

A 'sticky' interhemispheric switch in bipolar disorder?

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Despite years of research into bipolar disorder (manic depression), its underlying pathophysiology remains elusive. It is widely acknowledged that the disorder is strongly heritable, but the genetics are complex with less than full concordance in monozygotic twins and at least four susceptibility loci identified. We propose that bipolar disorder is the result of a genetic propensity for slow interhemispheric switching mechanisms that become 'stuck' in one or the other state. Because slow switches are also 'sticky' when compared with fast switches, the clinical manifestations of bipolar disorder may be explained by hemispheric activation being 'stuck' on the left (mania) or on the right (depression). Support for this 'sticky' interhemispheric switching hypothesis stems from our recent observation that the rate of perceptual alternation in binocular rivalry is slow in euthymic subjects with bipolar disorder ($n=18$, median=0.27 Hz) compared with normal controls ($n=49$, median=0.60 Hz, $p<0.0005$). We have presented evidence elsewhere that binocular rivalry is itself an interhemispheric switching phenomenon. The rivalry alternation rate (putative interhemispheric switch rate) is robust in a given individual, with a test-retest correlation of more than 0.8, making it suitable for genetic studies. The interhemispheric switch rate may provide a trait-dependent biological marker for bipolar disorder.

Keywords: interhemispheric switching; bipolar disorder; binocular rivalry; mood; genetics

1. INTRODUCTION

Bipolar disorder is a common condition with a lifetime prevalence of 1.2–1.6% (Weissman *et al.* 1988; Kessler *et al.* 1994). It is characterized by recurrent episodes of mania and depression with symptomatic recovery between episodes. The pathophysiology of bipolar disorder remains poorly understood despite considerable research (Goodwin 1998). Although it is strongly heritable, the genetics are complex, with less than full concordance in monozygotic twins (Mitchell *et al.* 1993). At least four different susceptibility loci have been identified (Adams *et al.* 1998). A trait-dependent biological marker would assist genetic linkage studies (which are dependent upon the identification of the clinical phenotype) and would potentially lead to an understanding of the underlying molecular defect.

(a) *Interhemispheric switching*

In the present investigation we have focused on interhemispheric switching as a way of understanding bipolar disorder. This interest was stimulated by work that emphasizes the contrasting cognitive styles of the cerebral hemispheres (Ramachandran 1994). Stroke patients with anosognosia (denial of disease) usually have right-sided parietal lesions (McGlynn & Schacter 1989). Patients with similar left-sided lesions rarely exhibit anosognosia and are usually fully aware of their deficits. Ramachandran (1994) has therefore suggested that the left hemisphere's cognitive style is goal-directed with a coherent

plan of action that denies or smoothes over discrepancies, whereas the right hemisphere's style is that of a 'devil's advocate' that monitors and seeks to raise discrepancies. If the lesioned hemisphere permits the opposite hemisphere to engage its preferred cognitive style unopposed, this would explain the observed hemispheric asymmetries associated with anosognosia.

Antithetical viewpoints of each hemisphere would pose problems for a neural executive that tried to act upon them simultaneously. From our observations of a fish with an interhemispheric switch that is apparent to visual inspection of its eye movements (Wallman *et al.* 1995), we hypothesize that in humans the complementary viewpoints of the hemispheres are adopted successively. In this way we could explain the mood shifts seen in bipolar disorder in terms of the cognitive style associated with the activated hemisphere: left-hemisphere activation being associated with confidence, elation or mania, according to the intensity and/or duration of activation, whereas an increasing degree of right-hemisphere activation would be associated with caution, apprehension or depression.

(b) *Binocular rivalry*

To study the putative interhemispheric switch in bipolar subjects we have used binocular rivalry: that is, the alternating perceptual states that arise when viewing different images, presented separately to each eye, in the same retinal location. Rivalry has been thought to be mediated by reciprocal inhibition of neurons in the separate channels for each eye, in early visual cortex (Blake 1989). Recent single-unit (Sheinberg & Logothetis 1997) and psychophysical (Logothetis *et al.* 1996; Kovacs *et al.*

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1996; Andrews & Purves 1997) studies, however, support the early suggestions of Diaz-Caneja (1928) that rivalry is a high-level attentional process that cannot be explained by neural activity early in the visual pathway.

