understanding of diseases and new drug targets (e.g., Klein et al., 2005; Sanseau et al., 2012). In this field, massive sample sizes and phenotypic homogeneity are critical to replicating genetic associations, as is meta-analysis of data from multiple centres (see e.g., Evangelou et al., 2018; Maier, Visscher, Robinson, & Wray, 2018). With this in mind, BR presentation methods were described and reviewed in detail by Law et al. (2013) and Law, Ngo and I proceeded to compare BR rates elicited with the type of presentation methods we used in prior work with those using a simple anaglyph viewing method. The anaglyph method (Figure 2d; see Law et al., 2013) involves inexpensive foldable cardboard glasses that can be readily mailed to participant cohorts already recruited to existing large-scale psychiatric genetics studies. This means BR could, with appropriate validation data, be collected in subjects' homes via an online test platform, drastically reducing the resources required to obtain massive samples sizes for genetic studies. We are embarking on such validation studies and initial psychophysical work has shown that BR rates collected using the anaglyph method and blue/red stimuli are highly correlated with those collected using one of our previous BR presentation methods (i.e., polarization filters with monochrome green stimuli), in both healthy and BD subjects (Law et al., in preparation).

Whichever way the prospects for massive-scale online BR testing turn out, there is a need to *standardize* BR test methods for clinical biomarker studies. Despite extensive research on psychiatric biomarkers, translation into useful clinical tools has been lacking. White papers (Kapur, Phillips, & Insel, 2012; Kupfer, First, & Regier, 2002) and think tanks (Scarr et al., 2015) state that two important reasons for the failure of biomarker translation are research using: (a) nonstandardized protocols, and (b) small study samples. Translational clinical studies of BR may not require the massive sample sizes needed for genetic endophenotype studies, but they do require reasonably large sample sizes and certainly standardized test protocols. Common test protocol differences in BR studies include use of different BR stimuli, different total BR viewing times, and different approaches to recording and excluding mixed percepts when calculating BR rate. All such factors can affect BR rate and suggest the need for protocol standardization. To this end, Law and I are pursuing a BR test presentation and recording method and associated software that will be readily accessible to researchers to facilitate standardization and thus comparison and combination of data from different centres. Specific clinical translation prospects are discussed in Section 5.5.

As well as focusing on the presentation methods described above, we have progressed BR data collection in twins at Martin's group. That study recently ceased and BR data for more than 1,200 twins are currently being analyzed. Following our earlier twin heritability study (Miller et al., 2010), two GWAS of BR in healthy subjects were published. Bosten et al. (2015) studied 1,051 Caucasian subjects and Chen et al. (2018) studied 2097 Chinese subjects. The latter did not replicate the former's findings, underscoring the need for massive sample sizes for BR GWAS. Although both had impressive sample sizes by psychophysics standards, they were small for GWAS. Moreover, their BR protocols differed from each other and from our study protocols, and such differences may have confounded obtained BR rates. Like clinical translational BR studies, genetic BR studies also need protocol standardization to improve multicentre comparison and collaboration (irrespective of whether testing occurs in the lab or at home). With progression of GWAS of BR and GWAS of psychiatric diseases such as BD, schizophrenia and major depression, and reporting of novel genetic associations (see e.g., Gordovez & McMahon, 2020; Ripke et al., 2014; Ruderfer et al., 2018; Stahl et al., 2019; Wray et al., 2018; discussed in the next section), there will also be opportunity for utilizing animal models suitable for molecular genetic studies—such as *Drosophila* (Miller et al., 2012) and mice (e.g., Hagihara et al., 2016; Zhang et al., 2012; Zhu et al., 2017)—to probe phenotypic biomarkers, disease pathophysiology, and new drug targets.

5.3 | Further testing the sticky switch model

Like the IHS model of BR, the sticky switch model of BD has been appealed to in many articles since its proposal (again as a glance at PubMed will attest). It has also been directly tested by way of assessing the model's CVS therapeutic predictions, albeit in just two case studies to date. I describe these cases here and discuss other important

BOX 3 Key elements of the sticky switch model of BD

- Because BR is slow in BD, and on the basis of the IHS model of BR, the sticky switch model proposes explanation of how a slow BR switch can be linked to development of the fluctuating mood states that characterize BD.
- The model incorporates existing data-based proposals of: (a) complementary cognitive styles of the cerebral hemispheres, (b) hemispheric asymmetries of mood and mood disorders (with approach/positive/mania being left-lateralized, and withdrawal/negative/depression being right-lateralized), and (c) ultradian rhythms of alternating hemispheric (prefrontal) activation.
- The IHS processes underlying BR and other phenomena such as prefrontal ultradian rhythms, are driven by subcortical or brainstem bistable oscillators; these oscillators are nonetheless subject to extrinsic input from the cortex.
- BR oscillator switch rate is genetically (pleiotropically) coupled to the switch rate of other oscillators (e.g., visual cortex, prefrontal ultradian rhythms); hence, a slow BR rate in an individual predicts slow visual cortex and slow prefrontal oscillation rates in the same individual; there is a precedent in *Drosophila* for such genetic coupling of behavioral rhythms of vastly different time scales.
- The genetically slow prefrontal ultradian rhythm IHS oscillator in BD is prone to becoming "stuck" in one or the other state by external synaptic input (cortical top-down input from environmental cues/stressors); this is because slow oscillators are biophysically "sticky" and more prone to being modulated by extrinsic input.
- Hence mania arises from "stuck" greater relative left hemisphere activation in mood-related brain regions, and depression from "stuck" greater relative right hemisphere activation in such regions.
- CVS can restore to normal these pathophysiological functional hemispheric asymmetries and thus potentially treat mania (when activating the right hemisphere) and depression (when activating the left hemisphere).
- The molecular defect in BD may be the number of cationic channels controlling I_h current in the IHS bistable oscillators; several cationic channels affect oscillator switch rate, consistent with the polygenic genetic architecture of BD.
- Documented increased cellular and neuronal sensitivity in BD is the result of secondary cortical compensation for reduced channel number in the oscillator, and this further predisposes the switch to becoming stuck (by strengthening extrinsic input to the switch).
- Slow BR could be a trait marker or endophenotype for BD, able to be used in genetic studies of BD and with a range of potential translational applications in clinical psychiatry; consistent with this proposal are data showing that: (a) BR rate varies widely between individuals but is reliable within an individual, (b) there is substantive genetic contribution to individual variation in BR rate, (c) state and medication do not generally affect BR rate (with some conflicting data on these issues), and (d) some first-degree relatives of BD probands also exhibit slow BR.

developments on key aspects of the model. The sticky switch model proposed specific clinical predictions: left ear CVS, by activating mood-related regions in the right hemisphere, should reduce the signs and symptoms of mania, and the converse should hold for right ear CVS and depression. Though not citing our model, but indeed setting out to test its CVS mania prediction, Dodson (2004; personal communication) applied left ear CVS in a manic patient who had previously responded to electroconvulsive therapy (ECT) but had become refractory to further ECT and other attempted treatments. She had consequently been manic for 2 months. With little else to try, left ear CVS was applied and induced a striking reduction in mania, from 32 to 10 points on the Young Mania Rating Scale (YMRS). There was an immediate slowing of thoughts and speech, a reduction in spontaneous laughter and movement, a calming of behavior, and the patient stated she was embarrassed about her recent behavior (i.e., her insight improved). These effects were still evident 24 hr later but had disappeared by 72 hr, and a repeat CVS induced a longer duration of effect.

