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Guest Editorial

Differential sensitivity: not more or less

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Although posited as an explanation for reproductive endocrine-related mood disorders, differential hormone sensitivity is an elusive concept. In this editorial, we define differential sensitivity, embed it in current understanding of the generation of brain states and discuss its practical utility.

Keywords
Brain dynamics; depression; differential sensitivity; hormones; state.

The model for most disorders involving the endocrine system can be traced back to Charles-Edouard Brown-Sequard[1] who, in an article in the *Lancet* in 1889, proclaimed the miraculous effects of self-injected lysates of dog and guinea pig testes. His report initiated a movement in which the 'organotherapists' administered a variety of ground-up animal organs as treatments for an amazing array of disorders. Among these clinical experiments, administered thyroid and adrenal glands were indeed efficacious in treating hypothyroidism and Addison's disease, respectively, thus establishing hormone deficiency as a physiological explanation for clinical syndromes. Accordingly, efforts to define the underlying physiology of reproductive-related mood disorders – premenstrual syndrome/premenstrual dysphoric disorder (PMS/PMDD), perimenopausal depression (PMD) and perinatal depression (PND or PPD) – sought the responsible deficient hormone, with little success (and inconsistent findings).

In 1998, we suggested an alternative to the hormone deficiency model. After first showing that the hormonal events of the late luteal phase play no role in what was then called late luteal phase dysphoric disorder, we attempted to rule out the possible role of ovarian hormones earlier in the cycle by suppressing ovarian function and then blindly adding back oestradiol and progesterone. Surprisingly, ovarian suppression prevented PMDD and hormone add-back (but not placebo) reprecipitated the symptomatic state.[2] This suggested the causal relevance of reproductive hormones in PMDD. However, the failure of the same hormone manipulations in 'control' women (no history of PMDD) to affect mood in any way led us to suggest that women with PMDD were 'differentially sensitive' to the effects of the hormones – i.e. these clearly triggered PMDD but did so only in the context of a pre-existing susceptibility to mood state dysregulation. But what did that actually mean?

What do we mean by differential sensitivity?

We first have to disentangle the terms sensitive, sensitisation and differential sensitivity. If you're comfortable at 70 °F and I think that's too hot, is that differential sensitivity? Well, you might say that I'm more sensitive to heat (as measured by comfort) but increasing the heat will make you uncomfortable, just at a higher temperature; I could be described as heat sensitive, but not differentially sensitive (i.e. mine is not a qualitatively different response). A semi-qualitatively different response is seen with sensitisation – a process whereby the same stimulus elicits a much larger response as a product of prior, usually repeated, exposure. Such a process underlies the benefit of vaccines, which stimulate a more robust immune response to subsequent antigen exposure. A more qualitatively different response (arguably, differential sensitivity) is seen with repeated administration of amphetamine, which leads not only to an amplified dopamine release (sensitisation) in response to the same original dose, but also produces behavioural progression from alertness to paranoia and even psychotic behaviour. A final and clear example is that of seizure models and disorders: kindling, an animal model of epilepsy in which response to repeated administration of a small electrical stimulus will grow from barely detectable to a seizure; and photic epilepsy, a human genetic disorder in which flashing lights will precipitate a seizure – same stimulus, qualitatively different response.

What produces a differential response?

A plausible inference is that a particular environmental context, antecedent risk factor or physiologic event(s) transforms the response to a stimulus in a way that cannot simply be described as 'more than' or 'less than'. In the case of photosensitive epilepsy, for example, certain genes may render the brain's neurons more excitable and more easily synchronised in response to flashing lights. This abnormal processing propagates to other brain regions, triggering a seizure. Thus, a heritable susceptibility translates a harmless environmental stimulus into a seizure. Analogously, with PMDD and PPD, normal, physiological changes in reproductive steroids trigger a discrete, dysphoric mood state (encompassing affective, cognitive and behavioural characteristics) which, despite otherwise identical hormonal variation, does not appear in women without these disorders.

What do we mean by dysphoric state?

A behavioural state is a transient, self-organised, recurrent set of affects, perceptions, memories or self-concepts – in essence, a programme for interpreting the world and one's place in it. By this definition, PMDD is not an arbitrary collection of symptoms but a recurrent behavioural state. Although reproductive mood disorders like PMDD could be viewed as just one end of a symptomatic continuum, the replicable coherence of the symptoms and the dynamics of PMDD – including its intractable persistence during the luteal phase and often sudden departure with onset of menses – suggest otherwise. Rather, it is as if a certain threshold is crossed – the dysphoric state emerges and resists destabilisation until menses occurs. Few would have trouble recognising this switching between discrete behavioural states in bipolar disorder. And, as with bipolar disorder, the value of the state model is that it directs our attention to the kinetics of state change as the locus of dysfunction. Women with PMDD are 'stuck' in their dysphoric state, just as those with major depressive disorder are stuck in theirs.

