Neuroplastic Man Untangled

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Remember Plasticman©? He was (and apparently still is) the adaptive mid-twentieth century comic book hero who couldn't fly or bend steel, but could reconfigure himself into any shape necessary to catch criminals and defeat danger. The bad news was that enemies could sometimes use his flexibility against him—twisting him up in his own elastic extremities. Nevertheless—skinny, smart, and vulnerable, Plasticman was a hero for the rest of us — especially those who knew what it felt like to be tied up in knots.

I thought of Plasticman in preparing to chair a symposium on depression for the next A.P.A. annual meeting. The connection? Well, in case you missed the news, the proposed biological lesion in depression has shifted in recent years from *neurotransmitter imbalance* (not enough serotonin or norepinephrine in the synapse) to *impaired neuroplasticity* (inability of the depleted neuron to adapt to changing conditions). According to recent evidence, when antidepressants increase synaptic monoamine concentrations, they change the intracellular environment all the way down to the genetic level, enabling neurons to modify receptor sensitivities and reconfigure synaptic connections. The timing of these gradual processes corresponds to the course of clinical recovery.

The inability of depressed patients to "just snap out of it" seems to have its parallel in their "stuck" neuroplasticity — neuronal nets caught in a dysplastic "tangle" (like our hero in the illustration) from which *specific* types of treatments gradually liberate them. I say "specific" because improved scientific tools are finally helping us move beyond Kraepelin's seventy-five year-old unitary characterization of depression towards an awareness that there are specific types of depression which may tend to be selectively responsive to specific antidepressants. That is what I will be talking about in Chicago this May. I call it "the targeted treatment of depression."

The belief that "all antidepressants are the same except for side-effects" mirrors Kraepelin's lack of diagnostic discrimination and stems from the fact that no antidepressants have improved more than two-thirds of patients receiving them in *undifferentiated* depressed populations. Recent studies of *selected* depressed populations suggest new possibilities. To summarize the conclusions:

1. Serotonergic antidepressants (e.g., SSRI's) seem especially helpful in treating depressions associated with *demodulated* states (anxiety, panic, irritability, anger, impulsivity, obsessiveness and compulsivity).
2. Catecholaminergic agents (e.g., bupropion) tend to be more useful in deactivated states (psychomotor retardation, apathy and fatigue).
3. Dual-mechanism antidepressants (e.g., venlafaxine or regimens combining serotonergic and catecholaminergic agents) are more effective with *mixed* states (melancholic, atypical and anxious/fatigued depressions, etc.)

Obviously, there are exceptions to these patterns. Limited neuroplastic dysfunctions involving one set of pathways may respond to treatments affecting alternate systems - as if we were helping Plasticman free one trapped arm by untying the other. Serotonergic and catecholaminergic pathways have complex, non-linear inter-relationships, and the numerous receptors for each neurotransmitter often have contradictory functions. Targeted treatment is therefore, at best, probabilistic. Good psychopharmacological management will, as always, require adjusting dosages, modifying regimens and addressing the psychosocial factors affecting treatment. Nonetheless, there is now reason to believe that by paying closer attention to the *differences* between depressions, we may be able to treat people more effectively.

In sampling the charts of my own depressed patients, I've seen a 65% improvement rate among those I had treated using traditional non-targeted methods and a 96% improvement rate when I targeted depressions according to an algorithm based on the findings summarized above. A controlled study is in preparation.

Perhaps, in this brave new century, we can help neuroplastic man become disentangled from the brain states that bind him by letting clinical research loosen some of the outdated conceptual bonds that have restrained our own best efforts.

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