In another case report of CVS therapeutic effects that directly supported our clinical prediction for mania, a patient with schizoaffective disorder had reduced mania and psychomotor agitation, increased insight, and calmer, more cooperative behavior following left-ear, but not right-ear, CVS (Levine et al., 2012). This effect was for a shorter duration than Dodson's (2004) case, lasting only 20 min, diminishing by 60 min, but also being repeatable. Reports of CVS modulation of cognitive, affective and mood processing, consistent with the hemispheric asymmetries in our sticky switch model, have also since appeared (discussed in Miller, 2016).[16] Improved insight following CVS reportedly occurs not just in mania, but also in schizophrenia spectrum disorders (Gerretsen et al., 2017; Levine et al., 2012; as predicted by Miller & Ngo, 2007) and following right-hemisphere stroke (Cappa, Sterzi, Vallar, & Bisiach, 1987; Ramachandran, 1994). While it is acknowledged that the case studies of CVS effects in mania described above do not sufficiently confirm our model, substantive modulation of well-established mania is no minor experimental finding, particularly when an intervention as powerful as ECT had ceased to alter the patient's clinical course. Possible reasons why clinical psychiatry continues to overlook these CVS mania case study findings are addressed in Section 5.5.

Another important development relevant to the sticky switch model concerns replicated reports of corpus callosum (splenial) and left lateralized (cingulate, arcuate fasiculus) white matter abnormalities in BD (see e.g., Sarrazin et al., 2014). In a recent wide-ranging review

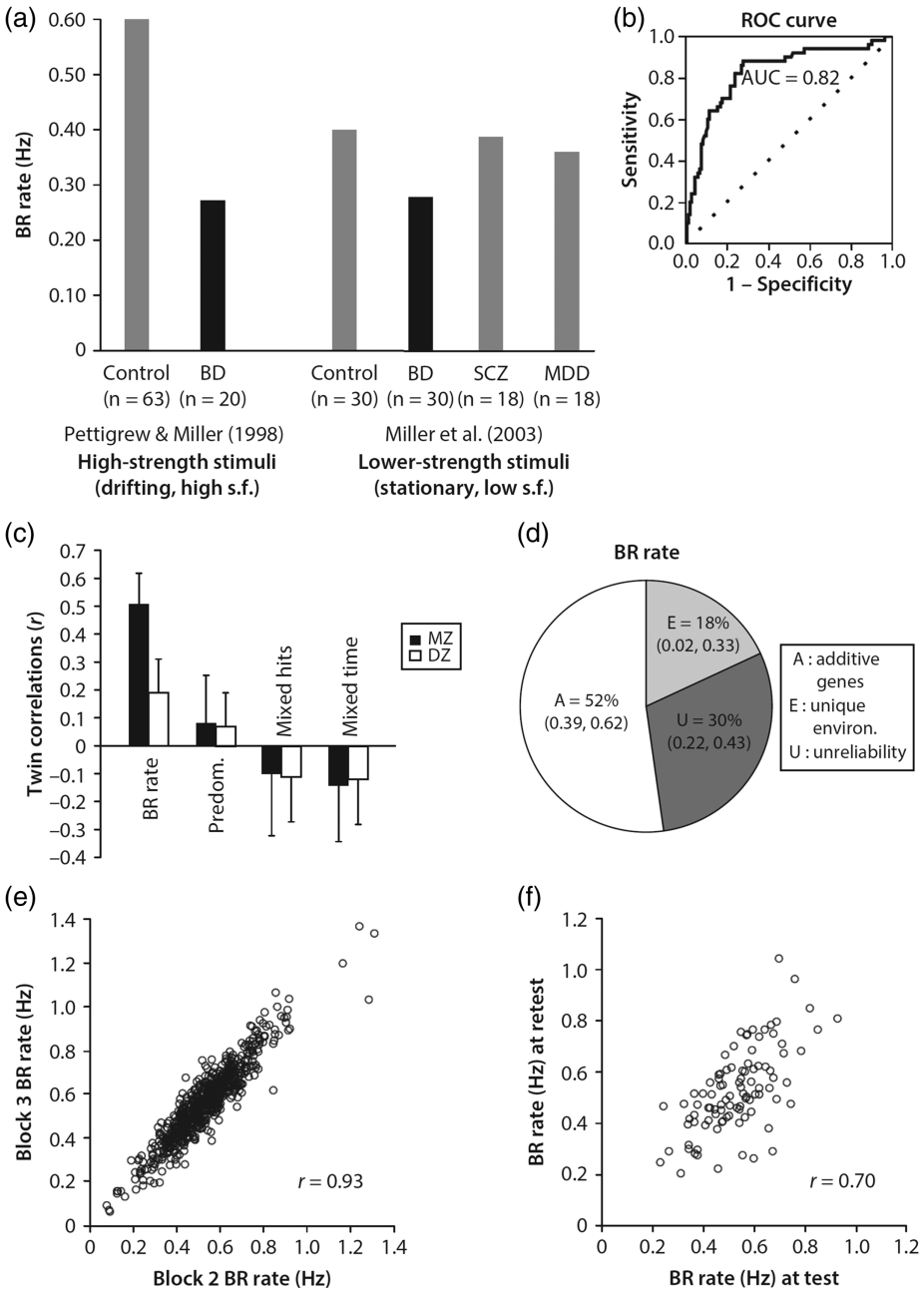

FIGURE 4 (a) Slow BR rate in BD. The bars show the central tendency of BR rate for each group (medians in Pettigrew & Miller, 1998; means in Miller et al., 2003). These studies suggest that high-strength stimuli distinguish BD subjects from non-BD subjects better than lower-strength stimuli (s.f., spatial frequency). (b) An ROC (receiver operating characteristic) curve of high- and lower-strength stimuli, generated from subjects' data in (a) with BD as "positive" and controls, schizophrenia (SCZ) and major depressive disorder (MDD) as "negative". The area under the curve of 0.82 indicates that from random selection of a pair of subjects in (a), 82% of individuals would be correctly identified as a BD subject or a non-BD subject on the basis of their BR rate. A large-scale heritability study of BR (Miller et al., 2010) demonstrated the following: (c) monozygotic versus dizygotic twin correlations for BR rate were significant but this was not so for other BR measures; (d) genetic modeling analyses indicated a substantial genetic contribution to individual variation in BR rate; (e) wide individual variation and very high within-session reliability of BR rate; and (f) high between-session (retest) reliability of BR rate. Figure and caption reprinted from Ngo et al. (2013)

of structural, functional and connectomic BD studies (Perry, Roberts, Mitchell, & Breakspear, 2018), the authors highlight callosal and interhemispheric abnormality findings associated with the disorder, as well as involvement of key regions such as insula and cingulate cortices—both of which are activated unilaterally by CVS (Miller, 2016; see also Downar, Blumberger, & Daskalakis, 2016). Asymmetry findings are also frequently reported in the Perry et al. (2018) review (though it should be noted the majority of neuroimaging studies examine trait findings in BD, with only a few focusing on the manic or depressive state).[17] Callosal abnormalities in BD suggest, in one way or another, impaired interhemispheric functional communication and/or connectivity. In a *JAMA Psychiatry* editorial (Cullen & Lim, 2014), which appeared alongside the large tractography study by Sarrazin et al. (2014), it was suggested that findings of white matter abnormalities in BD ought to stimulate the field to revisit the sticky switch model that Pettigrew and I proposed.