Because the cerebral hemispheres can function independently of each other during perceptual and attentional tasks (Luck *et al.* 1989; Zaidel 1995), we hypothesize that the resolution of the conflicting visual information in binocular rivalry might be resolved by alternating hemispheric activation. We therefore suggest that competition for awareness during binocular rivalry occurs between rather than within hemispheres. We have reported preliminary evidence that two unilateral hemisphere-stimulating techniques, caloric vestibular stimulation and transcranial magnetic stimulation can alter rivalry characteristics (Miller *et al.* 1997; Pettigrew *et al.* 1998). Within-hemisphere competition at any level would not predict an effect from unilateral hemisphere stimulation.

The present investigation aimed to assess the rate of binocular rivalry (and hence the presumed rate of inter-hemispheric switching) in subjects with bipolar disorder compared with 'normal' controls. We found that bipolar subjects who were not depressed or manic at the time of testing had a significantly slower rate of alternation than normal subjects. We discuss the implications of this finding for the genetics of bipolar disorder. In addition, we speculate from work on the biophysics of bistable oscillators, that a slow switch may be more easily held in one position than a fast switch (i.e. slow switches are 'sticky').

2. MATERIALS AND METHODS

'Normal' subjects aged 19–55 years (22 females and 27 males) were drawn from university students and employees. They were screened by a medical practitioner for symptoms of mood disorder. Bipolar patients, aged 27–60 years (9 females and 9 males), were recruited with the help of local psychiatrists and hospitals. They either underwent an OPCRIT diagnostic classification (McGuffin *et al.* 1991), or had already been evaluated extensively for previous research purposes using a structured clinical interview for DSM-III-R. Inclusion criteria were at least one admission for mania or an OPCRIT diagnosis of either bipolar disorder or bipolar disorder with psychotic features. All bipolar subjects were euthymic at the time of testing. Three were unmedicated and the remaining bipolar patients were on one or a combination of the following medications: lithium, clonazepam, valproate, carbamazepine, a variety of antidepressants, haloperidol and risperidone. There was no significant difference between the rivalry rates of unmedicated subjects ($n=3$), subjects on lithium only ($n=6$), and subjects on combination therapy ($n=9$). Accordingly, we have pooled the data for all bipolar subjects. Subjects were paid for their participation and gave written informed consent as part of a protocol approved by the University of Queensland Medical Research Ethics Committee.

We used a VisionWorks package and liquid-crystal shutters to present a horizontal moving grating to one eye and a vertical moving grating to the other (figure 1). The liquid-crystal shutters allow the fields of view for each eye to be superimposed, so no special training in fixation was required. Subjects sat 3 m from the computer monitor and recorded their perceptual alternations by pressing one of three response buttons for vertical, horizontal or mixed/indeterminate percepts. The latter were

