Binocular rivalry, brain stimulation and bipolar disorder

Trung T. Ngo, Wendy N. Barsdell, Phillip C. F. Law and Steven M. Miller*
Monash University, Melbourne

Mechanistic understanding of binocular rivalry (BR) has drawn upon psychophysical, electrophysiological and brain-imaging studies. The first brain *stimulation* approach occurred in the late 1990s and assessed a new mechanistic proposal, the interhemispheric switch (IHS) hypothesis. Both caloric vestibular stimulation (CVS) and transcranial magnetic stimulation (TMS) modulated rivalry predominance when applied *unilaterally*. We describe the IHS model, its genesis and the brain stimulation evidence on which it rests. We also review more recent CVS and TMS rivalry studies, and discuss the findings of slow BR in bipolar disorder (BD) and genetic contribution to individual variation in BR rate. Finally, we describe a recent *Drosophila* model that can shed light on genetic, molecular and neurophysiological aspects of both BR and BD.

Rivalry mechanisms: A tale of two levels

Several centuries ago, scholars sought to understand what happens in the brain when different, overlapping signals are received by the two eyes (see chapter by Wade & Ngo, this volume). Since then, binocular rivalry (BR) induced by dichoptic stimulation has been extensively researched and has been complemented by examination of dioptic (normal viewing) presentation of well-known forms of ambiguous-figure rivalry (AFR; e.g., the Necker cube) and other two-dimensional bistable perceptual stimuli (e.g., structure-from-motion [SFM] rotating sphere). As has been described in detail elsewhere (Leopold & Logothetis, 1999; Miller, Ngo, & van Swinderen,

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2012; Ngo, Liu, Tilley, Pettigrew, & Miller, 2008; see also chapter by Brascamp & Baker, this volume), evidence is accumulating for at least some degree of shared neural mechanism between BR and these other types of perceptual rivalry.

Since Hering and Helmholtz, there has been debate over whether BR is a low-level sensory competition phenomenon, or one based on high-level attentional competition (see chapter by Wade & Ngo, this volume). Early mechanistic theories of BR and AFR proposed that the perceptual alternations involved a reciprocal relationship between neuronal activity representing the dominant image and that representing the suppressed image (see also chapters by Sengpiel, Sterzer, and Wilson, this volume). On this account, perceptual dominance of one stimulus leads to adaptation of its neuronal representation until activity representing the other stimulus sufficiently recovers from adaption, thereby initiating a perceptual switch, and so on. Subsequent psychophysical evidence was relied upon for proposing that BR involves reciprocal inhibition between separate monocular channel neurons responsive to one, but not the other, eye (Blake, 1989). However, in contrast, electrophysiological studies in awake, behaving monkeys (Leopold & Logothetis, 1996; Logothetis & Schall, 1989; Sheinberg & Logothetis, 1997; reviewed in Logothetis, 1998; Logothetis, Leopold, & Sheinberg, 2003) showed that single-unit activity of monocular neurons bore little relationship to the monkeys' rivalrous perceptions (see also chapter by Sengpiel, this volume). Although 18% of tested V1 neurons did show perception-dependent activity, all but one of these neurons were binocular (i.e., responsive to input from either eye). As the investigators progressed through the visual processing hierarchy, they found greater percentages of perception-dependent units, until reaching the inferotemporal cortex and superior temporal sulcus where ~90% of recorded cells demonstrated activity that correlated with the monkeys' perceptual reports.

This electrophysiological data conflicted with subsequent human fMRI studies (see chapter by Sterzer, this volume) that showed activity in V1 (Lee & Blake, 2002; Polonsky, Blake, Braun, & Heeger, 2000; Tong & Engel, 2001; Wunderlich, Schneider, & Kastner, 2005) and LGN (Haynes, Deichmann, & Rees, 2005; Wunderlich et al., 2005) covaried with the dominance and suppression phases during BR. Middle ground was therefore found in the form of an 'amalgam' view of BR (Blake & Logothetis, 2002), in which the phenomenon was seen to result from a series of processes at multiple levels in the visual pathway. Most recently, there have been yet further contradictory mechanistic studies. Keliris, Logothetis and Tolias (2010) reported that during binocular flash suppression in awake primates, V1 perception-dependent spiking activity (again in 20% of units tested) occurred equally in binocular *and* monocular neurons, thus in contrast to the original report with BR by Leopold and Logothetis (1996). However, Keliris et al. (2010) also reported weaker V1 local field potential (LFP) modulations than

those seen in higher areas, and could not rule out the possibility that they were the result of modulatory top-down input (see chapter by Sengpiel, this volume). There is now also, remarkably, report of perception-dependent neural activity (both neuronal discharges and power modulation of high-frequency LFPs) in macaque lateral prefrontal cortex during binocular flash suppression (Panagiotaropoulos, Deco, Kapoor, & Logothetis, 2012).

As the above electrophysiological and brain-imaging evidence demonstrates, and as the psychophysical evidence reviewed by Brascamp and Baker (this volume) and Bressler, Denison and Silver (this volume) similarly demonstrates, mechanistic understanding of BR has exhibited a point-counterpoint history. This has been particularly so with respect to whether the phenomenon is mediated by low- or high-level mechanisms. Perhaps not surprisingly, given suggestions of common mechanistic processes underlying BR and AFR, the BR amalgam view has been mirrored by a 'hybrid' model of AFR (Long & Toppino, 2004). This hybrid model consists of a conceptual, multi-level framework (i.e., from low- to high-level: parallel feature-extraction channels, intermediate processing and representation, higher-order global operations) to account for the wealth of conflicting sensory (low-level) and cognitive (high-level) evidence in AFR studies.

Consistent with this pendulous history (Blake, 2001), the amalgam view of BR and corresponding hybrid view of AFR now acknowledge a role for processing at multiple stages in the visual hierarchy, and indeed even in non-visual areas concerning attention, behavior and decision-making. Whilst this consensus view brings perspective to low-level and high-level views of rivalry, there remains debate over the relevance of processing at each level (discussed in Ngo, Liu, Tilley, Pettigrew, & Miller, 2007). Moreover, too ready an acknowledgement of multi-level processing during rivalry could stifle proposals for more specific mechanistic clarification across and within levels.

The interhemispheric switch (IHS) model of rivalry

We previously proposed a specific high-level mechanistic model of BR and AFR (Miller et al., 2000) – the interhemispheric switch (IHS) model. This model is not inconsistent with the notion of multi-level processing, but has at its mechanistic core, a high-level process in which the attentional resources within each cerebral hemisphere act independently and in alternation. On this view, the perceptual switching that characterizes rivalry correlates with a process of alternating hemispheric activation, i.e., interhemispheric switching. The evidence garnered in support of the IHS model, and a range of issues raised therein, has been reviewed in detail elsewhere (Miller, 2001; Miller & Ngo, 2007; Miller et al., 2012; Ngo et

al., 2007, 2008; Pettigrew, 2001). Here, the genesis and key aspects of the model are discussed, and an updated commentary on its status is provided in light of recent developments in both rivalry research and comparative studies of inter-hemispheric switching.

The IHS hypothesis arose from the conjunction of separate lines of thinking by Pettigrew and Miller in the late 1990s (see Figure 1). Pettigrew, Collin and Ott (1999) had observed independent eye movement patterns in a small fish, the sandlance, and because this animal has completely crossed eye–hemisphere pathways, they reasoned that the alternating eye movements must be driven by an IHS process. Inspired by this observation, by Ramachandran's (1994) proposal regarding complementary (lateralized) cognitive styles of the cerebral hemispheres, and by a desire to examine neural mechanisms of the psychiatric condition, bipolar disorder (BD; manic depression), Pettigrew sought to identify an IHS process in humans that would help explain the extreme mood swings of BD. On this background, Miller proposed that BR could be exactly the sort of IHS process that Pettigrew was seeking to identify in humans. Miller's proposal was based on the convergence of three factors: (i) rivalry had been considered fundamentally attentional in nature (Helmholtz 1867/1925; see also Brascamp & Blake, 2012; Ling & Blake, 2012; Zhang, Jamison, Engel, He, & He, 2011; and chapters by Wade & Ngo and Bressler et al., this volume, and below), (ii) split-brain studies showed that the cerebral hemispheres are able to *independently* draw on attentional resources (Luck, Hillyard, Mangun, & Gazzaniga, 1989; see also Alvarez & Cavanagh, 2005; Alvarez, Gill, & Cavanagh, 2012), and (iii) hemispherectomy studies (removal of an entire cerebral hemisphere) showed that the remaining single hemisphere is able to sustain a coherent visual percept (Bogen et al., 1998; see also Bogen, 2000). Thus, Pettigrew and Miller proposed a rivalry model in which an IHS drives the perceptual alternations, with high-level regions in each hemisphere representing one, but not the other, rivaling percept.

To test their model, Miller reasoned that if each cerebral hemisphere mediated perception of one, but not the other, image during rivalry, then preferentially activating one hemisphere should alter the relative time spent perceiving each image (predominance). He therefore hypothesized that the *unilateral* cortical activation properties of caloric vestibular stimulation (CVS), as had been used by Ramachandran (1994) in developing his cognitive style proposals, would alter perceptual predominance during rivalry if an IHS process indeed mediated the phenomenon. The strategy of examining the IHS model by unilateral brain stimulation was further bolstered by Pettigrew's hypothesis that transcranial magnetic stimulation (TMS) applied in this way should also alter predominance during BR. TMS was a relatively nascent technique in the late 1990s but is now in widespread use in the cognitive and clinical sciences. The technique is described in detail in

the chapter by Thomson and Fitzgerald (this volume). Below, we briefly review the CVS technique including the range of its neural and phenomenological effects, before describing results of the ensuing CVS and TMS studies of rivalry. Thereafter we turn to an unexpected finding encountered when Pettigrew and Miller commenced examination of the IHS model, one that enabled the linking of the notion of an IHS mechanism to the clinical condition, BD.

CVS technique overview

CVS is a commonly used technique for testing vestibular functioning and brain death. It involves slowly irrigating the ear with cold (or warm) water while the subject's head is reclined, to induce vertigo and nystagmus. Although CVS has primarily been used for clinical diagnostic purposes in the past century, in recent decades it has been applied to the examination of a wide range of cognitive and clinical phenomena such as attention, somatosensory representation, memory, mood, and pain. Several brain-imaging studies have shown that the technique consistently activates a network of structures known to be involved in mediating such phenomena, in addition to vestibular processing. CVS administration with cold water induces activation of cortical structures in the contralateral hemisphere, including anterior cingulate cortex, posterior insular and retroinsular cortices, temporoparietal junction, somatosensory area SII, inferior parietal lobule, parietal operculum and superior temporal gyrus (reviewed in Been, Ngo, Miller, & Fitzgerald, 2007; Lopez, Blanke, & Mast, 2012; Miller & Ngo, 2007; zu Eulenburg, Caspers, Roski, & Eickhoff, 2012). Figure 2a depicts the CVS technique and the key brain regions it activates.