I have discussed above the role of the corpus callosum in our IHS and sticky switch models, noting that neither Pettigrew nor I considered this structure to be the site of the IHS, but also that neither of us discounted some role for it either. Here I would distinguish callosal abnormalities in BD *causing* a slow IHS (which Pettigrew and I doubted, focusing instead on a slowed subcortical or brainstem bistable oscillator) from such abnormalities being the *consequence* of a slow IHS (or indeed of repeated periods of being "stuck" in the left- or right-activated state). It is interesting to note that callosal agenesis is known to be associated with slow rates of perceptual rivalry (Fagard

et al., 2008), and reversible callosal lesions—such as those associated with the clinical condition, mild encephalitis with reversible splenial lesion—can present with mania when the callosal lesion is present, that settles when the lesion disappears (Bellani et al., 2020). The relationship between altered callosal anatomy and unihemispheric sleep in several species has also been detailed (Dell et al., 2016; Lyamin et al., 2008; Manger & Siegel, 2020). Understanding the role of callosal and lateralized white matter abnormalities in BD pathophysiology (as well as the role of the callosum in IHS phenomena like unihemispheric sleep across species) will be an important issue for future research, and the sticky switch model may indeed provide a useful heuristic in this regard.

A further relevant development concerns the notion of IHS period-coupling described earlier. Recall the sticky switch model proposed that individual variation in the BR IHS would be proportionately evident in other types of IHS, such as in prefrontal regions or visual cortex. A recent electrophysiological study of 84 healthy subjects has reported just such a coupling (albeit not on an IHS basis) between BR rate and the peak frequency of EEG alpha oscillations (Katyal, He, He, & Engel, 2019). That is, slower alpha frequencies were associated with slower BR switch rates, and conversely for the fast end of the distribution (with the highest correlation evident at occipital channels). Like BR rate, peak alpha frequency exhibits high retest reliability (Katyal et al., 2019). The authors appropriately situated their findings in the context of our prior work, drew links between the findings and the growing literature on how perception may be modulated by neural oscillations, and additionally pointed out that a study predating our work had reported slow peak alpha oscillations in BD (Clementz, Sponheim, & Iacono, 1994). Had Pettigrew and I been aware of this latter published EEG finding prior to publishing our model, we would have no doubt referred to it as additional support for the period-coupling element.[18]

Interestingly in the context of Katyal et al.'s (2019) alpha oscillation and BR rate finding, and the earlier IHS model discussion, Carter et al. (2020) discuss a recent honeybee electrophysiological study (Popov & Szyszka, 2020) in which spontaneous (high) alpha oscillations regulated functional connectivity within and between hemispheres. Power of the alpha oscillation was positively correlated with spike rate, and analysis of cross-frequency coupling confirmed that (high) gamma amplitude was modulated by the phase of the alpha oscillation. The timing of spikes in the right hemisphere was phase-coupled to alpha oscillation in the left hemisphere and there was also observed to be an asymmetry (right>left) in interhemispheric information flow. As Carter et al. (2020) note, IHS processes and hemispheric lateralization may therefore be evolutionarily ancient in organisms with paired neural structures (see also Miller et al., 2012). Returning to the human realm, another recent electrophysiological study reported that slow BR was associated with greater evoked intermodulation frequency responses in a cortical network that overlaps with the DMN, from V1 through higher visual and attentional regions (Bock, Fesi, Baillet, & Mendola, 2019). These authors also utilized our work in discussing their findings, but additionally noted that while slow alpha oscillations are associated with slow BR rate, the converse is in fact the case for gamma peak frequency (i.e., faster gamma oscillations have been associated with slower BR rate; Fesi & Mendola, 2015).

Most recently, Abhilash Dwarakanath, Vishal Kapoor, Nikos Logothetis, Theofanis Panagiotarapoulos and colleagues (Dwarakanath et al., 2020) reported striking new electrophysiological findings obtained during BR in alert macaque monkeys during a no-report protocol. These findings are highly relevant to the work Pettigrew and I started. We had often discussed whether the fluctuations of BR reflected an endogenous switching process that existed even when BR was not occurring or whether the BR switch was only initiated upon the detection of visual conflict. Most of our work is consistent with the former, referring as we did to pacemaker neurons, clocks, and genetic period-coupling of BR to ultradian and other biological rhythms (Pettigrew & Miller, 1998; Pettigrew, 2001; Pettigrew & Carter, 2005; Miller et al., 2012). The new data from Dwarakanath et al. (2020) speak directly to the question of whether the BR oscillator is endogenous.

Dwarakanath et al. (2020) found LFP recordings revealed that transient low frequency (1–9Hz) perisynaptic bursts in lateral prefrontal cortex *precede* spontaneous perceptual switches during BR and that these transients suppress oscillatory bursts in the beta (20–40Hz) range. The latter selectively synchronize discharge activity of feature-specific neural ensembles that signal conscious content, so their suppression by the low frequency transients potentially allows for increasing neural spiking in the suppressed population, thus increasing the likelihood of perceptual reorganization. Beta, as the authors note, is known to be suppressed during cognitive operations like attention and decision-making. Importantly, the prefrontal state fluctuations reported in the study by Dwarakanath et al. (2020) were evident even during the *resting* state (i.e., when BR is not occurring) at a similar timescale to BR alternations. This shows there are indeed *endogenous* electrophysiological fluctuations which appear to be causally relevant to mechanisms and timing of BR. It should be noted, however, that the macaque study recorded from a single hemisphere and so could not address the issue of the existence of an IHS mechanism. Moreover, Pettigrew and I expected the BR oscillator to target temporo-parietal regions rather than prefrontal regions (Pettigrew & Miller, 1998). In light of the new data from Dwarakanath et al. (2020), our proposal that fast switches target more posterior regions and slower switches target more anterior regions may need revision to include the notion of *nested* oscillations of different timescales within the same cortical region. As well as concluding that prefrontal state fluctuations relevant to mechanisms of BR are endogenous, Dwarakanath et al. (2020) also concluded that their data suggest an important role for top-down selection and ignition processes (i.e., *high*-level feedback processes) relevant to the generation of visual consciousness. An important question also raised by identification of an endogenous prefrontal resting state fluctuation, with a seconds-long timescale similar to that of BR, is what function(s) such fluctuations perform when not disambiguating visual conflict. In this regard, general perceptual and attentional selection and disambiguation processes come to mind, as well as other cognitive and decision-making processes relevant to

behavior (see e.g. Andrews & Purves, 1997; Leopold & Logothetis, 1999; see also Miller et al., 2012; Pettigrew & Carter, 2005).

