The vicissitudes of preclinical psychiatric research: justified abandonment by big pharma?

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It is a well-worn tale by now: most of the remarkable psychiatric medicinal concepts currently in use were discovered by chance. First, the use of phenothiazines for presurgical relaxation of patients led to chlorpromazine, the first blockbuster antipsychotic. Second, the inadvertent discovery that putative antituberculosis agents cheered patients without benefitting their lung diseases led to antidepressants. Third, in a last-ditch effort by an about-to-be-closed laboratory at Hoffman-LaRoche, some aggressive zoo animals were injected with benzodiazepines and a taming effect was seen; this led to the anti-anxiety revolution of Librium and Valium. Serendipity, rather than scientific knowledge has led the way. Since the inception of the psychopharmacology revolution 60 years ago, and despite the outlay of billions of research dollars, few new psychiatric medicinal concepts have been discovered. Science has mostly fine-tuned therapeutics after they were discovered by chance.

It is no secret that the majority of pharmaceutical firms have decided to cut their losses and abandon psychiatric drug development. The cost and difficulty of bringing totally new therapeutic concepts to market is surely one reason. But the abandonment of preclinical neuropsychiatric drug development also rests on accruing doubt that traditional preclinical (animal) approaches to human emotional problems can provide new solutions. What has gone wrong?

Here I will focus on the case of depression, especially since the recent STAR*D trials brought home the reality of how weak our antidepressant medications really are. There are dozens of animal models of depression, from social defeat to sustained stressors, with abundant objective measures – from increased ‘giving up’ in swimming rats (the Porsolt test) to more recent hanging of mice by their tails to see how long they struggle. But such models and measures have brought us no new antidepressants. Yes, the many stress-evoked behavioral changes currently monitored are well operationalized, but perhaps they are not providing any clear neural information about why depression feels so bad. For instance, reductions of sucrose intake are taken to reflect diminished positive affect, even though depressed humans show no diminished liking of sweets. The field is full of such ambiguous links: Is a rat’s behavioral hesitation in various situations an index of depression or simply adaptive cognitive caution that promotes survival? Do rodents subjected to forced swimming cease struggling because they have given up in despair, or have they decided that further struggle in such situations is a waste of energy, and it is ‘wiser’ to wait until testing is finished? Are any of the commonly used behavioral end points valid affective measures of depression? Surely without accurate brain network based measures of affective change, scientists are severely limited in their ability to determine the causes of depression and to find effective preventions and cures.

Perhaps the failure of psychiatric drug development reflects widespread failure to explicitly discuss and study the affective feelings of animals? Indeed since its inception, animal modeling has been guided by behavior-only approaches, with little discussion of their emotional feelings. Why this impasse? Ever since the advent of modern behavioral science, the emotional feelings of animals have been deemed outside the bounds of empirical measurement. As Skinner famously intoned in 1953: “The ‘emotions’ are excellent examples of the fictional causes to which...
we commonly attribute behavior” [1]. Likewise, 2 years earlier, Nobel-heralded ethologist Nico Tinbergen had asserted on page four of his influential ‘Study of Instinct’ that “Because subjective phenomena cannot be observed objectively in animals, it is idle to claim or deny their existence” [2]. Accordingly, animal models of psychiatric disorders have been premised on nonaffective behavioral end points rather than the most relevant changing feeling states that animals experience. Investigators painted themselves into a rigorous empirical corner that has yet to lead to any compelling and clear paths toward antidepressant drug development.

In sum, researchers supposed they could not ever objectively study the minds of other animals, only their behaviors, and so their feelings were not even topics for scientific discussion. Any talk about affective states in animals was commonly dismissed as idle anthropomorphism. But that was not a well-informed, evolutionarily based neuroscientific point of view.

Traditional biases against using affective concepts in brain research could have changed rapidly in 1954 when neuroscientists first demonstrated the rewarding and punishing properties of direct brain stimulation. These findings led to a renaissance of emotion research in the 1960s, affirming that all mammals share very similar emotional foundations within subcortical regions of the brain. We can evoke homologous emotional behaviors by electrically stimulating those deep areas of the brain. But even more importantly for understanding emotional feelings (i.e., affective shifts) was the well-established fact that wherever in the brain we evoke instinctual emotional action tendencies, those shifting central states uniformly serve as ‘rewards’ and ‘punishments’ in simple learning tasks. That is the unrecognized gold standard for affective changes in animal brains and minds.

But such affective, neuroethological studies remained sparsely represented in the agenda of antidepressant drug development, because the robust connection between instinctual emotional behavior patterns and internal affective changes [3–6] was not widely recognized. Because of this, no valid animal models were developed to provoke depression by over-stimulating the most relevant negative affective circuits directly, and to monitor the decline of positive affects equally directly. Instead, models employing pervasive external stressors and rather global behavioral measures assumed to reflect depression, commonly with little face validity, have continued to prevail.

If we could just identify which emotions to focus on in preclinical models, we might find that the cross-species affective underpinnings of depression might be remarkably easy to analyze. According to traditional psychiatric theory, first clearly enunciated by John Bowlby, the main causes of depression are the separation-distress and eventual despair that many people feel when confronted by the psychological pain of social loss. The amotivational state that follows reflects a dire lack of enthusiasm for social interaction and the pursuit of essential and interesting life activities [7]. To get at the affective roots of depression in animals, perhaps we should be monitoring the underlying affective tides that characterize human melancholia.

So how specifically might we optimally peer into the minds of other animals? Certain emotional behaviors are remarkably discrete and highly quantifiable, for instance emotional vocalizations [8]. They can potentially be used as direct readouts of emotional states, as long as the following criteria are first fulfilled. Will animals treat brain stimulation that evokes positive emotional sounds as ‘rewards’ and stimulation that evokes negative sounds as ‘punishments’? These criteria have been amply fulfilled for rat vocalizations [8,9], allowing investigators to consider using such emotional outputs as assays evaluating where animals are in positive and negative affective space.

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Such validated emotional vocalizations for modeling shifting affective states in preclinical models of depression can now be readily used [10,11]. Our own use of such measures, has served as a launching pad for the development of new potential therapeutic agents, one of which is currently undergoing US FDA-approved clinical testing [12]. This unique agent, a glycine receptor partial agonist, may also be useful in other neurological disorders, such as autism, for which no generally effective therapies exist [13].

With this new vision of antidepressant drug development, we are generating models where both the input stressors and affective outputs are based on our emerging understanding of the relevant affective networks of the brain [14].
Our hope is that future antidepressant agents will not just reduce the prevailing negative affects but also facilitate the most relevant positive social affects. They will not only sustain struggle in horrendous circumstances, but also have neural effects that promote psychological resilience by enhancing positive affects that make life worth living. And there are many other ideas. We have long known that opioids are the most effective agents to reduce the psychological pain that characterizes depression [4,15], but safe opiates, such as buprenorphine, remain underutilized in modern psychiatric practice – languishing for lack of institutional will to use opioids in psychiatry. Buprenorphine could be harnessed to help many treatment-resistant patients, if used systematically at incredibly low doses (e.g., [16]).

In sum, perhaps if neuroscientists would take the emotional feelings of animals seriously, we would make more rapid progress in development of new medicinal concepts for psychiatric disorders. A better understanding of the ancestral emotional capacities of other animals is surely critical for better treatments of depression, and thereby improving human well-being. Once we begin to realistically analyze the relevant affective states of animals, based on reasonable neuro-evolutionary premises and evidence, the more likely we are to synthesize better mind medicines (e.g., [12,13]).

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