In accordance with such activation, administration of CVS has the ability to modulate attentional disorders such as unilateral neglect following right-hemisphere lesions (Figure 2b), along with modulation of related conditions including anosognosia (denial of disease), somatoparaphrenia (bizarre beliefs), macrosomatognosia (misperception of body part size) and hemianesthesia (Bottini et al., 2005; Chokron, Dupierrix, Tabert, & Bartolomeo, 2007; Rode et al., 2012; Rossetti & Rode, 2002). CVS appears also able to modulate the manic phase of BD (Dodson, 2004; Levine et al., 2012; see also Pettigrew & Miller, 1998) (Figure 2c), as well as a variety of persistent pain disorders (André, Martinet, Paysant, Beis, & Le Chapelain, 2001; Kolev, 1990; Le Chapelain, Beis, Paysant, & André, 2001; McGeoch & Ramachandran, 2008; McGeoch, Williams, Lee, & Ramachandran, 2008; McGeoch et al., 2009). In healthy subjects CVS has been shown to affect a wide range of cognitive functions including spatial perception and localization (Karnath, 1994; Karnath, Fetter, & Dichigans, 1996; Karnath,

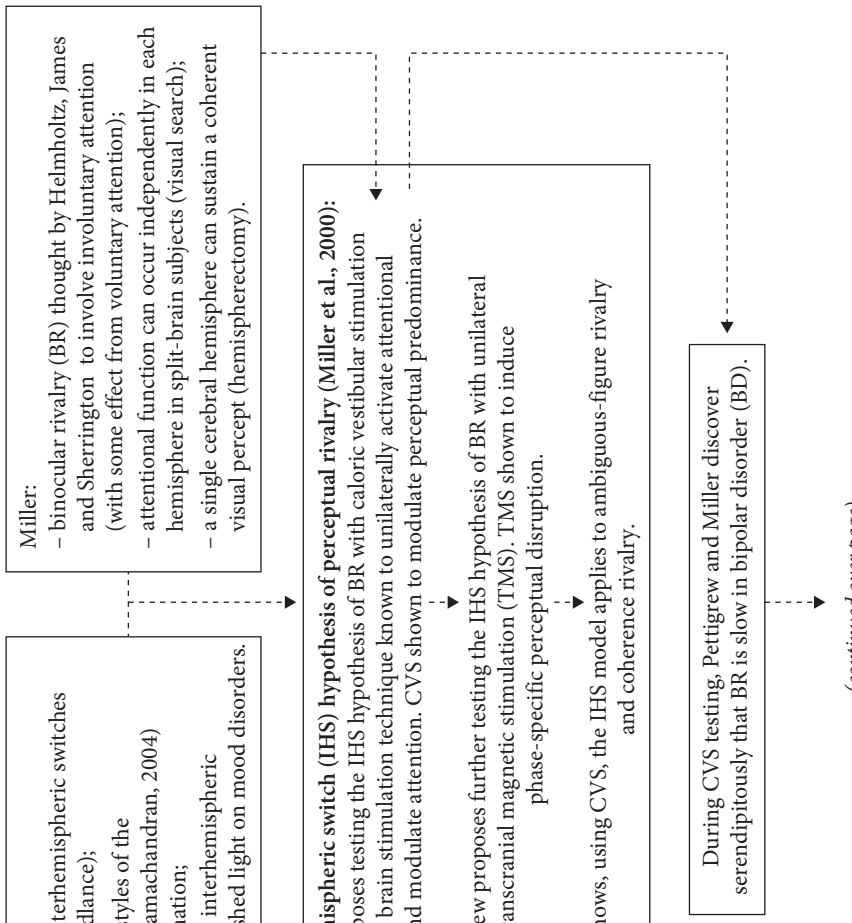

Figure 1. Genesis of the IHS model of rivalry and sticky switch model of BD, and recent genetic developments.

Pettigrew & Miller (1998) confirm BR is slow in BD and link IHS model of BR to slow BR in BD:

'Sticky switch' hypothesis of BD

Model incorporates exsiting data-based proposals of:

- complementary cognitive styles of the hemispheres
- hemispheric asymmetries of mood and mood disorders
- ultradian rhythms of alternating hemispheric activation

Model proposes:

– IHS driven by subcortical bistable oscillator (Pettigrew), subject to top-down influence;
– slow BR oscillators genetically (pleiotropically) coupled to slow ultradian rhythm oscillators (*Drosophila* precedent);
– ultradian rhythm IHS oscillators, by being slow in BD, are prone to being stuck in one or the other state by external synaptic input (cortical top-down input from environmental cues/stressors);
– thus mania = 'stuck' left hemisphere (relative activation) and depression = 'stuck' right hemisphere;
– CVS could restore hemispheric imbalances and thus potentially treat mania and depression;
– molecular defect in BD may be the number of cationic channels controlling Ih current;
– because several cationic channels can affect oscillator switch rate, this could explain multiple genetic candidates for BD;
– increased cellular and neuronal sensitivity in BD is the result of cortical compensation for reduced channel number, which further predisposes the subcortical switch to being stuck (by increased output from cortex to switch);
– slow BR could be a trait marker of BD for use in genetic studies of the disorder.

Slow BR in BD explored as a potential diagnostic aid in clinical psychiatry and endophenotype for BD. BR does not appear to be slow in schizophrenia or major depression (Miller et al., 2003).

Heritability of individual variation in BR rate examined in twin study with Martin and Wright. Substantial genetic contribution to BR rate demonstrated (Miller et al., 2010).

Drosophila attentional switching (Tang & Juusola, 2010) proposed as model to explore genetic and molecular determinants of switch rate (Miller, Ngo, & van Swinderen, 2012).

Multi-center study established to examine clinical diagnostic and endophenotype applications of slow BR in BD (Ngo et al., 2011).

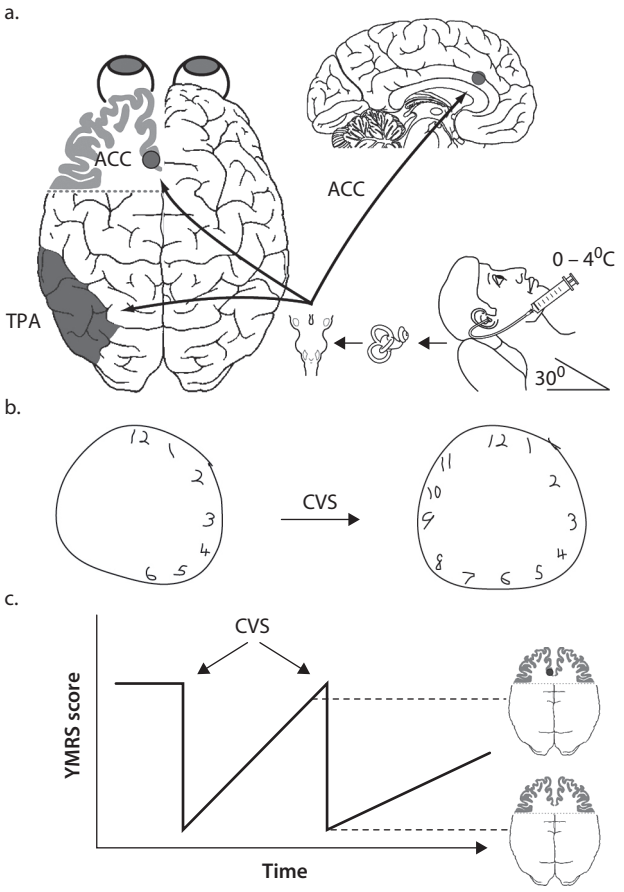

Figure 2. **(a)** The CVS technique. Irrigation of cold water with the head reclined activates, via the semicircular canals and vestibular pathways, contralateral cortical structures implicated in attentional and mood processing. These structures include the anterior cingulate cortex (ACC), insular cortex (not depicted) and various temporo-parietal areas (TPA). **(b)** CVS temporarily ameliorates left-sided attentional neglect following right-sided damage, as depicted by drawing of a complete clock face following the procedure. **(c)** Pettigrew and Miller's (1998) sticky switch model of BD predicted that right-hemisphere activation (via left-ear CVS) would alleviate the signs and symptoms of mania by restoring toward normal the greater relative left-hemisphere activation asymmetry associated with mania (Blumberg et al., 2000). This therapeutic effect was verified in a case study by Dodson (2004), as depicted by a dramatic reduction in the patient's Young Mania Rating Scale (YMRS) score following the procedure.

Himmelbach, & Perenin, 2003; Karnath, Sievering, & Fetter, 1994; Schmäl, Kunz, & Stoll, 2000), spatial and verbal memory (Bächtold et al., 2001), auditory space perception (Lewald & Karnath, 2000), visual imagery (Mast, Merfeld, & Kosslyn, 2006), tactile perception (Ferrè, Bottini, & Haggard, 2012; Ferrè, Bottini, Iannetti, & Haggard, 2013; Ferrè, Sedda, Gandola, & Bottini, 2011; Lopez, Schreyer, Preuss, & Mast, 2012), and positively biased beliefs (McKay et al., in press). Below we summarize a large series of studies we previously conducted in healthy controls, which demonstrated the ability of CVS to modulate perception during both BR and AFR. We then discuss more recent CVS studies and go on to review both earlier and recent TMS studies of rivalry.

Review of brain stimulation studies of rivalry

CVS and predominance modulation

In accordance with the predictions of the IHS model, unilateral CVS was found to modulate perceptual predominance during BR with drifting vertical and horizontal gratings, at least with respect to left-hemisphere activation (Miller et al., 2000; see Figure 3a). Hence, on an IHS interpretation, by activating attentional regions in the left hemisphere relative to the right, subjects spent more relative time perceiving the left hemisphere's image (though exactly which image that was could vary between individuals; see below). This result was difficult to interpret on models of rivalry that did not involve separate distribution of the two images, one to each hemisphere. However, an alternative explanation was that residual eye movements from the CVS-induced nystagmus would differentially affect perception of the horizontal and vertical gratings. Hence, we next repeated the experiment using orthogonal stationary oblique gratings to induce BR, thus excluding such eye movement interpretations. The same CVS-induced predominance shifts were demonstrated (Miller et al., 2000).