Finally, the sticky switch model made a specific genetic prediction: that the genetic defect in BD is reduction in the number of the many different types of cationic channels that govern the putative oscillator's rate of depolarization (Pettigrew & Miller, 1998). This prediction was driven by Pettigrew, drawing on discussions he had with neuroethology colleagues who worked on oscillator neurophysiology. The status of our model's ion channel prediction is complex, particularly because we distinguished the primary genetic defect (which slowed the oscillator's switch rate) from secondary (compensatory) cortical responses which *increased* neuronal excitability and sensitivity in BD. Nonetheless, the latest genetic association findings for BD do implicate channels (particularly calcium—see next section—and potassium channels) as well as clock genes (Ruderfer et al., 2018; Stahl et al., 2019), and support the notion that BD may be fundamentally a channelopathy (see e.g., Judy & Zandi, 2013). In this regard, it has also been noted that BD shares many features in common with epilepsy—the signature channelopathy disorder (Gargus, 2006)—such as several antiepileptic medications also being used for acute mania treatment and for BD maintenance treatment (Judy & Zandi, 2013). Also relevant to the current discussion, the *ANK3* locus, which encodes for a protein involved in axonal myelination, has been repeatedly implicated in BD GWAS (Gordovez & McMahon, 2020; Stahl et al., 2019). Axonal myelination is potentially relevant to fractional anisotropy and other diffusion tensor imaging metrics (Perry et al., 2018), raising potential links between large scale GWAS and connectomic studies of BD. In accordance with this, an *ANK3* conditional mouse knockout that results in loss of pyramidal neuron voltage-gated sodium and potassium channels, exhibits a behavioral phenotype reminiscent of human mania, ameliorated by both lithium and the antimanic and antiepileptic medication, valproate (Zhu et al., 2017).

However, despite sample sizes now in the tens of thousands, BD GWAS remain at a relatively early stage. It already appears clear though, that BD involves an extensive polygenic genetic architecture and that its genetics overlap substantially with those of other psychiatric disorders such as schizophrenia and major depression (Gordovez & McMahon, 2020; Stahl et al., 2019). This overlap may well be relevant to the fact that at least some individuals in our schizophrenia and major depression data exhibited slow rates of BR (Miller et al., 2003), and that more recently, other groups have reported slowing of BR rate across all three clinical groups—BD, schizophrenia, and major depression (as discussed in the previous section).

5.4 | Related research

There are several lines of additional research related to the work Pettigrew and I started. In this section, I briefly mention some of these. Our finding of slow BR in BD has been followed by studies looking at BR rate in other clinical conditions. Above I have mentioned studies of BR rate in conditions often misdiagnosed as BD, such as schizophrenia and major depression. However, BR rates in other conditions have also since been examined, in particular in autism (Freyberg, Robertson, & Baron-Cohen, 2015; Mentch et al., 2019; Robertson, Kravitz, Freyberg, Baron-Cohen, & Baker, 2013; Spiegel, Mentch, Haskins, & Robertson, 2019; but see Said, Egan, Minshew, Behrmann, & Heeger, 2013) and attention deficit hyperactivity disorder (Amador-Campos, Aznar-Casanova, Moreno-Sanchez, Medina-Pena, & Ortiz-Guerra, 2013). The autism work is worth highlighting to illustrate how empirical findings can be given different interpretations depending on the investigator's focus. BR rate was reported to be slow in autism (though with longer periods of mixed percepts being a potential confound), and the authors interpret their findings in the context of excitation/inhibition imbalance in visual cortex. However, in light of the discussion above on callosal abnormalities in BD, it could be proposed that slow BR in autism reflects callosal abnormalities in this condition, rather than (or perhaps in addition to) excitation/inhibition imbalance in V1. There is indeed evidence to support this contention, with reports that autism is associated with smaller corpus callosum size and lower fractional anisotropy (Frazier & Hardan, 2009; Hardan et al., 2009; Keary et al., 2009), as well as autism being associated with callosal agenesis (Lau et al., 2013; Paul, Corsello, Kennedy, & Adolphs, 2014). Just as it has been proposed that autism is a disconnection syndrome (Williams & Minshew, 2007), a similar proposition exists for BD (Perry et al., 2018; who referred to it as a "dysconnection" syndrome) and it is also not difficult to see the sticky switch model in a disconnection or dysconnection light.[19]

A further line of research that can be seen to have, at least indirectly, emerged from the work Pettigrew and I started, concerns renewed interest in individual variation in BR temporal dynamics. At the time of our discoveries, there was a trend in BR research to smooth over individual variation in psychophysical BR studies, focusing instead on what was similar between subjects rather than what was different. Our work helped refocus attention on just how different the psychophysics of BR can be between individuals in terms of basic parameters such as switch rate, which can vary by an order of magnitude. This type of individual variation in BR temporal parameters was historically a focus of interest (reviewed in Wade & Ngo, 2013; see also Miller et al., 2012) but as mentioned, the trend in BR research prior to our 1998 publication was to divert attention from inter-individual differences. The current literature is reporting interesting new findings regarding individual variation in BR dynamics (e.g., Brascamp, Becker, & Hambrick, 2018; Brascamp, Qian, Hambrick, & Becker, 2019; Patel, Stuit, & Blake, 2015) and we continue to contribute to such research (Law, Miller, & Ngo, 2017; Law et al., in preparation). Here again, fluctuations of perspectives in science can be observed.[20]

Finally, an element of related research worth mentioning to try to encourage its further development concerns the characterization and understanding, at systems, molecular, and chronobiological levels, of mechanisms underlying mood states and their fluctuations. Pettigrew was acutely aware of his own mood state fluctuations and indeed on more than one occasion commented to me on modulation of his mood following CVS. In particular, left-ear CVS (activating the depressive right hemisphere) could cause him to experience a

negative mood state for around 2–3 days. I have earlier discussed CVS modulation of mania. The reported effects of CVS on subclinical mood and cognition (see e.g., Preuss, Hasler, & Mast, 2014) are discussed more fully in Miller (2016) and illustrate the type of shifts in mood—in addition to the more extreme mood state shifts of mania and depression—that Pettigrew wanted to probe and understand physiologically. Pettigrew was struck by the suddenness with which moods could fluctuate and this reinforced to him the appeal of a bistable oscillator driving such fluctuations (see Pettigrew, 2001). Indeed, the suddenness of mood fluctuations may well be relevant to understanding some suicides, and the unexpected timing of these devastating events when the individual's mood may have appeared otherwise relatively stable.[21]

Although speculative, from my discussions and observations with mood disorder and healthy subjects, I would expect that in addition to subtle ultradian (hours-long) positive/negative IHS mood rhythms, there will exist a 2–3 day infradian positive/negative IHS mood rhythm (with potentially wide individual variation therein). Just as the hypothalamic-driven ultradian nasal cycle IHS appears to exist in the majority of, but not all, subjects (Kahana-Zweig et al., 2016; Lenz, Teelen, & Eichler, 1985; Price & Eccles, 2016), so too mood-related ultradian and infradian IHS rhythms may not exist in all subjects. Nonetheless, the hours-long and days-long timeframes accord with descriptions of mood shifts in patients and healthy subjects, and ultradian and infradian positive/negative mood rhythms at their extremities, driven by endogenous oscillators, could provide new insight on mechanisms underlying mixed states, ultra-rapid cycling, and ultradian cycling in BD (Blum et al., 2014; Kramlinger & Post, 1996; MacKinnon & Pies, 2006). These rhythms may also mediate mood instability in personality disorders and a range of other clinical disorders, with similar ultradian and infradian timeframes (Mackinnon & Pies, 2006; see additional citations in the next paragraph). The specific new mechanistic proposal here is that nested endogenous IHS oscillators with different timescales ranging from hours to days (perhaps even seconds; MacKinnon & Pies, 2006) can explain how shifts between mania and depression in ultra-rapid and ultradian cycling BD, as well as cycling in other disorders, can occur so rapidly and on such different timescales. [Correction added on September 29, 2020, after first online publication: the previous sentence was inserted.] Moreover, just as the nasal cycle rhythm becomes more obvious when the subject has a respiratory infection affecting the nasal mucosa, so too mood-related ultradian and infradian rhythms may become more obvious when the subject is dealing with a major life stressor. In addition, CVS may be modulating the putative infradian IHS mood rhythm, given Pettigrew's descriptions of the duration of CVS effects on him, and it is notable in this context that Dodson's (2004) case study showed CVS-induced mania modulation for 1–3 days.