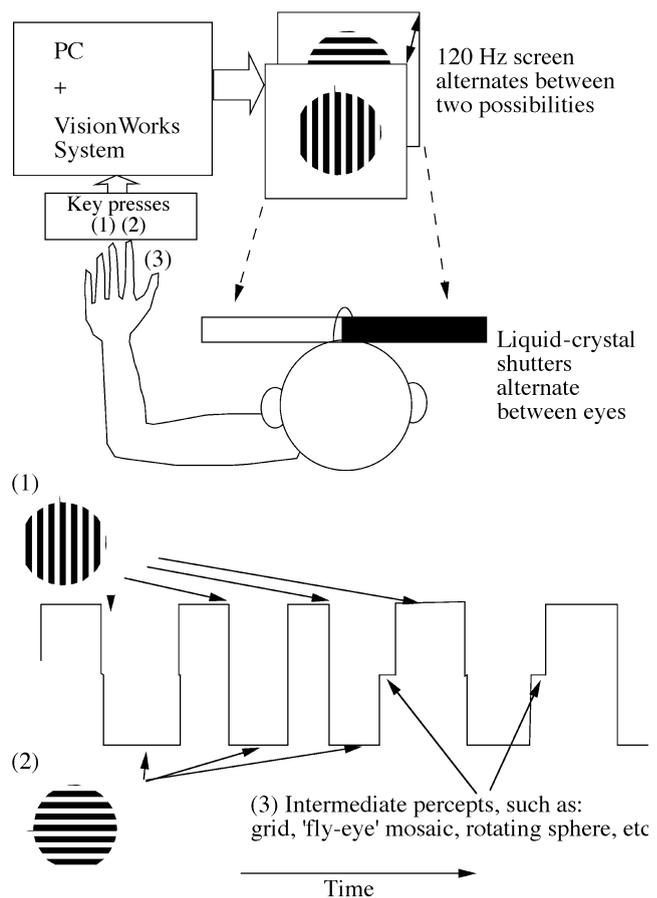


Figure 1. Psychophysical set-up used to examine binocular rivalry. To avoid problems with binocular fixation and alignment, the rivalrous stimuli are presented at the same location on the screen. By alternating rapidly between the rivalrous stimuli in phase with liquid-crystal shutters, each eye's view can be restricted to its intended stimulus. The subject reports the perceived stimulus using one of three key presses (including the intermediate states, labelled '3', which often seem to be creative attempts to combine the incompatible stimuli). Only the time information from states 1 and 2 was used for analysis. The monitor was located 3 m from the subject's eyes so that the stimulus subtended 1.5 arcdeg. The square wave grating had a spatial frequency of 8 cycles deg^{-1} and drifted at 4 cycles s^{-1} .

removed before analysis. Perceptual alternations were recorded for 30 min divided into three blocks, each consisting of four 100-s trials. Each trial was separated by a rest period of 30 s and each block by a rest period of 2 min. The first block was considered as a training block and discarded before analysis. Alternation rate (Hz) was calculated by dividing the number of perceptual switches by the total time of rivalry, excluding mixed percepts. The stimuli subtended 1.5 degrees of visual angle with spatial frequency 8 cycles deg^{-1} , moving at 4 cycles s^{-1} . The contrast of the gratings was one.

3. RESULTS

Bipolar subjects were clustered on the tail of the distribution representing slower alternation rate. This is shown in figure 2, which gives the distribution of alternation rates in bipolar (median=0.27 Hz) and

