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Commentary

Psychotherapy as an epigenetic 'drug': psychiatric therapeutics target symptoms linked to malfunctioning brain circuits with psychotherapy as well as with drugs

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SUMMARY

What is known and Objective: **Psychotherapy has traditionally competed with psychopharmacology. As drugs have become the more dominant treatment in psychiatry and primary care, this approach is increasingly criticized as limited in scope, lacking in robust outcomes and too heavily influenced by the pharmaceutical industry. Our objective is to show that recent advances in neurobiology are clarifying that learning and environmental experiences, such as psychotherapy, change brain circuits as do drugs. The leading notion of how therapeutic effects occur in psychiatric disorders is that they happen when symptoms are reduced by improving the efficiency of information processing in hypothetically malfunctioning brain circuits.**

Comment: **With this formulation of psychiatric symptoms and their relief, it is not surprising that both psychotherapy and psychopharmacology can be clinically effective for treating psychiatric disorders, or indeed that combining them can be therapeutically synergistic. Psychotherapy, including a new spinoff of cognitive behavioural therapy called trial-based therapy, like many other forms of learning, can hypothetically induce epigenetic changes in brain circuits that can enhance the efficiency of information processing in malfunctioning neurons to improve symptoms in psychiatric disorders, just like drugs.**

What is new and Conclusion: **Psychotherapies can be conceptualized as epigenetic 'drugs', or at least as therapeutic agents that act epigenetically in a manner similar or complementary to drugs. These findings are leading to a paradigm shift in psychiatry such that psychotherapy is experiencing a comeback as various standardized, brief, goal-directed psychotherapies are being integrated with drug treatment of psychiatric disorders by psychopharmacologists who have traditionally relied on a drugs-only approach.**

WHAT IS KNOWN AND OBJECTIVES

Psychotherapy is traditionally based upon psychodynamic and psychoanalytic principles, not neurobiology. Psychopharmacology is traditionally based upon molecular mechanism of action.[1] Both are now converging upon the neurobiology and functional outputs of brain circuits, that is, different brain circuits have different actions, resulting in a topographical distribution of cognitive, emotional and behavioural functions.[1,2] Modern neuroimaging techniques allow 'psychiatric stress testing' of these circuits, especially those in prefrontal cortex and amygdala in patients with psychiatric disorders.[2] An explosion of new information from this approach demonstrates that inefficient information processing in specific circuits correlates with specific psychiatric symptoms, from anxiety to depression to cognitive dysfunction and beyond, in patients with a wide range of psychiatric disorders. Genes as well as psychotropic drugs known to modify various neurotransmitter systems can alter the activity of these circuits, and thus create or alleviate psychiatric symptoms by altering the efficiency of information processing in these circuits.[1,2] More recently, it has been shown that environmental experiences, learning and even psychotherapy can do this too.[3–6] This has led to the question: If drugs and psychotherapy converge upon brain circuits, why cannot psychiatrists use both? Our objective is to comment on the basis and evidence for, and potential synergy to be derived from, this approach.

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COMMENT

Psychiatric stress testing of brain circuits

Just as cardiology has its stress testing, so does psychiatry, that is, numerous mental tasks can 'stress' specific brain circuits and activate them.[2] For example, a cognitive task like the N-back test can stress the dorsolateral prefrontal cortex (DLPFC; Fig. 1), and scary faces can stress the amygdala (Fig. 2).[1,2] Applying a functional load like this on various brain circuits can serve as a stress test for a wide range of psychiatric disorders, and the results show that such stress testing uncovers inefficient information processing (too high or too low), indicating malfunctioning in specific brain circuits. As the brain has a limited number of circuit 'highways' on which it can carry its symptoms, it is not surprising that patients with the same symptoms, but who have different psychiatric disorders, may, nevertheless, express the same inefficiencies of information processing in the same circuits, for example, fear in any number of anxiety disorders

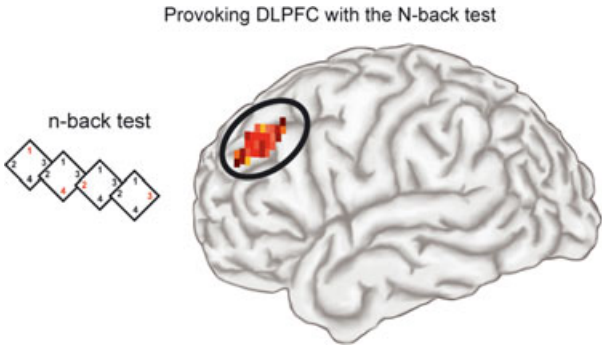

Fig. 1. Provoking dorsolateral prefrontal cortex with the N-back test.