It is also notable that expression of many circadian genes correlates with an infradian locomotor activity rhythm in a mouse model of BD (Hagihara et al., 2016). Links between circadian rhythms and mood are well established and circadian and sleep/wake anomalies, governed by molecular clocks, are key features of mood disorders (reviewed in McClung, 2013). A dopaminergic ultradian oscillator in the mammalian brain has also been reported, identified using locomotor activity, and usually synchroniszd to the circadian clock but able to become desynchronized from it and lengthened from ultradian to infradian (~2 days) timescales (Blum et al., 2014). These authors specifically linked their findings to ultradian and infradian switches in mania and depression, though not on an IHS basis. Interestingly, Pettigrew (2001) suspected the dopaminergic ventral tegmentum as a potential site for the BR IHS, noting a large literature on this region's role in mood and motivation (for a recent review see Ashok et al., 2017) and also that its electrical stimulation in patients with Parkinson's disease could cause rapid mood changes. Pettigrew (2001) nonetheless discussed other candidate switch sites in paired midline structures containing pacemaker neurons, including the raphe nucleus (see also Carter et al., 2005a; 2007) and hypothalamus (see also Pettigrew & Carter, 2005). The serotonergic raphe nucleus has since been implicated in oscillatory ultradian rhythms linked to mood disorders (Salomon & Cowan, 2013) and the wider serotonergic connection to mood disorders is well-known. Pettigrew (2001) noted the hypothalamus' relationship to the nasal cycle and its exhibiting of an even slower IHS rhythm (de la Iglesia, Meyer, Carpino, & Schwartz, 2000). In addition to circadian clock function, the hypothalamus more recently has been shown to generate hours-long ultradian rhythms in intracellular calcium levels whose amplitude is associated with the frequency of milliseconds-long calcium transients (Wu et al., 2018).[18,22] [Correction added on September 29, 2020, after first online publication: the previous seven sentences were inserted.]

Despite these exciting chronobiological mechanistic developments, current biological psychiatry has a poor understanding of the neurophysiology of mood and affective state fluctuations in mood and other disorders. There is nonetheless mechanistic work in this area utilizing the notion of “affective instability” (and related terms such as “mood instability”, “mood swings”, “affective lability”, “emotional or affective dysregulation”, and “emotional impulsiveness”; Broome, He, Iftikhar, Eyden, & Marwaha, 2015; Broome, Saunders, Harrison, & Marwaha, 2015; MacKinnon & Pies, 2006; Marwaha et al., 2014, 2016). [Correction added on September 29, 2020, after first online publication: the previous two sentences were edited.] Moreover, contemporary connectomic and computational psychiatry approaches are seeking to identify “dynamic instabilities” in BD and to identify the disorder's “chronoarchitecture” (Perry et al., 2018). Conjoining studies of affective/dynamic instability, neuroimaging, and systems and molecular chronobiology, with a focus on period-coupled oscillations and endogenous IHS mechanisms, may shed light on these complex issues. Indeed, when referring to time series analyses of mood variations in BD, Perry et al. (2018, pp. 1308) note, “they suggest an intriguing role for dynamic models of brain activity to disclose the origin of multiscale temporal phenomena”. The relevance of this statement to the sticky switch model of BD should by now be self-evident.

5.5 | Clinical translation

It is important to comment on specific translational prospects of the work Pettigrew and I started. The finding of slow BR in BD has potential to be clinically translated in a number of ways. If further research—conducted with sufficiently large sample sizes and standardized BR test protocols—indicates that slow BR is specific to BD (and the trait is not usually present in schizophrenia or major depression; see Miller et al., 2003), then this would suggest possibilities for using slow BR to help delineate, and thus appropriately treat, BD (for details, see Ngo et al., 2011). This would be particularly useful for early presentations of depression or psychosis, where the underlying diagnosis can be uncertain and where misdiagnosis is common (Angst, Sellaro, Stassen, & Gamma, 2005; Bruchmüller & Meyer, 2009; Smith et al., 2011; Wolkenstein, Bruchmüller, Schmid, & Meyer, 2011). In such cases, accurate diagnosis of an underlying BD would direct specific treatment choices and improve patient outcomes. However, recent data have questioned the specificity of slow BR to BD as mentioned in Section 5.2 (Jia et al., 2015; Xiao et al., 2019; Ye et al., 2019) and though the specificity issue awaits clarification with larger samples and standardized protocols, it may well turn out that this potential clinical translation will not come to pass. If so, however, there remains the possibility that the presence of the slow BR trait, irrespective of underlying diagnosis, will predict a particular disorder sub-type or response to particular medications. There is an urgent need for biomarkers in clinical psychiatry that can offer such predictive capacity because treatment choices are commonly conducted by trial and error. These types of translational applications of BR rate in clinical psychiatry have not yet been explored.

Other potential translations include, for example, use of the presence of slow BR in first-degree relatives of BD probands to indicate risk of developing the disorder and to provide educational and risk mitigation strategies accordingly (Ngo et al., 2011; see e.g., Proudfoot et al., 2012). Longitudinal, prospective studies of BR rate directing medication or educational interventions are required, though further cross-sectional studies will be valuable to plan for those. As BD genetic studies continue to grow and yield positive, replicable genetic associations, clinical translation may also emerge with new potential drug targets and/or drug repositioning (Sanseau et al., 2012). Similarly, as our understanding of BD pathophysiology progresses, new treatments and biomarkers that direct specific treatment choices may emerge.

At this point however, it is worth making some frank comments about translation in clinical psychiatry. The most direct potential clinical application of the work Pettigrew and I started is CVS treatment of mania and depression. The CVS predictions were made as far back as our first publication (Pettigrew & Miller, 1998). A case study strikingly supporting our prediction for mania was published some years later (Dodson, 2004) and we highlighted the potential therapeutic effects of CVS in mania and depression (and a range of other potential CVS clinical applications) in two reviews shortly thereafter (Been, Ngo, Miller, & Fitzgerald, 2007; Miller & Ngo, 2007). A further supportive case study of CVS modulation in mania was published thereafter (Levine et al., 2012), along with supportive cognitive studies (e.g., Preuss et al., 2014), and I later presented detailed arguments in the high-profile specialist journal, *Bipolar Disorders*, for evaluation of CVS therapeutic effects in mania and depression (Miller, 2016). To date such evaluation has not occurred.

CVS is, however, being examined in other clinical contexts. Ngo and I, and colleagues, have assessed CVS effects in a variety of persistent pain states (Ngo et al., 2020; Ngo et al., submitted).[23] There is a small group of researchers worldwide (see Grabherr et al., 2015; Miller, 2016) who have and continue to explore potential clinical applications of stimulating the vestibular system, for example in pain states (as above; see also McGeoch et al., 2008; McGeoch et al., 2007), migraine (Kolev, 1990; Wilkinson et al., 2017), degenerative disorders such as Parkinson's disease (e.g., Pan, Soma, Kwak, & Yamamoto, 2008; Wilkinson et al., 2019), poststroke disorders (e.g., Wilkinson et al., 2014), and effects on sleep and memory (Kompotis et al., 2019; Perrault et al., 2019; see also Bächtold et al., 2001). This is in addition to application of vestibular stimulation techniques in a variety of attentional and cognitive modulation contexts (reviewed in Grabherr et al., 2015; Mast, Preuss, Hartmann, & Grabherr, 2014; Miller, 2016; Miller & Ngo, 2007). However, clinical and research psychiatry's lack of attention to the reports of CVS modulation of mania is a curiosity worthy of some discussion here. One can only imagine the level of interest at a pharmaceutical company if a new and patentable compound was presented with data showing it reduced refractory mania from 32 to 10 on the YMRS! The history of therapeutic developments in psychiatry is rich in examples of curious turns and fluctuations of perspectives (Healy, 2008; Shorter & Healy, 2007), and perhaps against this background the field's inattention to CVS modulation of mania should not be too surprising.