Ngo subsequently applied CVS to (i) Necker-cube rivalry (Miller et al., 2000), (ii) Rubin's vase-faces illusion (Ngo et al., 2008), and (iii) the grouped percepts during coherence rivalry (Ngo et al., 2007; see also below, Figure 3 in this chapter, and Figure 2 in chapter by Miller, this volume), again finding significant predominance modulation from left-hemisphere CVS in each case. Moreover, in all five experiments, the same *asymmetry* of CVS effects was observed (i.e., left-hemisphere but *not* right-hemisphere activation induced a significant predominance change). This asymmetry in the ability of CVS to modulate predominance during rivalry was interpreted (Miller et al., 2000) in terms of a previously demonstrated hemispheric asymmetry during BR (in which a right-lateralized fronto-parietal

region was active during perceptual transitions; Lumer, Friston, & Rees, 1998; see also chapter by Sterzer, this volume). Exactly why right-lateralized transition-related processing would mitigate CVS-induced predominance change is not clear, however hemispheric asymmetries relevant to rivalry dynamics have also recently been demonstrated with TMS applied to parietal regions (see below).

Thus, the ability of CVS to modulate predominance during perceptual rivalry contributes to evidence in support of (i) the IHS model, (ii) the relevance of attentional processing to perceptual rivalry, and (iii) structural overlap in the processing of apparently disparate functions such as vision, mood and pain (Miller & Ngo, 2007). However, in all of the above CVS rivalry experiments, it was clear the technique did not modulate rivalry in every subject tested (Miller et al., 2000; Ngo et al., 2007, 2008). Indeed, in two subsequent experiments, no significant group effects of predominance modulation were found following CVS (i.e., from either left- or right-hemisphere activation) (Ngo et al., 2007; Ngo, Blomberg, Liu, Pettigrew, & Miller, *submitted*).

The first of these experiments reported that CVS did not cause significant changes in predominance between the half-field percepts during multistable BR (Figure 3b). Multistable BR involves alternations between four different percepts: the two presented images (half-field rivalry) and two coherent images (coherence rivalry). Coherence rivalry is a phenomenon in which the brain synthesizes coherent aspects of each eye's image into coherent percepts with which to rival. First reported by Towne (1863) and then Díaz-Caneja (1928), this phenomenon attracted attention more recently through the work of Kovács, Papathomas, Yang and Fehér (1996), and was taken as evidence for rivaling stimulus representations rather than rivaling eyes during BR. In another study, stimulus representation rivalry was also supported by subjects reporting smooth and slow perceptual alternations during rivalry, despite the stimuli being rapidly swapped between the eyes (Logothetis, Leopold, & Sheinberg, 1996; so-called 'flicker-and-swap' rivalry). Ngo, Liu, Miller and Pettigrew (2000) showed that with Díaz-Caneja stimuli, coherent percepts occurred for around half the viewing time while half-field percepts (the same as those presented to each eye) occupied the remaining half (with some degree of individual variation in this temporal aspect). With this finding, and that of CVS modulating predominance of the coherent percepts, but not of the half-field percepts, Ngo and Miller (Ngo et al., 2007) developed a meta-rivalry model to explain interocular-grouping during rivalry (which may also extend to flicker-and-swap rivalry). This meta-rivalry model postulated that: (i) coherence rivalry occurs at a high level on an interhemispheric basis, (ii) half-field rivalry occurs at a low level on an intrahemispheric basis, and (iii) high-level stimulus rivalry and low-level eye rivalry themselves rival (i.e., meta-rivalry) for access to visual consciousness (see Figure 3b).

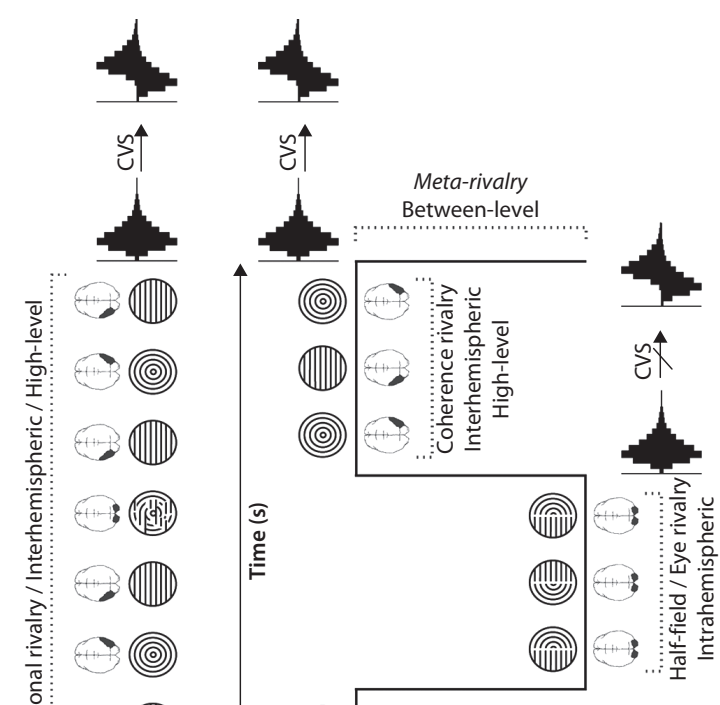

Figure 3. (**a**) The interhemispheric switch model of conventional BR and (**b**) the meta-rivalry model of interocular-grouping phenomena. (**a**) Unilateral activation induced by CVS modulates predominance during perceptual rivalry, thus supporting an IHS model of the phenomenon. CVS does not modulate rivalry predominance in all subjects however, or in all experiments, as depicted by the technique not inducing a significant change in group predominance with half-field/low-level rivalry (**b**), or with repeated CVS sessions to assess percept-to-hemisphere selection and retest reliability of predominance effects (see main text).

The second study in which CVS did not induce significant group predominance changes (Ngo et al., *submitted*) set out to investigate two aspects of the previous CVS data: (i) which hemisphere selects which percept during rivalry, and on what basis, and (ii) what the re-test reliability of CVS effects are, both generally and with respect to percept-to-hemisphere selection. To meet these objectives, Ngo employed a novel repeated-measures design involving multiple left-hemisphere CVS sessions within the same subjects, using three rivalry types: drifting horizontal/vertical BR, stationary oblique BR, and Necker-cube rivalry. Reproducibility of significant predominance change following CVS was found to be low both across the group and within individuals. Reproducibility was also low for the magnitude and direction of predominance changes. The substantial study-design differences in this experiment compared with the previous CVS rivalry studies may explain these negative findings, with possible habituation effects from repeated CVS. Further analyses of that data, based on such methodological considerations but limited by the consequent relatively low sample sizes, also revealed no significant group predominance change following CVS in any of the rivalry types (Ngo et al., *submitted*). Moreover, the negative findings made assessment of percept-to-hemisphere selection issues difficult, but scrutiny of group and individual data suggested that there was no apparent predilection for predominance to change in one or the other direction for any rivalry type. Interpreting the existing collection of CVS studies is discussed further below when the current status of the IHS model is considered.

Single-pulse TMS and perceptual disruption

Unlike CVS which induces relatively long-lasting unilateral hemisphere activation (approx. 10–15 min duration), and activates a wide network of inter-related cortical areas, single-pulse TMS (spTMS) induces short-term changes in brain activation in a more localized manner (though with possible secondary effects on connected neuronal populations). In the first application of the TMS technique to the study of rivalry (Miller et al., 2000), spTMS was delivered to temporo-parietal regions of the left hemisphere (given the CVS experiments' significant results with activation of this hemisphere), and caused disruption of underlying cortical activity. Therefore the key prediction for this experiment, on an IHS model, was that a TMS pulse timed to be delivered on a switch to one percept (the left hemisphere's percept, which could vary between individuals) would disrupt that percept, but that the same pulse (delivered at the same left hemisphere site) would have no effect when timed to occur on a switch to the *other* (the right hemisphere's) percept. Exactly this *phase-specific* pattern of spTMS effects was observed (Miller et al., 2000; see Figure 4).

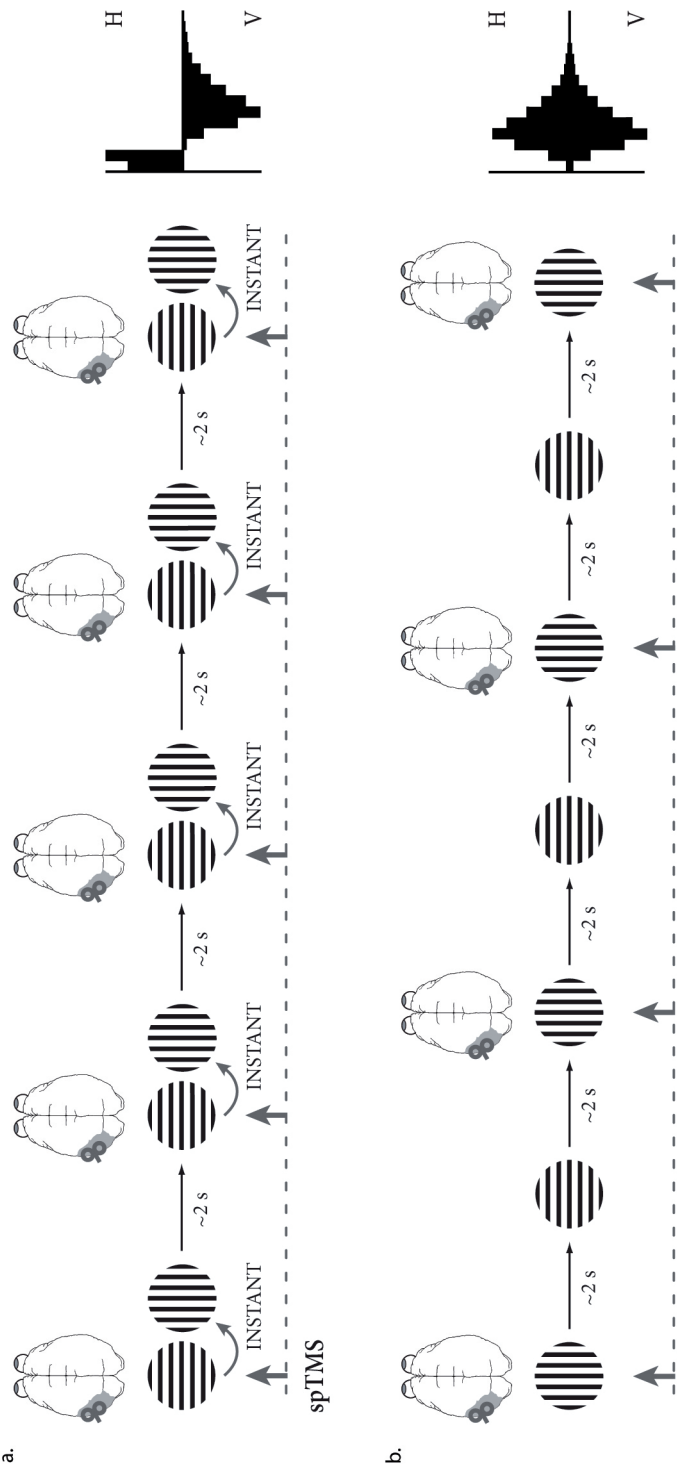

Figure 4. TMS evidence for the IHS model of rivalry. (**a**) spTMS delivered contingent on a subject's switch to the horizontal image immediately disrupted that percept, causing an instant switch to the other (vertical) rivaling percept. This phase-specific effect is shown in the frequency histogram with a substantial reduction in the perceptual interval duration for the horizontal image. (**b**) Response-contingent spTMS delivered when the same subject switched to the vertical percept had no corresponding effect, with regular rivalry alternations perceived. In some subjects the opposite pattern occurred (with disruption of the vertical but not horizontal percept; not depicted), and in 2 of 7 subjects, no perceptual disruption occurred. However, in 5 of 7 subjects, a phase-specific disruption effect (irrespective of direction) – the key prediction of an IHS model – was observed.