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Brain dynamics in the regulation of states

State generation and transitions are at the heart of current computational models of the brain. These models view the brain as a dynamical system in which behavioural states are generated and evolve over time, with certain states capable of becoming dominant and resisting perturbation. Such 'stuck' states are seen in an amygdala network under conditions of low levels of oestradiol or the neurosteroid allopregnanolone, as they are in Parkinson's disease.[3] Some of these models attempt to understand the dynamics of brain state by focusing on recurrent, brief (lasting about 100 ms or so) synchronised patterns of activation of neurons across the brain. These activation patterns are referred to as attractors (because other potential brain states evolve toward them) and microstates, any of seven brief electrical patterns that recur and account for most (about 80%) of the electro-encephalographic signal[4,5]). The features of these quasi-stable networks – their duration, speed of recurrence, sequence of appearance (in other words, their dynamics) – have been found to differ in depression and may constitute fractal-like building blocks of emergent behavioural states. Attractors and microstates remind us that the brain is not simply a bag of receptors waiting for an agonist. Rather, it is an information-processing organ that extracts meaning from the frequency, timing, patterns and coupling of neuronal electrical impulses. At the least, attractors and microstates suggest that inter-areal network communication and synchronisation are the brain processes where susceptibility and triggering converge. By analogy, they are the instruments in the behavioural orchestra that, depending on the timing of their interactions, give rise to harmony or cacophony. These dynamic interactions are the level at which environmental stimuli (e.g. stress), genes, the epigenome and physiological context meet to define the landscape and characteristics of behavioural states and the susceptibility to their appearance and dysregulation.

How does a hormone become linked to a disordered behavioural state?

An early demonstration of the ability of reproductive hormones to both create the capacity for different behavioural phenotypes and trigger those behaviours – organisational and activational effects, respectively – appeared in the classic paper by Phoenix et al.[6] These authors showed that early hormone exposure programmed a behavioural sensitivity to the same hormone during adulthood. Specifically, prenatal exposure of female guinea pigs to testosterone produced abnormal behaviour (aggression and male mating behaviour) when the females were given testosterone as adults. The brain substrate had changed – was reprogrammed – such that the hormone stimulus yielded a set of behaviours unseen in control animals that had not received the early exposure to testosterone. We do not know yet exactly how reproductive steroids programme subsequent response to hormone exposure, nor how they trigger a differential state, but we do know that the effects of reproductive steroids on the brain are widespread and profound. Behaviour reflects synchronised communication between networks of brain cells (neurons and glia), and virtually all cellular functions are regulated by reproductive steroids. Oestradiol, for example, regulates synaptic plasticity, microRNA expression, neurotransmitter synthesis and metabolism, all three RNA polymerases and a vast proportion of the entire transcriptome generating thousands of proteins responsible for effecting the cell's response to the environment (through receptors, ion channels and signal transduction proteins). Additionally, through regulation of epigenetic enzymes – histone acetyl transferases and DNA methyl transferases – reproductive steroids can also permanently alter the genetic response to a stimulus, providing at least a plausible explanation for the enduring, organisational impact on behaviour described by Phoenix et al. Consistent with this hypothesis, we demonstrated that induced lymphoblastoid cells lines from women with PMDD significantly differed from those from women without PMDD in the transcripts of a family of genes – the extra sex combs/enhancer of Zeste (ESC/E(Z)) complex – responsible for regulating epigenesis. Furthermore, when these cells were exposed in vitro to oestradiol or progesterone, the transcriptional readouts from women with PMDD differed from controls, in both amount and direction of response; in other words, the cells themselves demonstrated a differential response to reproductive steroids.[7]

What is the practical value of the differential sensitivity concept?

First, the findings that led to the notion of differential sensitivity enabled us and others[8] to combat the belief that, in the absence of abnormal hormone levels, PMDD must not have a definable physiological basis. By showing that reproductive hormones do trigger PMDD despite normal levels and changes, we could clearly define PMDD as a hormone-regulated disorder rather than a hormone disorder. Second, by recognising that a reproductive hormone can precipitate a change in affective state in some individuals but not others, we provided further justification for abandoning the one-size-fits-all approach to behaviour in favour of a model that embraces and explores individual differences as the 'royal road' to understanding behaviour. Third, the observation of differential sensitivity obligates us to attempt to identify the factors that underlie the susceptibility that alters the brain's response to a reproductive stimulus, just as we need to identify the activational effects that trigger the dysphoric state. Fourth, we are similarly obligated to adjust our models of behaviour to focus on the dynamics of the change in affective state, not simply the characteristics of the state itself. Individual symptoms exist along a continuum, but their integrated appearance in a behavioural state may reflect modal changes in the interactions of brain networks. Similarly, these modal, non-linear changes in brain network dynamics may manifest as a dysregulation of the ability to change affective state – either a switch to a dysphoric state or the inability to terminate the state once present. Seventy years ago, Bunney et al[9] suggested that the best way to understand bipolar disorder was to focus on the switch between states. It was with this intent in mind – the search for the biology of the switch – that our studies of PMDD began 45 years ago. Hopefully the concept of differential sensitivity to reproductive hormones, in replacing deficiency ('too much of this or too little of that') explanations of reproductive mood disorders, will put us in a better position to harness new biological insights and models in the service of understanding behaviour and serving our patients.

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