Psychiatry, it can be argued, has long yearned for biological tests and technological advancements that will bring it alongside its more biological and technological counterpart—neurology. So, a simple bedside intervention that instils cold water into the external ear canal may hold little appeal, despite reports of its clinically meaningful effects.[24] This may be all the more so given rTMS—a suitably high-tech new treatment for refractory depression—is now commercially available, helping patients, but also helping boost psychiatry's high-tech appearance (along with similarly high-tech neuroimaging techniques that await translation). While rTMS does help a proportion of treatment-resistant depressed patients (Kaster et al., 2019), there remains a need for new treatments of depression for those patients who do not respond to psychological therapies, pharmacotherapy, ECT or rTMS. Moreover, rTMS for mania has not been clinically translated. If the barrier to the examination of CVS as a mania (and depression) treatment is indeed the low-tech nature of the technique—which should in fact be its appeal: it is simple to administer, requires no special equipment, is safe, inexpensive and could be administered rapidly in emergency departments—then this may at least be surmounted in future as a high-tech CVS device becomes available. Such a device has already been FDA approved for migraine treatment (see Wilkinson et al., 2017).

Other possible barriers to examination of CVS treatment of mania (and depression) are worth considering. CVS requires a medical

practitioner or trained audiological personnel to administer.[25] This, however, should prove little barrier because most groups examining CVS therapeutic effects will include, or can readily access, medical personnel (indeed, hospital neurology and otolaryngology departments already perform CVS in one form or another). A more likely barrier is the misperception that CVS is poorly tolerated, with a high likelihood of inducing nausea and vomiting. Pettigrew and I noted these side effects in relatively few cases, with just 2 or 3 per hundred experiencing vomiting in our studies of healthy subjects.[26] We have since quantified CVS side effects in a clinical population of persistent pain subjects, and find the intervention to be generally well tolerated (Ngo et al., 2020; Ngo et al., submitted). CVS tolerability also needs clear assessment in light of the tolerability and side effects of alternative interventions (including polypharmacy and ECT in the case of mania and depression) and the impacts of otherwise poorly treated disorders. An additional barrier to examination of CVS in clinical psychiatry is the obtaining of informed consent from psychiatrically unwell patients for administration of an experimental intervention. However, overcoming this barrier could in turn *improve* consent processes in clinical psychiatry. This is because even short-term CVS-induced improvement in insight could yield opportunity to obtain informed consent for more extreme (though evidence-based) interventions such as ECT.

A further potential barrier may lie in the fact that vestibular stimulation in the form of rotation was historically utilized as a psychiatric treatment (Breathnach, 2010; Grabherr et al., 2015; Wade, 2005; Wade, Norrsell, & Presly, 2005; see also Winter, Wollmer, Laurens, Straumann, & Kruger, 2013). Notably, rotation had the capacity to bring about sleep in, and subdue, even "furious maniacs" (Breathnach, 2010), an effect that is not only impressive—given a cardinal feature of mania is the inability to sleep—but also accords with contemporary evidence on effects of vestibular stimulation on sleep (Kompotis et al., 2019; Perrault et al., 2019). These historical reports of the therapeutic use of rotational vestibular stimulation to induce sleep and manage psychiatric illness in times when there were few other therapeutic options, could be seen to in fact support arguments for a contemporary evaluation of the role of stimulating the vestibular system in treating psychiatric disorders. However, psychiatry may feel squeamish about any sense of a return to long since abandoned interventions, particularly because rotation also came to be used in a punitive fashion (Breathnach, 2010). That said, it is probably accurate to state that most clinical and research psychiatrists would be entirely unaware of this vestibular stimulation treatment history. Therefore, a more likely barrier to examination of CVS therapeutic effects in psychiatry is just general incredulity that such a simple technique could have any real and clinically meaningful effects.

Whatever the barriers to clinical psychiatry's lack of willingness to examine CVS as a treatment option, Pettigrew was incensed by hearing of cases in which pharmacotherapy and ECT for mania had failed and CVS had not been tried. On at least one occasion of which I am aware, he wrote to a prominent Australian academic psychiatrist specializing in BD and expressed his frustration and disbelief that such a simple and potentially effective intervention was being ignored by the field. In one of the last communications I had with him, Pettigrew asked whether I had plans to examine CVS therapeutic effects in mania and depression. I explained that Ngo and I had set up to do this many years ago but failed to recruit patients due to neither of us working directly on an acute psychiatry ward and not having the resources to fund a researcher to maintain a presence on the ward. Pettigrew was relieved to hear I hope to examine this issue in the future. The technique, however, is extremely easy to administer (for instructions, see Miller & Ngo, 2007) and any number of well-resourced clinical and research psychiatrists working day-to-day with manic and depressed inpatients would be better placed to trial this intervention in a timely fashion.

As a final comment on the issue of CVS clinical translation, it is worth considering that psychiatric brain imaging studies now number in the thousands with patient participants numbering in the tens of thousands (Downar et al., 2016). Yet the complexity of the findings, and the multiple layers of additional complexity in the growing field of connectomics and computational psychiatry (e.g., Perry et al., 2018), suggests the likelihood of identifying new and specific translational biomarkers or therapeutic interventions as a result of all of these studies may in fact be quite low (at least without many more rounds of studies and controversies therein). The same might be said of genetic studies with massive sample size requirements and similarly exquisite complexities. The question can be reasonably posed therefore—and notwithstanding my own involvement in large BR genetic studies—what is the point of the time, resources, and effort involved in international collaborative neuroimaging and genetic pursuits if not to identify promising new treatment targets for evaluation? As such, it is all the more remarkable that a promising new treatment for mania that was proposed many years ago, from an unlikely quarter and an unlikely set of experiments, that is supported by recent neuroimaging meta-analyses (Downar et al., 2016; Miller, 2016) and pilot data (Dodson, 2004; Levine et al., 2012), remains quietly awaiting its evaluation, seemingly unheard amid the noise of big science.

6 | CONCLUSION

More than two decades ago, Pettigrew and I started lines of research that continue to this day and that have developed in a variety of directions. We made discoveries that have been independently replicated and some that have yet to be so. We made clinical predictions that have been, albeit partially and preliminarily, confirmed. The work centered around the two new models detailed here, which emerged—along with the empirical findings supporting them—through a mixture of conceptual synthesis, serendipity and experimentation. My goal in joining Pettigrew's lab was to learn more about the brain and to better understand consciousness. I achieved that and more. Pettigrew's goal in accepting me as a student was to search for an IHS in humans and to learn more about the fluctuations of mood that characterize BD—the disorder which afflicted him. He achieved that and more. Though neither of us expected it when we started working together, we reached our goals by studying fluctuations of visual consciousness. It remains to be seen how fluctuations in scientific and clinical perspectives will dictate the further examination of our models, data, and

clinical predictions in the coming two decades. Whatever the future holds for our discoveries, Pettigrew's mark lies indelibly within them.