As might be expected, the predominance modulation observed in this original TMS experiment was far more dramatic than that seen in CVS experiments. The effect of CVS was visible in plotted frequency histograms of perceptual interval durations with (i) predominance induced where there was previously none, (ii) equalising of a previous predominance, or (iii) a previous predominance reversing its direction. However, the shape of the TMS frequency histograms on the other hand, reflected the immediate disruption of perceptual periods, i.e., causing very short percept durations for one of the rivaling images (see Figure 4). Moreover, as with the CVS experiments, the TMS data also revealed individual variation in response to stimulation. Two out of seven subjects did not exhibit the phase-specific perceptual disruption effects seen in the other five subjects. However, although the coil was always positioned broadly over temporo-parietal regions, there was no formal localization procedure employed, either stereotactically or with prior brain-imaging. Rather, the study's methods involved approximate positioning of the coil in temporo-parietal regions initially, followed by more detailed positioning based on trial and error (with the subject's verbal report of a disruption effect indicating the site for coil positioning for that subject's testing session). Whether non-responders would have showed an effect under more precise localization procedures is not clear. One aspect of this study that is clear however, is that the phase-specific effect could not be attributable to noise or motor artefacts, because for each subject, all aspects of the stimulation were held constant (cortical site, intensity, noise, motor artefact etc), with the only difference being the response-contingency triggering the TMS pulse.

The initial TMS rivalry study did not systematically investigate the effect of spTMS applied to *right*-sided temporo-parietal regions. Rather, as mentioned above, it concentrated on the left hemisphere due to the CVS experiments' significant results for this hemisphere. However, a few right-hemisphere pilot TMS sessions were conducted (data not reported in Miller et al., 2000), generally without phase-specific disruptions being observed. This mirrored the asymmetry seen in CVS experiments as described above. These CVS and TMS experimental asymmetries indicated that simple predictions of the IHS model – i.e., of equal and opposite effects from left- and right-hemisphere stimulation or disruption – were not observed, and hence that the relative hemispheric contributions to rivalry may be complex. Indeed, hemispheric asymmetries would a decade later be a feature of a series of studies on the effects on rivalry of repetitive TMS (rTMS), as discussed in the next section.

In a follow-up spTMS study, Funk and Pettigrew (2003) sought to examine whether the IHS model of BR and AFR also applied to another phenomenon that involved periodic appearance and disappearance phases – motion-induced blindness (MIB; Bonneh, Cooperman, & Sagi, 2001). As well as setting out to address

that issue, they sought to examine whether perceptual disruption effects could in fact be elicited with *right*-hemisphere TMS. Using a figure-of-eight coil delivering single pulses applied to the intraparietal sulcus (IPS) and superior parietal lobe (SPL), they employed two pulse-triggering conditions in the study. In one condition, as with the earlier study (Miller et al., 2000), the subject's report of the start of a perceptual phase triggered the pulse. This showed that MIB, like BR, exhibits phase-specific perceptual disruption when TMS is applied over the left hemisphere, thus suggesting that MIB may also be an IHS phenomenon. However, the converse effect from right-hemisphere stimulation was again difficult to elicit. This led to testing a second condition in which the TMS pulse was timed to occur 300 ms prior to an *expected* transition, with that expectation calculated according to baseline viewing (the period of MIB being relatively regular within individuals, as it is with BR). Although this timing strategy in effect yielded a TMS pulse that preceded, coincided with or followed a perceptual transition, the manipulation appeared to improve the ability of right-hemisphere parietal spTMS to induce phase-specific perceptual disruption (Funk & Pettigrew, 2003).

The third (and only other) spTMS study of rivalry conducted to date is that by Pearson, Tadin and Blake (2007). These investigators used a figure-of-eight coil over V1 and V2 centrally (thus stimulating both occipital cortices), with pulses triggered automatically every 3.2 seconds. When subjects viewed conventional BR and with analyses removing any effects time-locked to a pulse, the overall effect was a small increase in switch rate (observed in 5 out of 6 subjects), thought to possibly be an effect of arousal due to the TMS. More interestingly however, when analyses did examine time-locked effects, there was shown to be a disproportionately large number of perceptual switches that occurred following a TMS pulse (observed in all subjects). However, two important features of this effect were not reported: (i) whether the switch-inducing effect varied in a phase-specific manner as had occurred in previous studies (Funk & Pettigrew, 2003; Miller et al., 2000), and (ii) exactly what proportion of pulses were followed by a perceptual switch (discussed further below). Another main finding of Pearson et al.'s (2007) study was that there was a correlation between the time of onset of time-locked perceptual disruption effects and a subject's rivalry rate. Further, a control condition in which stimulus contrast was varied to alter a subject's rivalry rate showed that the TMS-induced modulation delay was linked to an individual's endogenous switch rate because the delay was independent of the contrast manipulations. Other controls employed in this study accounted for eye movements, auditory/tactile artefacts and transients that could potentially explain the data, though none of these factors were found to be relevant.

A further finding of the Pearson et al. (2007) study was that they repeated their protocol with flicker-and-swap rivalry. Under these stimulus conditions, as

described above, subjects reported perceiving smooth slow perceptual alternations rather than rapidly swapping images, indicating a likely high-level selection and stimulus representation process (Logothetis et al., 1996). When occipital TMS was applied during this rivalry type, the time-locked effects that the investigators had seen during conventional rivalry were not observed. This led Pearson et al. (2007) to argue that conventional rivalry and stimulus rivalry occur at discrete neural levels (i.e., low and high levels, respectively). This finding was partly in keeping with the proposal by Ngo et al. (2007) that the coherent percepts during Díaz-Caneja stimuli viewing (another type of stimulus representation rivalry) and half-field percepts with the same stimuli, occurred at discrete neural levels (see above and also chapter by Bressler et al., this volume). Indeed, Ngo et al. (2007) specifically argued that flicker-and-swap rivalry, as used by Pearson et al. (2007), might similarly engage the sort of meta-rivalry process proposed to mediate the perceptions with Díaz-Caneja stimuli and other interocular-grouping stimuli. However, Ngo et al. (2007) also maintained that conventional rivalry, in the absence of interocular-grouping or flicker-and-swap conditions, occurs via a fundamentally high-level IHS process. Given the IHS model does engage the notion of multi-level processing via feedback from high- to low-level regions (attentional selection mechanisms biasing pools of competing neurons; Miller, 2001), we consider it not entirely surprising that TMS applied to such low-level pools could also modulate perception, increasing the probability of inducing a switch by affecting input to, or the effect of feedback from, the higher levels. Another possibility is that conventional rivalry itself engages a meta-rivalry process, though further TMS data would be needed to explore that proposal. A summary of existing single-pulse TMS studies of rivalry is presented in Table 1.

Repetitive TMS and rate modulation

If interpretation of CVS and single-pulse TMS studies of rivalry is hampered by conflicting data (which by now should not be surprising given similar conflict in electrophysiological, brain-imaging and psychophysical data), the results of applying rTMS to rivalry have been even further conflicting. We provide a summary in Table 1 of rTMS rivalry studies, the methodologies employed including stimulation parameters and sites targeted, and the findings of each study. As noted in the chapter by Thomson and Fitzgerald (this volume), rTMS differs from spTMS in that repeated stimulation can progressively alter the activity of neuronal populations during the course of stimulation and for some time after its cessation. The technique has localized effects on the targeted brain regions and associated neuronal populations (like spTMS), with the perceptual outcome being partly dependent on the stimulation protocol that is employed (see below).

As shown in Table 1, studies have focussed on rTMS of the SPL and found that depending on various methodological aspects, rivalry switch rate can be increased or decreased following rTMS, including with BR, an ambiguous SFM rotating sphere and a bistable spinning wheel illusion (SWI; which induces alternating directions of motion perception). Using the SWI, Iramina and colleagues (Ge, Ueno, & Iramina, 2007a, 2007b, 2008) focussed on the SPL based on findings from previous brain-imaging studies of rivalry (Lumer et al., 1998; Sterzer Russ, Preibisch, & Kleinschmidt, 2002). This work was the first of a series of experiments by this group, which are discussed in more detail below.

Using a bistable SFM rotating sphere, Kanai, Bahrami and Rees (2010) examined the effect of rTMS on switch rate by targeting the posterior SPL. rTMS was applied in between periods of rivalry recording to left SPL and right SPL (with the vertex as control) in separate sessions using a continuous theta-burst stimulation protocol (i.e., 3 pulses at 50 Hz, every 200 ms for 40 s). Rivalry rate was found to be significantly slower following rTMS of either left or right SPL. Using structural brain-imaging and diffusion tensor imaging (DTI), this study also examined rivalry rate in relation to measures of cortical thickness, local grey matter density and local white matter integrity. Cortical thickness of bilateral SPL and bilateral post-central gyrus (but not any other brain area, including prefrontal regions) was found to be negatively correlated with percept duration, i.e., the thinner the cortex, the slower the switch rate. In relation to grey matter density and white matter integrity, bilateral SPL similarly showed this association with alternation rate. These brain-imaging findings suggested SPL structure could account for the wide inter-individual variation observed in rivalry rate. The authors also note the overlap of their identified relevant regions and those subserving attention and attention-switching functions, and consider the possibility that feedback from SPL to lower regions is the mechanism of influence (i.e., the larger the SPL, the stronger the feedback signal to switch and hence the faster the switch rate). The authors base their conclusions on an inhibition-based interpretation of their protocol.

