Published in final edited form as:

Biol Psychiatry. 2018 August 15; 84(4): e27–e28. doi:10.1016/j.biopsych.2018.06.017.

Changing the way we think about (and with) antidepressants

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In 2004, the Archives of General Psychiatry published a study that transformed the way we think about the treatment of depression (1). It is cited in textbooks of psychotherapy and psychopharmacology alike; inclusion of the key figures seems requisite to any PowerPoint presentation. The study went like this: a group of researchers led by Helen Mayberg were interested in comparing how the brain responded to different types of treatment. They recruited two groups of patients with depression. One group was treated with cognitive behavioral therapy (CBT); a separate group of patients (whose data had already been published) were treated with the antidepressant medication paroxetine. All patients received PET scans before and after treatment. Both groups showed comparable improvements in their depression. And both groups showed changes in functional activation in the hippocampus and frontal cortex. What was surprising – and what made the paper so impactful – was that the brain activation patterns in CBT and paroxetine were exact opposites of each other (patients who received paroxetine showed decreased hippocampal activation and increased prefrontal activation; patients who received CBT showed increased hippocampal and decreased prefrontal activation). How could it be that such different effects on the brain could both lead to improvements in depression? The authors hypothesized that the net *change* to the hippocampal-frontal cortex pathway was the same. The difference was that CBT, by targeting attention, cognition, and emotional processing, works by a “top-down” mechanism whereas antidepressant drugs work from the “bottom-up”, targeting vegetative processes in more subcortical regions. This narrative – of dissociable “top down” vs “bottom up” processes – has become a dominant way of framing how treatment works, both within the research community and also in how we communicate with patients.

Over the past 20–30 years, the field has become increasingly enamored with the bottom-up part of the story. Research into conventional antidepressant medications – as well as on new, rapid-acting treatments, like ketamine and scopolamine – has converged on a model in which the therapeutic mechanism involves increases in brain derived neurotrophic factor (BDNF) and plasticity in key brain regions (including the prefrontal cortex and the hippocampus). Other emerging models – from inflammatory pathways, to the microbiome, to fatty acid metabolism – all similarly reinforce a “bottom up” perspective. Yet despite the

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impressive work done to understand the molecular mechanisms of antidepressants these data do little to address our most challenging question: How do we bridge the chasm between the changes observed at the molecular level and the subjective changes our patients experience in their thoughts and feelings?

Fascinated by this question, Catherine Harmer and her colleagues at Oxford set out on a series of studies to explore the direct impact of antidepressants on cognition and emotion (2, 3). Harmer was struck by the extensive delay between the initiation of antidepressant treatment and the expected response. This gap is both vexing for patients and clinicians and equally complicated from a biological perspective – how do our meds work? And what (if any) acute effects do they have? The research team began with a clever idea: administering antidepressants to *healthy* volunteers and then measuring the effects on emotional processing and cognitive bias at various points in time. They gave subjects 20 mg of citalopram or of placebo and then administered a battery of emotional, cognitive, and perceptual tasks. The citalopram group experienced a surprisingly heterogeneous set of cognitive and perceptual changes within a matter of hours. On one hand, the single dose of citalopram increased recognition of fearful faces and also increased startle response. This is in line with both pre-clinical and clinical data that acute treatment with SSRIs can increase anxiety symptoms. At the same time, the single dose also resulted in participants paying increased attention to positive words, suggesting an acute beneficial effect on emotional processing. When the citalopram was continued for seven days, the initial anxiogenic effect on emotional processing was reversed: the participants demonstrated reduced recognition of fearful and angry faces. And while the acute treatment resulted in biased *attention* for positive words, after seven days the subjects demonstrated an additional biased *memory* for positive over negative words. Intriguingly, these effects occurred without any measurable change in mood, suggesting that antidepressants have an immediate effect on cognition and emotional processing prior to the expected therapeutic response.

Having shown these changes in healthy controls, the Oxford group then asked the critical question of whether similar processes may occur in clinical populations. Immediately following the initial dose of citalopram, the clinical population demonstrated decreased recognition of fearful faces. Moreover, after seven days their neuroimaging data showed normalization of amygdala hyperresponsiveness to fearful faces. Harmer hypothesized that these early changes in emotional processing might be an essential part of the antidepressant response, facilitating eventual changes in behavior and mood. Consistently perceiving the environment as more positive might encourage new behaviors and a more positive emotional experience.

If this hypothesis was correct, then we might also be able to *predict* who will benefit from an antidepressant based on whether they show these early cognitive changes. This would be an enormously significant finding for the field, with direct clinical relevance – it would suggest that if a patient fails to have an early response to a drug in tests of emotional processing, one should switch therapy immediately and forego the cost (both emotional and financial) of waiting an additional 4–6 weeks for the treatment to fail. Harmer's group went on to show that this was the case with citalopram: they found that patients who demonstrated the greatest early improvements in emotional processing were also the ones who demonstrated

the greatest reductions in depressive symptoms at 6 weeks (4). Importantly, the group has also confirmed that early effects can be expected with other common antidepressants: escitalopram, mirtazapine, bupropion, and the selective norepinephrine re-uptake inhibitor, reboxetine.

Knowing that many antidepressants induce early cognitive changes offers a tantalizing possibility: what if this early response could be used, more broadly, to screen whether a new drug compound is likely to have efficacy for depression? Harmer's techniques would thus be akin to a human version of the rodent forced swim test: a way to evaluate potential antidepressant compounds using only acute dosing. After pre-clinical work suggested antidepressant properties of the hormone erythropoietin (EPO), Harmer and her colleagues confirmed that EPO had acute positive effects on emotional processing. This then spurred phase 2 testing which demonstrated EPO had promising effects in reducing depression severity (5). Perhaps emotional processing testing offers a way to invigorate the antidepressant discovery pipeline.

Going beyond clinical trials and predicting treatment response, Harmer and her colleagues have given us a way to think about antidepressants that challenges the simple dualism of "top-down" vs "bottom-up." In addition to the well-described molecular mechanisms, we can now appreciate a potentially synergistic neuropsychological model of antidepressant action. Early changes in emotional processing result in the perception of a safer, more positive environment. This, in turn, may facilitate more positive social interactions with others (6, 7), which would allow the individual to perceive the environment as more positive. As this positive feedback loop gains strength, we may see increases in reward responsiveness as well as increases in BDNF as neural adaptations to the "new" environment.

The 2004 paper by Mayberg's group remains an important piece of work for the field of biological psychiatry, emphasizing the biological underpinnings of psychotherapy and how it differs from antidepressants. Because of its easily sensationalized findings, it unintentionally helped bolster a false dualism between drugs and therapy, "top down" and "bottom up." In many ways, Harmer's work helps bridge the gap between synapse and experience: early responses to medications may be real and biologically mediated; and, moreover, the changes they induce in emotion perception and cognition may be integral to their therapeutic action. Changing the conversation about treatment is critical not only for shaping our research agenda but for helping our patients craft a more accurate narrative of their own experience of recovery.

Acknowledgements

AMN received support from the National Institutes of Health Grant No. R25 MH101076 (PI: Tyrka). AMN reported no other biomedical financial interests or potential conflicts of interest.

Clinical Commentaries are produced in collaboration with the National Neuroscience Curriculum Initiative (NNCI). David Ross, in his dual roles as co-chair of the NNCI and as Education Editor of *Biological Psychiatry*, manages the development of these commentaries but plays no role in the decision to publish each commentary. The NNCI is supported by the National Institutes of Health Grant Nos. R25 MH10107602S1 and R25 MH08646607S1. DAR reported no other biomedical financial interests or potential conflicts of interest.

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