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CONFLICT OF INTEREST

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ORCID

Steven M. Miller https://orcid.org/0000-0003-1802-1574

ENDNOTES

[1] McCoombes and I have since agreed that for lecturers like Pettigrew, we should have just put our pens down and watched and absorbed what was going on, instead of trying to capture lecture notes for later study (however medical students are generally obsessed by exams). Another no doubt standout memory for Pettigrew's students, and indeed for anyone who crossed his path, was Pettigrew's unshakable wearing of shorts, no matter the season or occasion.

[2] As noted by David Vaney in a tribute article following Pettigrew's death, Pettigrew's openness about his BD diagnosis is a model approach to mental health disorders: https://www.ans.org.au/images/Newsletters/ANS_News_July_2019.pdf

[3] Pettigrew mentioned having met Crick while in California. He told me that both Crick and physicist, Richard Feynman (whom he also met during his Caltech days), possessed minds so sharp that they were clearly distinguishable from the rest of us mere mortals.

[4] Pettigrew's analogy here was that of a spinning top: spin it fast and it is difficult to knock over but as it slows, it becomes much easier to knock over.

[5] The logic of the TMS experiment, based on the IHS hypothesis, was as follows: a TMS pulse delivered on a switch from say vertical to horizontal in a subject would cause an immediate reversion to the vertical percept, but the same pulse delivered to the same hemisphere in the same subject, though rather on a switch from horizontal to vertical, should not change perception at all. In this way, the perceptual disruption effect is specific to the BR phase of the spTMS pulse's delivery.

[6] We also quantified Diaz-Caneja's (1928) early finding and reported individual variation in the relative time spent perceiving reconstituted versus half-field images (Ngo et al., 2000). In addition, we dubbed the phenomenon "coherence rivalry" to distinguish it from "stimulus representation rivalry", because the latter did not necessarily imply the synthesizing of aspects of each eye's image into coherent rivaling wholes (Ngo et al., 2000; Ngo, Liu, Tilley, Pettigrew, & Miller, 2007).

[7] Pettigrew's (2001) article also argued that BR and Bonneh's motion-induced blindness (MIB) shared features in common, in particular susceptibility to perturbation by TMS and correlated switch rates within individuals. The former claim Pettigrew later published in a study with Agnes Funk (Funk & Pettigrew, 2003; discussed in Ngo et al., 2013) and the latter in a study with Olivia Carter (Carter & Pettigrew, 2003; Carter joined Pettigrew's lab shortly after I departed). While Carter and Pettigrew (2003) provided data to support the notion of a correlation between BR and MIB switch rates in individuals—thus arguing for a common oscillator underlying different types of perceptual rivalries—this particular data claim has since been challenged (Brascamp, Becker, et al., 2018; Cao, Wang, Sun, Engel, & He, 2018; Gallagher & Arnold, 2014), but with arguments for both shared and independent mechanisms for different types of bistable perception phenomena (Cao et al., 2018). Here it should be noted that even though some rivalry types may show poor rate correlations with BR, such as the Necker cube and structure-from-motion stimuli (Brascamp, Becker, et al., 2018; Cao et al., 2018), they can still show features in common with BR such as a slow rate in BD (Hunt & Guilford, 1933; Krug, Brunskill, Scarna, Goodwin, & Parker, 2008) and predominance modulation with CVS (Necker cube; Miller et al., 2000). There are other data claims in Pettigrew's (2001) article that are not consistent with subsequent experimental findings, such as effects of both mood state and medication on BR predominance (Miller et al., 2003), and an inverse relationship between an individual's switch rate and their susceptibility to rate modulation by stimulus strength (Law et al., in preparation). However, Pettigrew's (2001) article was written during early days of this research.

[8] Pettigrew was not averse to discussing consciousness but he was not overly interested in the topic, particularly on theoretical issues like the correlation/constitution distinction problem. He nonetheless took the time to ascertain my broad views on consciousness, and to express his. He felt consciousness was widespread, present even in bacteria for example, thus taking a largely panpsychist view. I rather believe there to have been a jump from nonconsciousness to consciousness in phylogeny (and that there similarly occurs a jump in ontogeny), at some (probably unidentifiable) point of critical neural complexity (Miller, 2007). Pettigrew was, however, interested in and acutely aware of how his own consciousness altered during periods of mania/hypomania, in particular sensory alterations such as a heightening of auditory and color perception.

[9] Recent developments on aspects of the sticky switch model of BD (see Section 5.3) might prompt more interest in directly testing the IHS model of BR. I am also informed by Chris Klink, Matthew Self, and colleagues—who did set out specifically to examine the IHS model of BR (using frequency-tagged EEG signals)—that a preliminary look at their data could neither confirm nor exclude support for the model (i.e., with highly variable signals including all manner of symmetric and asymmetric activation patterns observed).

[10] For a wide range of other perspectives on the BR phenomenon and its mechanisms, including perspectives on the future of BR research, see the many excellent articles in Miller (2013).

[11] Interestingly, although the ~40 s period of this reported IHS in sleep is much slower than that for BR, it is nonetheless more closely matched by a different perceptual rivalry type—structure-from-motion (Krug et al., 2008).

[12] Nir and colleagues have also recently reported unihemispheric memory consolidation during sleep, with concomitant modulation of cortical sleep oscillations, when using unilaterally-presented odor cues (Bar et al., 2020). This is interesting in the current context because: (a) perceptual rivalry also exists in the olfactory domain (Zhou & Chen, 2009); (b) the nasal cycle is a slower IHS not unrelated to

olfaction (Kahana-Zweig et al., 2016); and (c) vestibular stimulation not only modulates rivalry, but also sleep and memory consolidation (Kompotis et al., 2019; Perrault et al., 2019; see Section 5.5).

[13] Tamaki et al. (2016) also cite several previous studies showing sleep electrophysiological interhemispheric asymmetries associated with prior sleep deprivation and somatosensory stimulation, and with insomnia and sleep apnoea. They also discuss reasons why their observed sleep EEG IHS may have been missed in earlier studies of the first night effect.

[14] While I have commonly encountered expressions that the IHS model of BR is unlikely to be true, I have also encountered the converse opinion that it would be unlikely if IHS mechanisms were not biologically ubiquitous. It remains to be seen just how general a neurophysiological principle interhemispheric switching will turn out to be in organisms with neural structures that are paired across the midline (Ngo et al., 2013).