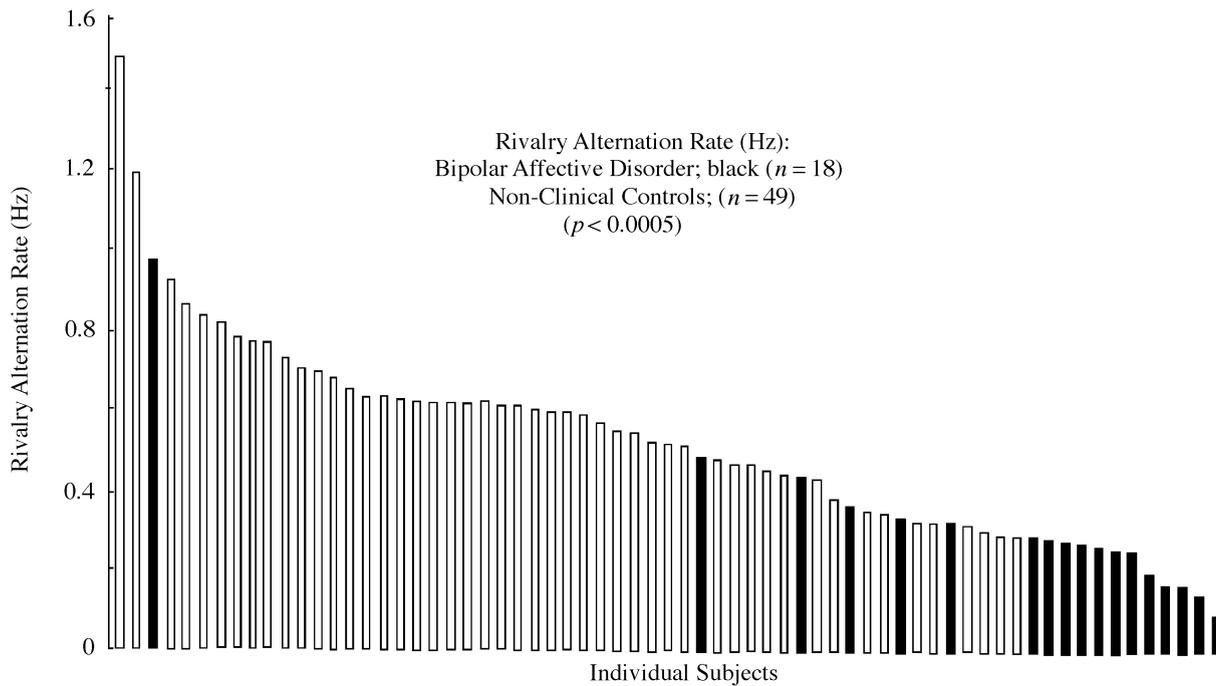


Figure 2. Distribution of rivalry switch rate in normal (open bars) and bipolar (filled bars) subjects. The height of each column gives the rivalry alternation rate (Hz) for one individual over two blocks of trials totalling 20 min. Rate is calculated by dividing the number of perceptual switches by the total time of rivalry (excluding mixed percepts; see state 3 in figure 1). There is general conformity to a gamma distribution, with fewer individuals having short intervals, a distinct plateau of common rates around 0.6 Hz and a long tail reaching out to subjects with slow rates. Bipolar subjects ($n=18$, median=0.27 Hz) have the slowest rates and are highly significantly different from normal subjects ($n=49$, median=0.60 Hz, $p < 0.0005$).

non-clinical (median=0.60 Hz) subjects. These results are highly significant (Mann–Whitney U -test, $Z = -4.569$, $p < 0.0005$). The range of slow rivalry rate varied quite markedly with some bipolar subjects experiencing average perceptual intervals only one to two seconds longer than controls, whereas others perceived intervals for up to 10–20 s, an order of magnitude longer than the usual interval duration. Previous studies have shown that the time intervals collected from a single subject undergoing rivalry form a gamma distribution (Logothetis *et al.* 1996). In the present study, subjects all have gamma-like distributions with the scale of the abscissa varying considerably between subjects (figure 3). The distribution of rivalry intervals across our population of normal and bipolar subjects is also gamma-like, with only a small number of individuals having intervals that are shorter than the mode of the distribution, compared with the extended tail of the distribution where individuals have long intervals. Despite this marked variation across the population, a given individual has a fairly repeatable distribution of intervals when retested. Although the bias for one of the two alternative rivalry states may vary from trial to trial, the overall rate is relatively constant. When subjects were retested several weeks or months later, the test–retest correlation coefficient was greater than 0.80 (figure 4).

Because all bipolar patients were euthymic at the time of testing, slow rivalry rate is a candidate trait marker for bipolar disorder. We do not as yet have sufficient data on specificity. Some subjects with unipolar depression have demonstrated slower than usual rivalry rates, although to a lesser extent than bipolar subjects. The results presented here should be considered preliminary. Formal assessment

of sensitivity and specificity data, and state-effects, will be forthcoming.

4. DISCUSSION

(a) *Genetics*

Interhemispheric switching in binocular rivalry may be mediated by bistable oscillator neurons located in the brainstem. Although the switch is likely to have top-down influences, the fundamental rhythm may be determined intrinsically, as for other bistable oscillators, by the number of cationic currents that drive the rate of depolarization (figure 5). The rate would be directly proportional to the number of channels present (Rowat & Selverston 1997; Marder 1998). If the slowed rivalry rate that we have observed in bipolar patients proves to be a reliable trait marker for the disorder, we would predict that the relevant genes would be associated with some of the many cationic channels that have been described so far. There are multiple different cationic channels, each of which might contribute to the rhythm of the switch, such as the family of hyperpolarization-activated channels (Gauss *et al.* 1998, Ludwig *et al.* 1998). This functional multiplicity could explain the well-recognized failure of linkage studies to settle on a single chromosomal locus (e.g. Adams *et al.* 1998; McGue & Bouchard 1998). We are currently assessing the slow rivalry trait in family studies to assess its pattern of inheritance, and in twin studies to look at heritability. A quantitative trait such as this may be more revealing in genetic studies than the more limited, qualitative information available from the presence or absence of clinical episodes.