In a follow-up study of rTMS on rivalry rate, Carmel, Walsh, Lavie and Rees (2010) used drifting BR stimuli to examine the effect of 1Hz pulses targeted at SPL. In contrast to the previous study (Kanai et al., 2010) however, they found that following rTMS of right SPL (cf. left SPL and no-TMS conditions), there was an *increase* in the rate of perceptual switches. The authors consider their stimulation protocol to be inhibitory and that the right SPL maintains a perceptual state (hence disrupting it leads to faster switch rate). The authors also provide an attention-based interpretation of their findings involving feedback from the right SPL to lower visual regions (i.e., impairing this maintenance function leads to a weaker top-down signal, making it easier for the suppressed image to overcome suppression).

Table 1. Summary of TMS studies of visual rivalry

Study	N	Stimulus-type	TMS type	Region	Key methodological points	Effects
Miller et al. (2000)	7	Stationary BR	Inhibitory spTMS; 0.66–1 T.	Left TPC.	Online; spTMS time-locked to reported reversal, triggered by button press indicating switch; No-TMS (control).	– Phase-specific spTMS disruption in 5/7 observers.
Funk & Pettigrew (2003)	13	MIB	Inhibitory spTMS; 50–70% of RMT.	Bilateral IPS/SPL.	Online; in one condition, triggered according to report; in another, triggered based on response pattern from baseline recording; 4 trials/region.	– Phase-specific left spTMS disruption; Right spTMS <300 msec prior to an expected transition improved phase-specific disruptive effect for this hemisphere.
Pearson et al. (2007)	6 5	Stationary BR Eye-swap BR	Inhibitory spTMS; 51–83% of maximum 1.8 kV.	Midline V1/V2 (central & peripheral phosphenes).	Online; spTMS computer-triggered at predetermined interval; Every 3.2 s; No-TMS (control); 3 trials/region.	– Midline V1/V2 spTMS increased switch rate in BR by 300 ms (10%) in 5/6 observers; this time-locked effect was not observed in eye-swap BR. – Subjects with slower switch rate experienced more delayed TMS effects – More perceptual switches following TMS pulse; but did not examine (i) if this was phase-specific or (ii) proportion of pulses followed by perceptual switch. – Positive correlation between onset of perceptual disruption effect & switch rate for stationary BR only.
Ge et al. (2007b)[1]	8	SWI	Inhibitory rTMS; 90% of RMT.	Right SPL, posterior TL.	Offline; Computer-triggered rTMS before stimulus viewing; 60-pulse & 240-pulse; 60 s; 1 Hz; No-TMS (control); 1 trial/region.	– Right SPL 60-pulse rTMS increased switch rate. – Right SPL 240-pulse rTMS decreased switch rate.

[1] These findings included 7 previous subjects' data reported in Ge et al. (2007a). The decrease in switch rate finding was subsequently shown in 4 more subjects (Ge et al., 2008).

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Study	N	Stimulus-type	TMS type	Region	Key methodological points	Effects
Nojima et al. (2010a)[2]	11	SWI	Inhibitory & excitatory rTMS[3]; 90% of RMT.	Right SPL, posterior TL.	Offline; Computer-triggered rTMS before stimulus viewing; All rTMS types delivered consecutively over each brain region; 0.25 Hz 60-pulse & 0.25/0.5/1 Hz 120-pulse; No-TMS (control).	– Right SPL 0.25 & 1 Hz[4] 60-pulse rTMS increased switch rate. – Right SPL 1 Hz 240-pulse rTMS decreased switch rate[4]. – No right SPL 0.25/0.5/1 Hz 120-pulse rTMS effects.
Nojima et al. (2011a)[5]	11	SWI	Inhibitory & excitatory rTMS; 90% of RMT.	Right SPL, posterior TL.	Offline; Computer-triggered rTMS before stimulus viewing; Biphasic; 0.25 Hz 60/120-pulse, 0.5 Hz 60/120-pulse, 1 Hz 60/120/240-pulse. 90% of RMT; >120-pulse is inhibitory based on reduced MEP amplitude; No-TMS (control).	– Right SPL 0.25/0.5/1 Hz 60-pulse rTMS increased switch rate. – Right SPL 1 Hz 240-pulse rTMS decreased switch rate. – No right SPL 0.25/0.5/1 Hz 120-pulse rTMS effects.
de Graaf et al. (2011)	10	SFM	Inhibitory; rTMS; 110% of RMT.	Right posterior PC, dorsolateral PFC, OP, hMT/V5.	Offline; Passive viewing & voluntary control conditions; Computer-triggered rTMS in between stimulus viewing; Biphasic; 300-pulse; 5 mins; 1 Hz 300-pulse; 2 trials/region.	– Right dorsolateral PFC rTMS reduced dominance duration during SFM voluntary control condition, with PC rTMS showing only trend effects. No OP or hMT/V5 rTMS effect on SFM voluntary control condition. – No PC, PFC, OP or hMT/V5 rTMS effect on passive viewing.
Carmel et al. (2010)	6	Drifting BR	Inhibitory[6] rTMS; 90% of RMT.	Bilateral anterior SPL	Offline; Computer-triggered rTMS before stimulus viewing; 30 mins; 1 Hz; No-TMS (control); 1 trial/region.	– Right SPL rTMS increased switch rate. – No effect on switch rate by left SPL rTMS.

[2] Paper also published in Japanese (Nojima et al., 2010c).

[3] It was reported that the number of pulses rather than frequency accounted for the results, following a previous similar study which employed slight variations in the rTMS protocols (Nojima et al., 2010b).

[4] Analyses included the previous data from Ge et al. (2007b, 2008).

[5] This study has also been presented elsewhere (Nojima et al., 2011b).

[6] This TMS protocol is considered by Zaretskaya et al. (2010) to have an excitatory effect.

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Study	N	Stimulus-type	TMS type	Region	Key methodological points	Effects
Zaretskaya et al. (2010)	15	House/face BR	Inhibitory rTMS[7]; 120% of RMT.	Bilateral posterior PC, SPL, anterior IPS.	Online; Order of stimulation randomised within & across sessions in each subject; rTMS computer-triggered; Biphasic; 9–15 trains; 2 Hz; Vertex (control); 3 trials/region; 1–2 sessions.	– Individual variation in baseline lateralized activation (left/right SPL & IPS) during rivalry transitions. – Right anterior IPS rTMS significantly decreased switch rate cf. left anterior IPS rTMS decreasing switch rate according to individual transition-related lateralized activation. – Greater baseline lateralization associated with greater lateralization of IPS rTMS effect on switch rate.
Kanai et al. (2010)	10	SFM	Inhibitory continuous theta-burst rTMS; 45% of stimulator output.	Bilateral posterior SPL.	Offline; Computer-triggered rTMS in between stimulus viewing; 40 s; 50 Hz 3-pulse; 200 ms intervals; Vertex (control); 1 trial/region.	– Right & left SPL rTMS decreased switch rate.
Kanai et al. (2011)	8	SFM	Inhibitory continuous theta-burst rTMS; 40% of stimulator output.	Right anterior SPL.	Offline; Computer-triggered rTMS in between stimulus viewing; 3-pulse; 40 s; 50 Hz at 200 ms intervals; Vertex (control); 1 trial/region.	– Right anterior SPL rTMS increased switch rate.

[7] Evidence from Arai et al. (2005) suggests an excitatory effect of this type of rTMS protocol may also be likely as biphasic rTMS tends to activate both inhibitory and excitatory neurons (cf. monophasic rTMS).

spTMS: single-pulse transcranial magnetic stimulation; rTMS: repetitive transcranial magnetic stimulation.

MIB: motion-induced blindness; SWI: spinning wheel illusion; SFM: structure-from-motion bistable motion illusion; BR: conventional binocular rivalry. All rivalry stimuli passively viewed unless otherwise stated.

RMT: resting motor threshold.

TPC: temporo-parietal cortex; PC: parietal cortex; IPS: intraparietal sulcus; PFC: prefrontal cortex; OP: occipital pole; hMT/V5: human middle temporal/V5 complex; V1/V2: early visual cortex.

Another study of rTMS effects on rivalry employed fMRI to first identify brain regions that were associated with the perceptual alternations (Zaretskaya, Thielscher, Logothetis, & Bartels, 2010). By comparing rivalry to replay activation scans, left and right SPL along with left and right anterior IPS were identified, with nine subjects showing right-lateralized activity during BR while six other subjects showed left-lateralized activity in these regions. In all subjects, 2Hz continuous rTMS was subsequently applied to these four parietal areas during BR viewing (with the vertex as control). TMS-induced inhibition of right IPS was found to significantly decrease rivalry rate, whereas no significant effect of left-sided TMS was found overall. However, when the TMS data were examined according to individual subject's lateralized activation identified with fMRI, left-sided rTMS of IPS was also found to decrease rivalry rate. The investigators concluded that IPS, mainly in the right hemisphere, has a destabilizing function on perceptual continuity in BR, in accordance with its role in perceptual selection, including with respect to attention. They also note that their TMS data were consistent with Kanai et al.'s (2010) findings, despite the use of different rivalry types and stimulation protocols (i.e., online cf. offline rTMS). Other methodological differences (cf. Carmel et al., 2010; Kanai et al., 2010) that were highlighted included pulse frequency, duration of TMS, effect on cortical activity (i.e., facilitatory rather than disruptive; Carmel et al., 2010), small sample size (Carmel et al., 2010), and the lack of a vertex control condition (Carmel et al., 2010; i.e., not controlling for arousal with the no-TMS condition).

To resolve the conflicting findings concerning rTMS effects on switch rate between two previous studies mentioned above (Carmel et al., 2010; Kanai et al., 2010), Kanai, Carmel, Bahrami and Rees (2011) employed a more precise structural imaging approach to first identify sub-regions within right SPL for subsequent testing with TMS. Using a SFM rotating sphere, they found that grey matter density in right anterior SPL was positively correlated with switch rate, in contrast to their previous finding of the opposite association in posterior SPL (Kanai et al. 2010). They also showed that rTMS applied to anterior SPL (with the vertex as control) resulted in decreasing percept duration (i.e., faster switch rate), which was consistent with the findings of Carmel et al. (2010), but in contrast to those of Kanai et al. (2010) who targeted posterior SPL. These authors argued that the previous discrepant results were unlikely to be due to different neural bases for different forms of perceptual bistability or to dissimilar stimulation protocols. Rather, they considered the conflicting results as reflecting a fractionation of parietal cortex function, such that different regions within parietal cortex play opposing roles in the control of bistability. They also note that their findings are in contrast to Zaretskaya et al.'s (2010), who found that *online* rTMS applied to a region of SPL close to an area they targeted with *offline* rTMS, instead decreased

the rate of perceptual alternations, which could therefore be due to stimulation protocol differences between the studies.