[15] It has also been commented to me that the IHS model may have struggled to gain traction because it does not readily accord with a more general theory of brain function, unlike, for example, dynamic systems and predictive coding accounts of multistable perception (for details and citations see Brascamp, Sterzer, et al., 2018). My first response to this contention is that the IHS model does in fact accord with wider general contexts (if not wider specific theories). I consider these wider general contexts in particular to be: (a) neuroethological/comparative (i.e., cross species evidence for IHS mechanisms and their evolutionary roles; Miller et al., 2012; Carter et al., 2020), and (b) attentional processing (Miller, 2001; Miller et al., 2012). One could also add here (as outlined in detail in Section 5) the linked wider general contexts of: (c) genetics and individual differences, (d) biological rhythms/chronobiology, and (e) clinical anomalies. My second response relates to each of the two examples noted above. Dynamic systems principles are usually applied to multistable perceptual phenomena in the context of competing pools of cortical neurons, with inhibition, adaptation and neural noise processes contributing to perceptual dynamics. However, such principles are readily able to be examined with respect to the dynamics between each side of a subcortical or brainstem bistable oscillator (see e.g., Akcay, Huang, Nadim, & Bose, 2018; Manor & Nadim, 2001; Marder, 1998; Rowat & Selverston, 1997), including taking into account the oscillator's output to cortical pools of neurons or circuits and extrinsic input to the oscillator from such pools or circuits (as well as with respect to—albeit slower—callosally-mediated interhemispheric processes). On the predictive coding front, multistable perception is usually dealt with by way of bottom-up and top-down processing along the posterior–anterior axis, in the context of perceptual inference. On an IHS account, however, perceptual inference would instead be accommodated by way of interactions between the switch and cortical pools of neurons or circuits encoding priors and posteriors.

[16] It is beyond the scope of this article to review current evidence for hemispheric asymmetries of mood and mood disorders. However, a few points are worth making here. First, a recent meta-analysis (Barahona-Corrêa et al., 2020) confirmed that post-lesional mania is more commonly associated with right-sided lesions (and therefore relatively greater left hemisphere activation), in accordance with our sticky switch model. Second, there is laterality inherent in current rTMS treatment of depression. This treatment modality is now established as a means of treating refractory depression (Kaster et al., 2019). Since its inception it has involved a clear application laterality that accords with the hemispheric asymmetries in our sticky switch model. The aim of depression treatment with rTMS is to either stimulate the left or inhibit the right dorsolateral prefrontal cortex, or to do both concurrently (Kaster et al., 2019). This rTMS application laterality was already evident when Pettigrew and I published our model and we cited it in support of the model. There have since been challenges to the notion that the rTMS application laterality is necessary (Speer, Wassermann, Benson, Herscovitch, & Post, 2014), with suggestion that the technique should work equally well if applied with the opposite laterality. However, the treatment continues to be routinely applied with its original laterality. It is also interesting to note here that rTMS studies targeting the superior parietal lobe (reviewed in Ngo et al., 2013; in particular Kanai, Bahrami, & Rees, 2010) reported BR rate modulation in a cortical area previously reported to exhibit thinning in BD (Lyoo et al., 2006).

[17] Interestingly, one state study (Wang et al., 2015) reported interhemispheric resting state functional connectivity abnormalities in both major depression and bipolar depression (notably evident in PCC for major depression).

[18] Pettigrew continued to follow developments in BR research right up to his untimely death, including this period-coupling development. In a comment to Katyal on ResearchGate in January 2019, he stated: "Thank you for your paper. It was nice confirmation of a current 'mystery without a name' (viz., that all neural rhythms have correlated timing mechanisms). 'Fractal time' has been suggested by German researchers working on circadian rhythms. In their Nobel addresses, the 3 Nobelists, who shared the Prize last year for their work on circadian genes, referred to their embarrassing (they cannot readily explain it), unexplained, finding that a 'slow' PER mutant also has a slowed courtship rhythm in a distant part of the time spectrum. The work on Drosophila points to gene pleiotropy, but the ultradian rhythms that we have studied (like the nasal, rivalry, MIB, etc. rhythms) are each clearly driven by a very large number of genes, so the old concept of pleiotropy by a single gene might need elaboration. You might be interested to learn that Morre has shown that the very fast kinetics of mitochondrial enzymes can also be found to correlate with other slower neural rhythms in the same individual, an extension of this remarkable phenomenon to biological timing mechanisms that are even faster than those that you have shown. You might also be interested to know that the renowned Nobelist physicist, Richard Feynman, was actually preoccupied with this phenomenon in the years before his untimely death. He actually predicted it, well before he learned about its biological existence from my own lab. at Caltech!"
https://www.researchgate.net/publication/330563743_Frequency_of_alpha_oscillation_predicts_individual_differences_in_perceptual_stability_during_binocular_rivalry/comments?focusedCommentId=5c4e15103843b0544e62ab06
For more on Pettigrew's reference in the above to both Morre and Feynman, see Pettigrew and Carter (2005).

[19] It is also here interesting to note some overlap in genetic associations reported for BD and autism (Ruderfer et al., 2018), and links drawn between autism, vestibular dysfunction and vestibular stimulation (Grabherr, Macauda, & Lenggenhager, 2015; Miller & Ngo, 2007).

[20] Another target of investigation that clearly illustrates how perspectives in science and medicine can fluctuate is the use of psychedelic substances. Pettigrew, Carter, and colleagues examined BR in subjects under the influence of such substances (Carter et al., 2005a; Carter et al., 2007). The use of psychedelic substances in neuroscience and medicine is now growing at pace despite having previously fallen out of fashion (Kringelbach et al., 2020; Pollan, 2018). Pettigrew, Carter and colleagues also studied the effects of other altered states of consciousness on BR, such as meditation in highly trained meditators (Carter et al., 2005b). Carter et al. (2020) further discuss these lines of Pettigrew's research.

[21] I recall during medical case review work, reading of an individual with a history of major depression who woke feeling well (indeed jovial) but several hours later lay down onto train tracks (surviving, albeit severely disabled). This case illustrates the suddenness (and potential extremity) of mood state fluctuations and the appeal of pathophysiological models that can account for rapid mood state fluctuations.

[22] It is worth addressing the issue of just how 'rhythmic' BR is required to be when setting it in the context of biological rhythms. The same can be asked of mood state fluctuations. BR is not a classically rhythmic process and each successive phase duration is generally independent of

the former phase duration. That said, some rhythmic properties can be identified within BR (Cha & Blake, 2019) and it is clear there is high retest reliability of BR rate within an individual. It can be debated whether it is important or not for fluctuations in visual consciousness and mood to be classically rhythmic. Pettigrew argued that BR could be seen to be a free-running rhythm if one paid attention to the notion of *Zeitgebers* modulating BR dynamics (Pettigrew & Carter, 2005). For a discussion of how social *Zeitgebers* might relate to circadian rhythms in mood disorders, see Grandin, Alloy, & Abramson (2006).

[23] Notably, Pettigrew's colleague and former postdoc, Ramachandran, was an early investigator of CVS effects on persistent pain states, focusing on poststroke central pain (McGeoch, Williams, Lee, & Ramachandran, 2008; Ramachandran, McGeoch, Williams, & Arcilla, 2007).

[24] Interestingly, neurologists have no issues with using either bedside CVS in assessing brain death or more technological CVS set-ups with EM monitoring for vestibular disorder diagnosis, and have used CVS in this way for many decades (Shepard & Jacobson, 2016).

[25] This may be one reason why in the time since we jointly reviewed CVS and transcranial direct current stimulation (tDCS) as novel brain stimulation techniques (Been et al., 2007), the number of studies of tDCS has exploded (Kekic, Boysen, Campbell, & Schmidt, 2016) while that for CVS has been tiny in contrast. tDCS might also be perceived as more appealing than CVS on high-tech grounds.

[26] As I was reminded by Richard Carson when preparing this article, I in fact suffered my own bout of nausea and vomiting during a pilot run of our spTMS experiments when we applied the pulses in quick succession. In contrast, I have never felt nauseous or vomited from CVS, though I have certainly witnessed significant vomiting induced by CVS in a few individuals (around 1 in 40; Ngo et al., 2020).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ORCID

Steven M. Miller https://orcid.org/0000-0003-1802-1574

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