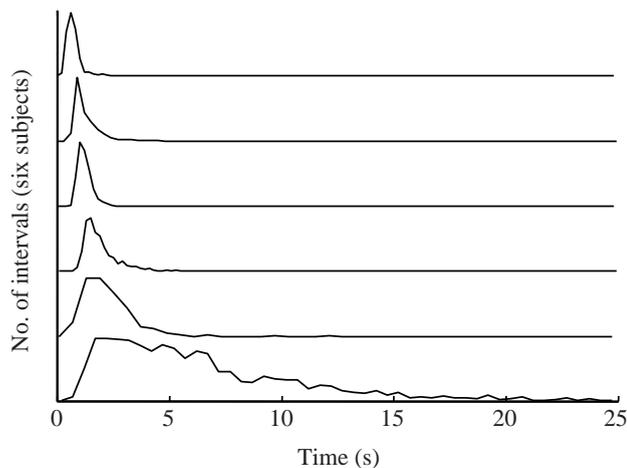


Figure 3. Individual variation in rivalry alternation rate: Different subjects, all under the same conditions on the apparatus shown in figure 1. Frequency histograms of intervals of rivalrous alternations for individual subjects show a gamma-like distribution, with the mode skewed left and a long tail to the right. Note the variation in the abscissa between normal (top four) and bipolar (bottom two) subjects.

(b) *A model of bipolar disorder*

Slow switches are 'sticky' switches because the intrinsic channel abnormalities that cause the slow oscillation rate also make the switch more likely to be held down in one state by external synaptic inputs (Rowat & Selverston 1997). At first sight, there is a conflict between our suggestion that the primary defect is a reduction in cationic channels and the many findings of increased cellular and neuronal sensitivity in bipolar disorder, as cationic-channel reduction would have the general effect of decreased neuronal sensitivity. Documented examples of increased neuronal sensitivity in bipolar disorder include: (i) elevated levels of G proteins (Mitchell *et al.* 1997); (ii) increased responsiveness of cAMP processes (Andreopoulos *et al.* 1997); (iii) increased sensitivity to light-induced melatonin suppression (Nurnberger *et al.* 1988); and (iv) increased sensitivity to cholinergic REM sleep induction (Nurnberger *et al.* 1983). We suggest that these apparent contradictions can be resolved if the primary effect on the timing of the oscillator is distinguished from the 'downstream' effects on other parts of the brain, such as the cerebral hemispheres, where compensatory mechanisms may be used to restore normal levels of excitability in the face of reduced cationic-channel function. For example, the cerebral hemispheres may be concerned more with neuronal excitability and plasticity than with clock rate. Because many effective medications for bipolar disorder (e.g. lithium) are known to decrease excitability via G-protein- and cAMP-mediated processes, we suggest that their mechanism of action may be upon these downstream effects rather than on the defect in the oscillator *per se*.

Because the cerebral hemispheres provide an important 'top-down' synaptic input to the brainstem switch, a compensatory increase in sensitivity would lead to increased hemispheric output (in response to a stressor) and might therefore increase the likelihood that the switch will be held down ('stuck') on the side favouring

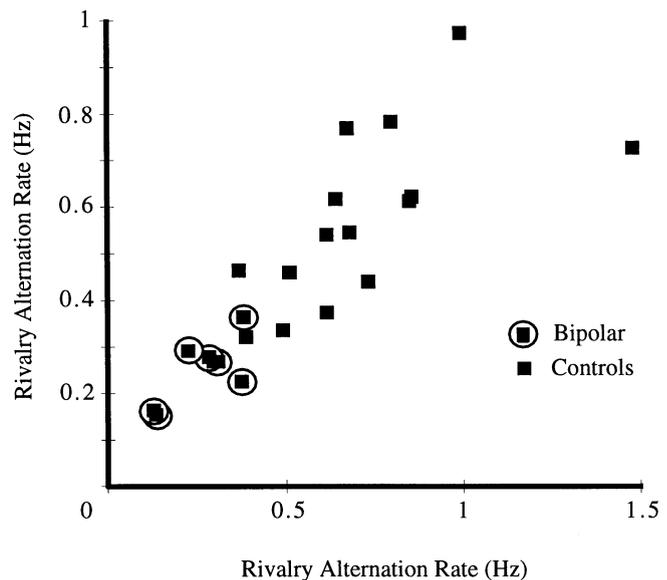


Figure 4. Test-retest correlation of rivalry alternation rate in bipolar and control subjects. There is a high correlation ($r=0.83$) between the rates obtained from the same individual on different occasions, including the bipolar patients, indicating that this is a fairly stable trait that would lend itself to genetic analysis.

that hemisphere. The switching process in bipolar patients might therefore be doubly afflicted; increased 'stickiness' because of reduced intrinsic currents and potentially greater extrinsic synaptic inputs from stressors by virtue of the compensatory increase in hemispheric excitability. We therefore envisage a manic or depressive episode being the result of a stressor that causes the switch to be 'stuck' in one of two positions: unrelieved left-hemisphere activation being associated with mania, in line with that hemisphere's cognitive style, unrelieved right-hemisphere activation being associated with depression, in line with its style.