The issue of protocol differences when comparing results from TMS studies is complex (e.g., de Graaf & Sack, 2011; Sandrini, Umiltà, & Rusconi, 2011). As indicated in Table 1, it is not always clear whether a TMS protocol is excitatory or inhibitory, and as outlined in the chapter by Thomson and Fitzgerald (this volume), individuals vary in their response to TMS. Comparisons are further complicated by the fact that reference to, and interpretation on the basis of, differences in one methodological element may only be relevant if all other methodological elements are held constant in the studies compared, which is often not the case. These issues make interpretation of conflicting TMS studies difficult and indicate that further studies will be required to examine cortical contributions to rivalry and its modulation (see also chapter by Sterzer, this volume). Studies such as those by Kanai et al. (2011), in which rTMS protocol elements were held constant and only cortical targets were varied, and by Miller et al. (2000), in which cortical site was held constant and only response-contingency was varied, are particularly informative in light of the methodological and protocol interpretation complexities associated with perceptual TMS research.

Another rTMS protocol issue that has been raised comes from studies using the SWI. Nojima et al. (2010a, 2010c, 2011a) examined the effect of differential rTMS protocols on SWI switch rate. These investigators applied rTMS trains varying in stimulation frequency and pulse number to the right SPL and right posterior temporal lobe. Pooling data reported in their previous studies (Ge et al., 2007b, 2008), they found that 1 Hz 240-pulse rTMS to the right SPL (cf. right posterior temporal lobe TMS and no-TMS conditions) significantly decreased switch rate. In contrast, rTMS to the right SPL using 60-pulse protocols significantly increased switch rate, whereas no effects were observed with 120-pulse protocols. The investigators interpreted these differential pulse-based results on the basis of previously reported biphasic rTMS effects (i.e., activation of both facilitatory and inhibitory neurons), suggesting that the rTMS protocol which decreased switch rate indicated inhibition of brain activity, and vice versa. However, the very high degree of voluntary control that we observe to be exercised over the SWI suggests these findings require confirmation with types of rivalry that are less amenable to voluntary control. Indeed, direct exploration of the effect of TMS on voluntary control during rivalry is informative and was examined by de Graaf, de Jong, Goebel, van Ee and Sack (2011). These investigators assessed the role of frontal cortical areas (classically implicated in attentional processing) using a SFM rotating sphere. They found that right-hemisphere rTMS applied to dorsolateral prefrontal cortex, the posterior parietal cortex, occipital pole and hMT/V5 had no significant effect on switch rate during passive viewing, but when subjects were

asked to voluntarily speed up switch rate, rTMS to right dorsolateral prefrontal cortex significantly impaired this control. These findings led to the proposal that a specialized mechanism exists for voluntary control during bistable perception (cf. spontaneous alternations during passive viewing; see also chapter by Sterzer, this volume).

Status of the IHS model

The TMS data just described are illuminating with respect to the CVS data discussed earlier and the IHS model of rivalry. Although the initial series of CVS experiments provided support for the IHS model, all with an identical asymmetry of modulation effects, more recent CVS experiments did not find significant predominance changes. While perhaps due to design issues, and while the consistent asymmetry observed in the first series of experiments would be remarkable to have occurred by chance, it could be argued that support for the IHS model in light of the recent CVS negative findings is questionable. However, we point out that the history of BR and AFR research, particularly with respect to mechanisms, has been one of evidence-based claim and counter-claim, exhibited most dramatically in the last decade by the electrophysiological and brain-imaging findings as discussed above (Blake & Logothetis, 2002; Keliris et al., 2010; Sterzer, Kleinschmidt, & Rees, 2009; Tong, Meng, & Blake, 2006). Similar conflicting data were evident in the recent series of rTMS studies of parietal cortex regions. It is thus hardly likely to expect a single experimental success or failure to conclusively resolve issues of perceptual rivalry mechanisms.

Moreover, the spTMS data showing a phase-specific perceptual disruption pattern cannot be explained on anything but an IHS model (which is perhaps why alternative explanations for this effect have not been forthcoming). In addition, the spTMS and rTMS data have shown, along with earlier brain-imaging findings, that the asymmetries observed in the early series of CVS experiments are very likely veridical, given the reports of asymmetries in the ability of left versus right-hemisphere TMS to modulate rivalry. In our view, mechanistic understanding of rivalry will benefit from further detailed and targeted TMS studies, particularly using single-pulse, online, phase-specific protocols with pulses applied at various processing regions, including high and low levels, unilaterally and even bilaterally (i.e., two coils). Additional brain-stimulation techniques may also be employed in the future, such as intracranial stimulation during surgery in humans (Mukamel & Fried, 2012) and microstimulation in primates (see chapter by Sengpiel, this volume). Stimulation at multiple sites and combined stimulation/recording protocols may prove to be particularly informative.

There has to date been only one independent attempt to falsify the IHS model of rivalry, by examining BR in subjects with a split brain (O'Shea & Corballis, 2001, 2003, 2005a, 2005b). These experiments showed that each disconnected hemisphere can experience its own rivalry (interestingly, at different rates), thus challenging the IHS model. However, this approach was not grounds for abandoning the IHS model, for several reasons that have been outlined in detail elsewhere (Miller, 2001; Ngo et al., 2007; Pettigrew, 2001). One such reason entailed Pettigrew and Miller's specific *prediction* that rivalry would survive callosotomy (Miller et al., 2000) because the IHS process was considered to be driven by a subcortical oscillator and not by the corpus callosum. This notion of a subcortical oscillator was proposed by Pettigrew and elaborated upon in a subsequent paper (Pettigrew, 2001; see Figure 1).

Miller's elaboration of the IHS model on the other hand, focussed on attentional mechanisms. This included how a subcortical oscillator and/or top-down activity might act, as mentioned above, via attentional processes that bias competition between populations of neurons, or response synchronization therein (Miller, 2001). He thus proposed that interhemispheric switching involves a process of *alternating unihemispheric attentional selection*. On this account, two further proposals included (i) an additional attention-based explanation for the asymmetry of CVS modulation effects, and (ii) the callosum not being entirely irrelevant to interhemispheric switching during rivalry. In relation to the latter, though inconsistent with the data from split-brain BR experiments, this is consistent with a report of slow AFR rate in subjects with callosal agenesis (Fagard et al., 2008). However, while studies have shown that aspects of bistable perception with the motion quartet and binocular rivalry are linked, respectively, to microstructural properties of specific callosal regions connecting human MT/V5 (Genç, Bergmann, Singer, & Kohler, 2011) and V1 (Genç, Bergmann, Tong, Blake, Singer, & Kohler, 2011), such findings rely on the use of stimuli that dynamically integrate across the two visual hemifields. Callosal microstructural properties (other than agenesis) have not as yet been assessed with respect to small, central rivalry stimuli that do not engage dynamic cross-hemifield integration. Examining correlations of rivalry rate using small, central stimuli with structural and DTI measures of callosal regions connecting cortical attentional regions would be an informative line of future research for assessing the IHS model, the callosum's role therein, and factors determining individual variation in rivalry rate (as has occurred for SPL; see above).

Also raised in Miller's elaboration of the IHS model was the distinction between mechanisms of attentional selection and mechanisms of visual consciousness during rivalry, and between mechanisms of attentional selection and mechanisms of feature representation (or between the 'sites' and 'sources'

of attentional selection; Miller, 2001). By refining the notion of 'alternating hemispheric activation' to include the possibility of 'alternating unihemispheric attentional selection', and considering the distinction between neural mechanisms of attentional selection and those of visual consciousness, Miller (2001) noted that brain-imaging or electrophysiological data showing neural activity that is synchronous across the hemispheres would not necessarily argue against an IHS model. Rather, the key observation of interhemispheric switching during rivalry would be the presence of hemispherically asynchronous activity (even if in other cortical regions, hemispherically synchronous activity was observed). There have been suggestions of just such asynchronous activity in a number of brain-imaging studies with centrally located stimuli (Brouwer, Tong, Schwarzbach, & van Ee, 2005; Freeman, Sterzer, & Driver, 2012; Hsu, Yeh, Tien, & Lin, 2008; Kamphuisen, Bauer, & van Ee, 2008), though without explicit reference to the IHS model. Alternating hemispheric activation has also been shown in a brain-imaging study using an AFR stimulus that was horizontally elongated across the two hemifields (Slotnick & Yantis, 2005), however this finding may be purely due to the hemifield aspect rather than alternating unihemispheric attentional selection.

Most recently, direct electrophysiological evidence of an IHS mechanism underlying perceptual rivalry has been demonstrated in *Drosophila* (Tang & Juusola, 2010). This involved counterphase (left-right) alternations in unilateral optic lobe spiking and LFP activity, in accordance with the fly's rivalry-like left-right switching behavior during dichoptic presentation of orthogonally moving stimuli (see Figure 6). We return to this *Drosophila* model of rivalry in the last section.

On the issue of the status of the IHS model of rivalry, we have noted two recurring comments in the literature and in discussion with colleagues and other investigators. The first is that the IHS model appears unable to be tested. We argue quite the opposite, holding that instead the model is one of the most readily testable in the literature (e.g., see Miller, 2001; Ngo et al., 2007). Electrophysiology, brain-imaging and brain stimulation methods can all be applied to its examination, though some care needs to be taken in the procedures used and conclusions made, given the multitude of conceptual and methodological complexities detailed in this chapter and previous papers. The second common comment we encounter is that the model is unlikely. This is despite the fact that in recent years, comparative evidence for IHS phenomena has been steadily growing.

In our view, biological IHS precedents make claims of the unlikelihood of the IHS model of rivalry less defensible. Indeed, the existing and emerging human and animal IHS literature raises an important conceptual and methodological issue: is interhemispheric switching a generally under-investigated neurophysiological principle in organisms with brain structures that are paired across the midline?