(c) *Hemispheric asymmetries of mood and mood disorder*

Hemispheric asymmetries of mood and mood disorder have been widely discussed (Kinsbourne 1988; Davidson & Hugdahl 1995; Heller & Nitschke 1997). Imaging studies suggest that there is greater relative right prefrontal activation in depression—i.e. left prefrontal 'hypometabolism'—which was not present when subjects were rescanned after clinical remission (Bench *et al.* 1995; Martinot *et al.* 1990). EEG studies also support greater relative right activation in depression (Henriques & Davidson 1991). Activation asymmetries favouring the left hemisphere have been reported in mania (Migliorelli *et al.* 1993). In keeping with these activation asymmetries, it has been shown that transcranial magnetic stimulation of the prefrontal cortex is therapeutic for depression when administered on the left (George *et al.* 1997; Pascual-Leone *et al.* 1996).

Unilateral hemisphere inactivation using sodium amobarbital has also been associated with asymmetrical mood sequelae. Inactivation of the left hemisphere has been shown to induce negative moods more commonly on subjective measures (Christianson *et al.* 1993), whereas

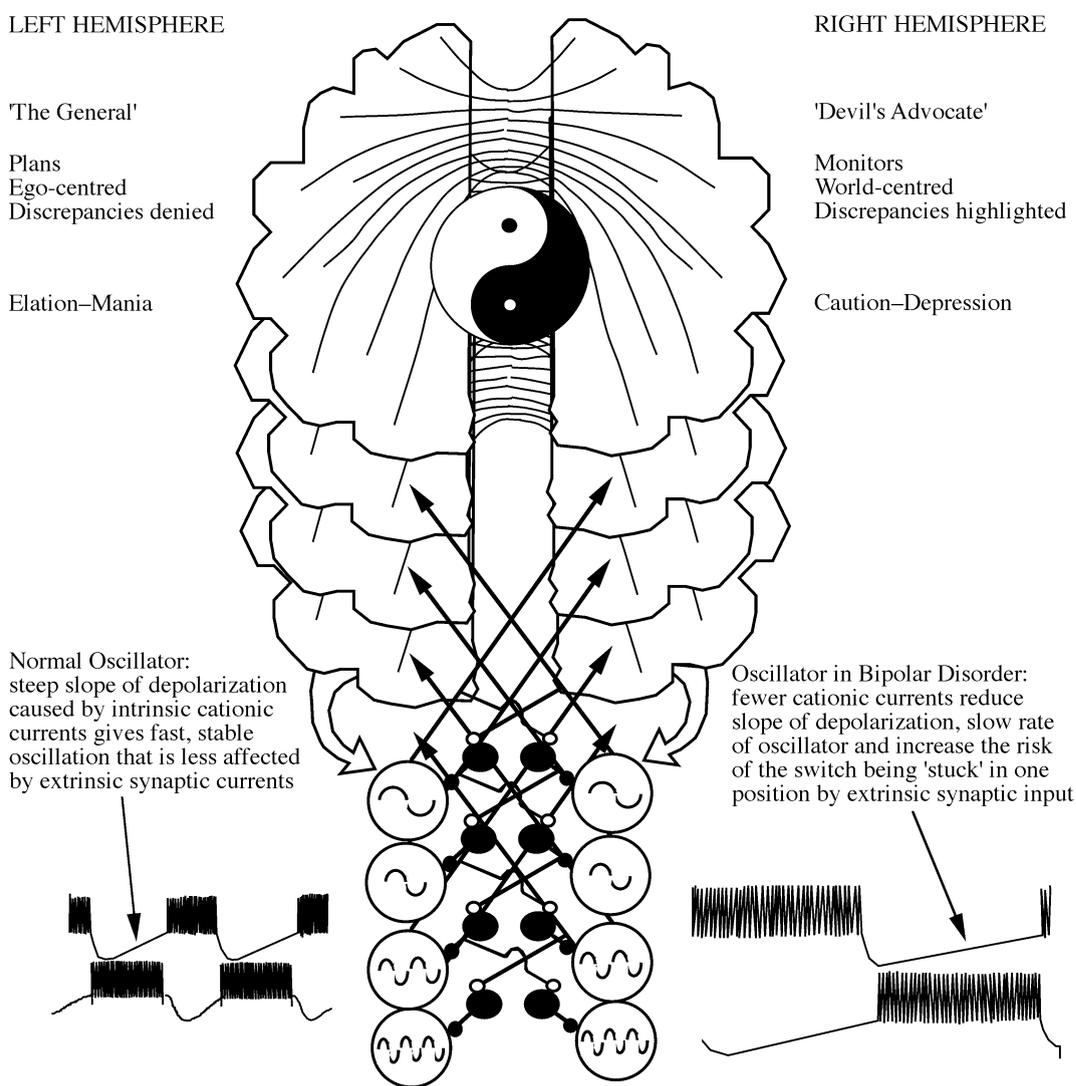


Figure 5. Interhemispheric switching and bistable oscillators in the brainstem. The hemispheres have complementary cognitive styles and modes of encoding information (yin–yang symbol). The complementary aspect may require that different styles be engaged successively, hence the hemispheric switch that alternates activation of each hemisphere. As well as the projection from one side of the oscillator/switch to the hemisphere, note that there is also top-down input from the hemisphere. These top-down synaptic influences would become more important in the presence of increased hemispheric sensitivity that we suggest follows an attempt to compensate for the reduced cationic currents that are the likely basis for the slowed switch rate in bipolar disorder. For this reason, a stressor that activates one hemisphere is more likely to cause the switch to stick in one position in a bipolar subject. The bipolar switch is therefore doubly vulnerable to becoming stuck: (i) the reduced cationic currents and slow rate make it more susceptible to extrinsic synaptic input, just as a more slowly spinning top is more susceptible to an external influence that knocks it to one side; (ii) attempts to compensate for the reduced currents by other parts of the brain may increase the effects of the extrinsic stressors on an already more susceptible switch.

The switch is shown as a bistable oscillator, the rate of which is a function of the number and/or efficacy of the cationic channels that cause the ramp of depolarization following the hyperpolarization induced by activity on the other side of the switch. The slower switch in bipolar disorder may then be produced by a reduction in some of the many cationic channels known. The involvement of many different cationic channels could explain the multiplicity of linkage sites that have been identified with bipolar disorder in genetic studies.

A number of oscillators with different alternation rates are shown, to emphasize the difference that may be found in switch rate at different locations in the cortex (e.g. minutes to hours for the prefrontal/limbic cortex compared with seconds for the temporoparietal cortex). Oscillators with different rates have been shown to be coupled genetically in some organisms, so it is reasonable to propose that a slow temporoparietal (rivalry) switch may accompany an even slower switch, in proportion, in frontal/limbic regions and thereby explain the clinical features of mania (when the switch is stuck on left-hemisphere activation for days to weeks) and depression (stuck on right-hemisphere activation for days to weeks). Heterogeneity of this proposed coupling might also be responsible for exceptions, such as our single bipolar subject without a slower rivalry rate.

objective measures of affect showed crying to be related to left-hemisphere injections and laughter/elation to right-sided injections (Lee *et al.* 1990). Lesion studies have been particularly enlightening with respect to asymmetries. Robinson & Downhill (1995) report that left-sided lesions in prefrontal and basal ganglia regions are more commonly associated with depression than similar lesions on the right, and secondary mania more commonly follows right-sided lesions (basotemporal cortex, orbito-frontal cortex, basal ganglia, thalamus) than similar left-sided lesions.

Robinson & Downhill (1995) suggest that the dependence of mood change on lesion site may be the result of asymmetrical pathophysiological responses to injury. Although such mechanisms may be relevant, studies of emotion and mood in 'normal' subjects (Davidson 1995) support the notion of underlying physiological asymmetries, which would also explain the lesion data. This interpretation does not exclude an asymmetrical response to injury, as asymmetries of physiologic function may be mediated by neurochemical asymmetries.