The list of biological IHS phenomena now includes: (i) slowly alternating unihemispheric activity in humans (Bemelmans, Heijdanus, Jansen, & Rietveld, 1984; Shannahoff-Khalsa, Gillin, Yates, Schlosser, & Zawadzki, 2001; Werntz, Bickford, Bloom, & Shannahoff-Khalsa, 1983); (ii) alternations between relative left and right nasal patency (the nasal cycle) in humans and other species (Eccles, 2000; Kikuta, Kashiwadani, & Mori, 2008; Sobel, Khan, Saltman, Sullivan, & Gabrieli, 1999); (iii) alternating unihemispheric EEG activity during REM sleep in humans (Imbach et al., 2012); (iv) alternating unihemispheric slow-wave sleep in birds and aquatic mammals (Fuchs, Maury, Moore, & Bingman, 2009; Low, Shank, Sejnowski, & Margoliash, 2008; Lyamin, Manger, Ridgway, Mukhametov, & Siegel, 2008; Rattenborg, Lima, & Amlaner, 1999); (v) independent alternating eye movements in the sandlance and chameleon (Pettigrew et al., 1999); (vi) birdsong production (Long & Fee, 2008; Wang, Herbst, Keller, & Hahnloser, 2008); and (vii) alternations between left and right suprachiasmatic nucleus electrophysiological activity and *Per* mRNA expression in rodents (de la Iglesia, Meyer, Carpino, & Schwartz, 2000; Ohta Yamazaki, & McMahon, 2005; Schaap, Albus, Eilers, Détári, & Meijer, 2001; Yan, Foley, Bobula, Kriegsfeld, & Silver, 2005). To this list can now be added, direct electrophysiological evidence for an IHS mechanism underlying perceptual rivalry in *Drosophila* (Tang & Juusola, 2010; Miller et al., 2012). Thus we continue to argue for a multi-pronged attempt to examine the IHS model of human rivalry, employing brain-imaging, electrophysiological and brain stimulation methods, in the hope of arriving at its verification or falsification.

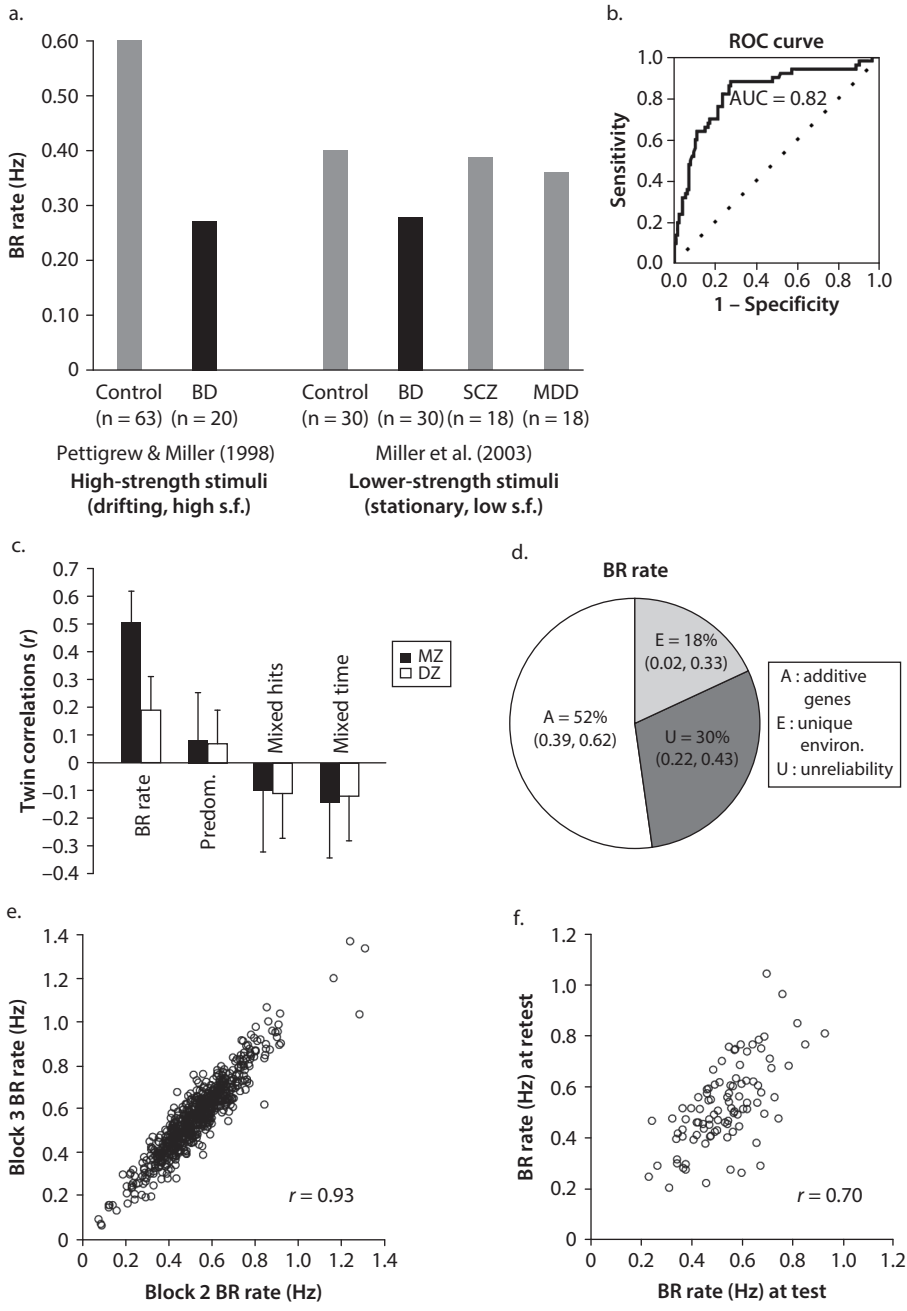
Clinical, genetic and molecular aspects of rivalry

On the first day of testing the IHS hypothesis with CVS, Pettigrew and Miller serendipitously observed that the rate of BR was notably slower in a subject with BD. They pursued this observation and confirmed in two studies (Miller et al., 2003; Pettigrew & Miller, 1998) that BD was indeed associated with slow BR rate (Figure 5a). The slow BR finding was evident in BD subjects who were well at the time of testing, suggesting that it may represent a trait (as opposed to state) marker of the disorder. It also did not appear to reflect the type of medication being taken by the subject and in some cases was evident in un-medicated subjects. Slow BR rate was also not found in groups of subjects with schizophrenia or major depression, disorders which can often be difficult to distinguish from BD. On this basis, and given BD is known to be strongly heritable, Pettigrew and Miller proposed that slow BR rate may serve as a useful 'endophenotype' for BD (discussed further below). Consistent with their empirical findings, and

again supporting the notion of common neural mechanisms of BR and AFR, it was reported in the early 20th Century (Ewen, 1931; Hunt & Guilford, 1933), that Necker-cube rivalry was slower in BD ('manic depression') compared with controls and subjects with schizophrenia ('dementia Praecox'). Since Pettigrew and Miller's reports, there have been three independent replication studies of the basic finding of significantly slower rivalry rate in BD relative to controls, two using BR (Nagamine, Yoshino, Miyazaki, Takahashi, & Nomura, 2009; Vierck et al., 2013) and one using a bistable SFM rotating sphere (Krug, Brunskill, Scarna, Goodwin, & Parker, 2008).

The finding of slow BR in BD was utilized by Pettigrew and Miller (1998) to propose a detailed pathophysiological model of BD (the 'sticky switch' model), that also incorporated the IHS model of rivalry. This BD model involved a series of conceptual postulates that are detailed in Figure 1. Through a mixture therefore, of observation, hypothesis, experimentation, serendipity and conceptual development, Pettigrew and Miller were indeed able to link the notion of interhemispheric switching to the extreme mood *alternations* seen in BD. Their model entailed the notion of anterior hemispheric activation asymmetries underlying mania (greater relative left activation) and depression (greater relative right activation). The model also drew upon brain-imaging, hemisphere-inactivation, lesion, electrophysiological and rTMS studies (e.g., see citations in Pettigrew & Miller, 1998), with the latter showing that right-hemisphere application was required to treat mania (Grisaru, Chudakov, Yaroslavsky, & Belmaker, 1998) while left-hemisphere application was required to treat depression (Pascual-Leone, Rubio, Pallardó, & Catalá, 1996). The model also explicitly predicted hemisphere-specific mood-modulating effects from CVS, which have since been confirmed for mania, albeit in two case studies to date (Dodson, 2004; Levine et al., 2012).

Quite apart from aiding Pettigrew and Miller in their development of a BD pathophysiological model, the empirical finding of slow BR in BD has sparked renewed interest in the issue of individual variation in rivalry rate. It has long been known that rivalry rate exhibits wide individual variation but is relatively stable within individuals (e.g., Aafjes, Hueting, & Visser, 1966; Borsellino, de Marco, Allazetta, Rinesi, & Bartolini, 1972; Enoksson, 1963; Ewen, 1931; George, 1936; McDougall, 1906) (see also chapter by Wade & Ngo, this volume). The AFR studies mentioned above show that in the first half of the 20th Century, individual variation in perceptual rivalry was investigated from a clinical psychiatric perspective (Ewen, 1931; Hunt & Guilford, 1933). However, there was relatively little interest in this line of research again until decades later. Similarly, until the 1960s there was interest in examining individual variation in rivalry parameters (e.g., Bagby, 1957; Crain, 1961; Frederiksen & Guilford, 1934), but this approach waned thereafter (though with some interest in AFR with respect to psychiatric



conditions; e.g., Gorenstein, Mammato, & Sandy, 1989; Meldman, 1965). Most recently, and as described in detail above, the issue of individual variation in rivalry rate has been utilized in brain-imaging and rTMS studies. Thus, cortical thickness in SPL and other measures were shown to correlate with rivalry rate, while rTMS to this region modulated rivalry rate (Kanai et al., 2010). These authors also noted that cortical thinning of SPL had been shown in BD (Lyoo et al., 2006), consistent both with their findings and with the finding of slow BR in BD.

Again renewing interest in individual variation of BR rate, and to pursue investigation of the trait as a potential endophenotype for BD, a large twin study was embarked upon by Pettigrew and Miller in collaboration with genetic epidemiology researchers, Nick Martin and Margie Wright (Miller et al., 2010; Figure 5c, d, e, f). That approach sought to examine the heritability of individual variation in rivalry rate and found that additive genetic factors accounted for more than 50% of the variance in rivalry rate (with monozygotic twins, who have identical genotypes, showing significantly higher concordance of BR rates than dizygotic twins, who share only half of their genetic make-up). The remainder of the variance was accounted for by unique environmental factors (18%) and measurement unreliability (30%). This twin study involved a sample size of 722 individuals and is the largest published population dataset of any rivalry type. It conclusively showed the previously-reported wide individual variation in BR rate, and further that an individual's rate is very highly reliable within testing sessions ($r = 0.93$; $N = 722$) and highly reliable between tests, 2 years apart ($r = 0.70$; $N = 97$). This study was followed by a smaller twin study (Shannon, Patrick, Jiang, Bernat, & He, 2011) which confirmed the heritability finding for BR rate and reported a similar finding for AFR (with the Necker cube).