Thus a wide variety of data indicate that there are hemispheric asymmetries of mood and mood disorders. There are, of course, methodological limitations and several studies have been unable to replicate reported asymmetries. It is not pertinent to review such issues in this paper. Taken alone, each approach (psychiatry, neurology, neuropsychology) may be criticized. Taken together, the directional convergence of results from disparate modes of investigating asymmetries of mood and mood disorder seems unlikely to be solely due to issues of methodology or interpretation.

(d) *Slowed oscillator for frontal and limbic regions?*

The notion of alternating hemispheric activation has been suggested before and is supported by electrophysiological and psychological studies of ultradian rhythms (<20 h duration) of cerebral dominance (for a review, see Shannahoff-Khalsa (1993)). The typical period for such rhythms is in the range of minutes to hours. The oscillator for binocular rivalry targets regions at high stages of visual processing in the temporoparietal cortex, based on neurophysiological evidence from monkeys undergoing rivalry (Sheinberg & Logothetis 1997), and on magnetic resonance imaging studies of humans (Lumer *et al.* 1998). An interhemispheric switch for cognitive style and mood would be likely to engage frontal and limbic regions (Liotti & Tucker 1995) and to have a period similar to that of reported ultradian rhythms of cerebral dominance (i.e. minutes to hours). A slowing of the oscillator for rivalry, from 1–2 s to 10–20 s, would not account for any of the clinical phenomenology of bipolar disorder. It is conjecture on our part to propose that the slowing of an oscillator for the temporoparietal cortex might also be accompanied by a proportionate slowing of the putative oscillators that govern interhemispheric switching in other regions such as the prefrontal cortex. There is a precedent for such coupling in *Drosophila*, where a single mutation may simultaneously reduce the rate of both short-period (ultradian) and longer-period (circadian) oscillators (Hall & Rosbash 1988; Kyriacou & Hall 1980). The question of coupled oscillators is clearly relevant to mood disorders such as seasonal affective disorder

(Teicher *et al.* 1997; Madden *et al.* 1996; Corbera 1995) and to the way in which cortical regions activated by different rates might be coupled by virtue of their pooled outputs to the same switch (Pöppel *et al.* 1978).

(e) *Clinical effects of caloric stimulation in bipolar disorder?*

In view of the efficacy of caloric stimulation in inducing unilateral hemispheric activation (Bottini *et al.* 1994; Vitte *et al.* 1996), we suggest that caloric stimulation in acutely manic or depressed patients might support our model of bipolar disorder. The technique is known to temporarily reverse unilateral neglect and anosognosia associated with right-sided lesions (Cappa *et al.* 1987; Vallar *et al.* 1993; Ramachandran 1994). Thus, cold caloric stimulation of the left ear (activating the right hemisphere) might temporarily reduce the symptoms of mania, whereas depression might be temporarily reduced by cold caloric stimulation of the right ear.

(f) *Conclusion*

We have presented a readily testable neurophysiological model of bipolar disorder. It is based on our studies of interhemispheric switching and binocular rivalry, as well as on a substantial body of evidence on hemispheric asymmetries of mood and mood disorders. Our model also incorporates the possible molecular defects of different cationic channels, the multiplicity of which may help explain the difficulties encountered in genetic linkage studies. Identification of the molecular defects may in future lead to new therapeutic approaches. Interhemispheric switching may also be relevant to understanding physiological rhythms of mood, cognitive style and other aspects of human brain function. For example, there are reports that creativity is enhanced in people with mood disorders and their relatives, compared with the general population (Andreasen & Glick 1988; Richards *et al.* 1988; Goodwin & Jamison 1990). Although controversial (Waddell 1998), these reports raise the possibility that understanding the consequences of slower interhemispheric switching and rhythms of cognitive style will yield clues to the otherwise elusive neural mechanisms of human creativity.

We thank all participating subjects; The Prince Charles Hospital, Dr Marlene Wheeler, Dr Brian Kimbell, Dr Stanley Miller and Kerry Harrison for assistance with recruiting patients; Dr Guang Bin Liu for endless technical assistance; and Greg Hooper, Dr Bruce Gynther, Professor Laurie Geffen and Professor Gina Geffen for helpful discussions. This research was supported by the National Health and Medical Research Council of Australia and the Australian Research Council.

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