Figure 5. **(a)** Slow BR rate in BD. The bars show the central tendency of BR rate for each group (medians in Pettigrew and Miller, 1998; means in Miller et al., 2003). These studies suggest that high-strength BR 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 Figure 5a with BD as 'positive' and controls, schizophrenia (SCZ) and major depressive disorder (MDD) as 'negative'. The area under the curve (AUC) of 0.82 indicates that from random selection of a pair of subjects in Figure 5a, 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 (MZ) vs dizygotic (DZ) twin correlations for BR rate were significant but not 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.

Demonstration of substantial genetic contribution to individual variation in BR rate adds support to the notion of using slow BR as an endophenotype for BD. Endophenotypes are biomarkers that are 'intermediate' between genotype and phenotype (reviewed in Gottesman & Gould, 2003; Gould & Gottesman, 2006; Hasler, Drevets, Gould, Gottesman, & Manji, 2006). They are useful in studies of complex genetic disorders, such as BD, because they can accurately mark an affected genotype even though the individual may not have yet manifested (or indeed, may never manifest) the clinical disorder. By improving the accuracy of classifying affected (at-risk) and unaffected (not at-risk) genotypes in this way, endophenoptypes can increase the power of genome-wide association studies which aim to identify disease-causing genes (Kendler & Neale, 2010). Toward this end, we and our genetic epidemiology and clinical psychiatry colleagues have recently established a multi-center study to collect BR data and DNA samples from several different subject groups (i.e., BD Type I, BD Type II, schizophrenia, major depressive disorder, relatives of bipolar probands, and healthy controls; Ngo, Mitchell, Martin, & Miller, 2011). By collecting BR data from large numbers of clinical psychiatric subjects, this multi-center study will also enable assessment of the potential diagnostic utility of slow BR rate, such as in distinguishing psychosis due to BD from that due to schizophrenia, and depression due to BD from that due to major depressive disorder (in both cases, with treatment implications; Ngo et al., 2011; see Figure 5b).

For a trait to be an endophenotype, it must meet key criteria (Gottesman & Gould, 2003; Kendler & Neale, 2010): (i) high association with the condition (high sensitivity), (ii) high heritability, (iii) high reliability, (iv) be unaffected by clinical state (and medication), (v) co-segregate with illness in families, and (vi) be observed in first-degree relatives of probands more commonly than in the general population. Our studies have shown that the BR rate trait appears to satisfy the first three criteria (Miller et al., 2003, 2010; Pettigrew & Miller, 1998). Our data, and work by others (Nagamine et al., 2009), also suggested that state and medication did not account for slow BR (see also Ngo et al., 2011) though these factors required further assessment.

In a recently published study, further independent evidence has been demonstrated for slow BR rate as an endophenotype for BD. In a large sample of 96 BD subjects, Vierck et al. (2013) recorded BR rate, a range of clinical variables and several cognitive functioning measures. The BD subject group consisted of 71 participants with BD-I, 22 with BD-II and 3 with BD-not otherwise specified (the latter two groups being collapsed into a bipolar spectrum disorder group). Compared to a small group of healthy controls (N = 24), the BD-I and bipolar spectrum disorder groups both had significantly slower BR rates, whereas there was no difference in BR rate between the two BD subgroups. Furthermore, it

was found that medication, depressive mood state, lifetime comorbid psychiatric diagnosis, and diminished cognitive functioning were not associated with slow BR rate in the BD subjects, and hence could not explain the trait. Ultimately however, testing BR rate in large numbers (i.e., hundreds to thousands) of clinical subjects, control subjects and family members is required to confirm the endophenotype criteria listed above (Ngo et al., 2011).

In addition to potential genetic and clinical psychiatric diagnostic utility, the findings of slow BR in BD and of genetic contribution to individual variation in BR rate, suggest new mechanistic approaches to investigating rivalry and its modulation. Thus, examining molecular aspects of BR will not only help to understand pharmacological modulation of the phenomenon, but also provide further mechanistic clues. It has been reported for example, that both noradrenergic and serotonergic systems are relevant to rivalry (Carter et al., 2005; Einhäuser, Stout, Koch, & Carter, 2008; Nagamine, Yoshino, Miyazaki, Takahashi, & Nomura, 2008; see also Bressler et al., this volume). Indeed since then, the candidate gene approach has been applied to rivalry, in both visual and auditory domains, showing that serotonergic genes are relevant to the former and dopaminergic genes to the latter (Kondo et al., 2012). While these findings may not themselves reveal key mechanisms of rivalry, they provide pieces of the mechanistic puzzle that may ultimately be revealing. For instance, candidate genes shown to encode for particular neurotransmitter receptor systems may shed light on the role of particular subcortical, sensory and higher-level processing regions during rivalry.

Finally, one particularly promising approach to elucidating genetic and molecular aspects of both rivalry and BD is the *Drosophila* rivalry model mentioned above. *Drosophila melanogaster* has proven an immensely powerful tool for dissecting the genetic, molecular and neurophysiological aspects of development, memory, learning, circadian rhythms and attention, and can even shed light on neuropsychiatry (Bellen, Tong, & Tsuda, 2010; Miller et al., 2012; O'Kane, 2011; van Alphen & van Swinderen, 2013; van Swinderen, 2011). The existence of perceptual switching behavior in response to incongruent dichoptic visual stimulation in *Drosophila* (Figure 6), indeed switching behavior that exhibits individual variation in rate (Tang & Juusola, 2010), offers novel and exciting research strategies that we have recently outlined in detail (Miller et al., 2012). Thus fly rivalry can be compared to human rivalry, with a host of human rivalry characteristics examined for in the *Drosophila* model (e.g., temporal dynamics, stimulus factors, relationships with other cognitive functions such as memory and attention; see chapters by Brascamp & Baker and Bressler et al., this volume). The *Drosophila* model can also be used to explore neurophysiological aspects of rivalry, given its amenability to direct electrophysiological recording, pharmacological manipulation and emerging

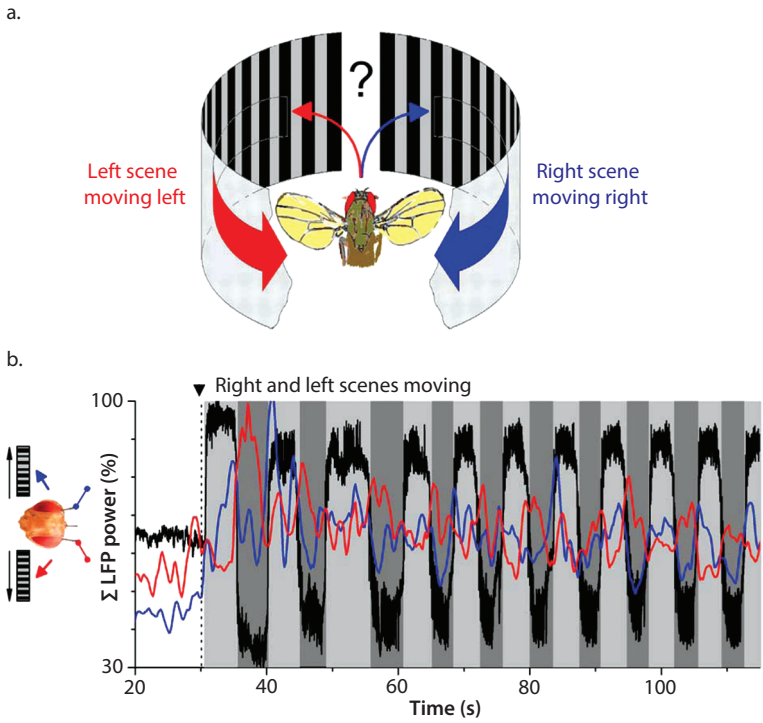


Figure 6. Rivalry in *Drosophila* and its IHS electrophysiological basis. **(a)** A fly presented with dichoptic visual stimulation in a tethered flight setup displays rivalry-like orienting behavioral switches between the left and right competing stimuli, which are measured using a torque meter (not shown). Bilateral electrophysiological recordings from the fly's optic lobes **(b)** revealed unilateral LFP activity preceded the switch towards 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 (reprinted from *PLoS One*, Tang & Juusola, 2010, 5, 12, e14455).

methods such as photostimulation (optogenetics). Indeed, the model enables mechanistic aspects of rivalry to be probed at molecular, cellular and systems levels. Moreover, known genetic mutants such as the short/long circadian and behavioral courtship rhythm *per* variants, can be examined, with short/long rivalry intervals hypothesized, to examine the notion of period-coupled oscillators, as proposed by Pettigrew and Miller (1998; see Figure 1) to underlie the link between slow BR in BD and the alternating mood states of BD. Other known *Drosophila* mutant strains can also be screened for rivalry rate anomalies, with results potentially shedding light on both genetic aspects of rivalry and of BD. Utilization of *Drosophila* to examine attention-like rivalry and visual competition has commenced (Paulk, Millard, & van Swinderen, 2013; van Swinderen, 2012) with frequency-tagging

methods previously used in attention and rivalry studies (e.g., Kamphuisen et al., 2008; Srinivasan, Russell, Edelman, & Tononi, 1999; Vialatte, Maurice, Dauwels, & Cichocki, 2010), and is continuing with a range of other neurophysiological and genetic methods (A. Paulk & B. van Swinderen, personal communication). Rivalry experiments have also recently been extended to mice (Zhang et al., 2012), thus providing further scope for probing the phenomenon from genetic through to systems levels.

Concluding remarks

In this chapter we have discussed the point-counterpoint nature of mechanistic rivalry research, and the high-, low- and multi-level processing engaged by the phenomenon. We discussed the genesis and status of one proposal in particular, the IHS model. On this background we reviewed brain stimulation approaches to studying rivalry, including CVS and TMS, noting that these methods too have yielded conflicting results, but that they also offer the potential for further mechanistic clarification. We have argued that the IHS model has yet to be conclusively verified or falsified and that it is one which is readily amenable to examination with electrophysiological, brain-imaging and brain stimulation approaches. Finally, we have outlined the links between the IHS model and the finding of slow BR in BD, and have described current and future research aimed at elucidating genetic and molecular aspects of both rivalry and BD. The renewed fascination with rivalry mechanisms looks set to grow and spread further to clinical, genetic and new comparative contexts.

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