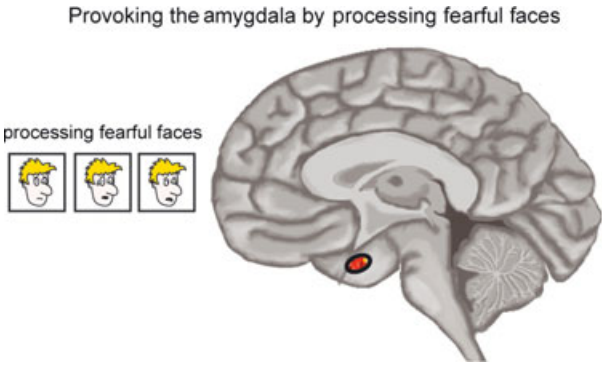

Fig. 2. Provoking the amygdala by processing fearful faces.

and depression maps to inefficient information processing in the amygdala; problems concentrating in disorders ranging from major depression to attention deficit hyperactivity disorder map to the DLPFC.[1,2]

Finding a treatment by first constructing and then deconstructing a psychiatric disorder

It is well known that major psychiatric disorders are defined according to the lists of symptoms agreed by various experts and published as the Diagnostic and Statistical Manual of the American Psychiatric Association (4th edition) and International Classification of Diseases (10th edition). Therefore, to diagnose a mental disorder, the symptoms must be *constructed* into a psychiatric disorder according to these agreed criteria. Treatment of these disorders with various psychotropic drugs can be evidence based or empiric according to expert guidelines, and without regard to neurobiology, but a modern treatment strategy is to *deconstruct* the psychiatric syndrome into its component symptoms, then match each symptom to its hypothetically malfunctioning neurocircuit, and finally choose a drug that targets the neurotransmitters in that circuit, thereby increasing the efficiency of its information processing, and thus relieving the symptom.[1] Until recently, the fact that certain psychotherapies could also relieve these same symptoms was not understood in terms of neurobiology, but more in terms of psychodynamics, and thus was largely thought to be just phenomenological, and unrelated to neurobiology and circuits.

Nature or nurture: genetics or epigenetics as the cause of psychiatric disorders and as the mediators of psychiatric treatments?

For a long time, it has been debated whether psychiatric disorders are because of genes or the environment, and it is increasingly clear that the answer is both,[1–5] that is, inheriting an 'abnormal' gene with an altered sequence of DNA may increase the risk of psychiatric illness, if this leads to the formation of 'abnormal' gene products in neurons, contributing to inefficient information processing in various brain circuits, and thus the risk of a psychiatric illness.[1–5] However, no major psychiatric illness is because of a single gene, and even multiple risk genes inherited simultaneously do not seem sufficient to create a psychiatric illness. The environment is the other part of the story, because it can powerfully impact on epigenetics, a parallel system that determines whether any given gene is actually made into its gene product or not (Fig. 3), that is, if normal genes make normal gene products, but at the wrong time, being epigenetically expressed in neurons when they should be silenced, or epigenetically silenced in neurons when they should be expressed, this, too, contributes to inefficient information processing in brain circuits, increasing the chances of developing a psychiatric disorder.[3–5] Put genetics and epigenetics together (i.e. nature and nurture), and brain circuits may decompensate with symptoms of a psychiatric disorder.

Drugs can change gene expression in brain circuits as a downstream consequence of their immediate molecular properties,[1] so can the environment (Fig. 3);[3,4,6] that is, both good and bad experiences can drive the production of epigenetic changes in gene expression, and indeed, epigenetic changes in gene transcription seem to underlie long-term memories, good and bad.[3,4] Bad memories of childhood trauma may trigger psychiatric disorders by causing unfavourable changes in brain circuits; good memories formed during psychotherapy may favourably alter the same brain circuits targeted by drugs, and similarly enhance the efficiency of information processing and thereby relieve symptoms.[3,4,6] Experimental animals have epigenetic mechanisms linked not only to normal hippocampus-dependent spatial memory formation but also to associative fear conditioning, a model of anxiety disorders, and to extinction of learned fear, a model of psychotherapeutic recovery from anxiety disorders.[3,4]

The amygdala as target of drugs and psychotherapy

The amygdala is emerging as a major brain centre for processing information from the environment and the site of molecular formation of memories from this interaction.[1,2] Two important aspects of this are fear conditioning and reward conditioning: the amygdala remembers what makes you fearful and also what was rewarding, and thus plays a critical role in the production of anxiety disorders and substance abuse disorders. Animal models of both suggest that once the fear conditioning or reward conditioning is formed, then the new synapses mediating them are essentially permanent and irreversible.[4,5] When animals recover from these conditions by undergoing various learning paradigms, they do not lose their original synapses that produced the fear or addiction, but they develop a new synapse

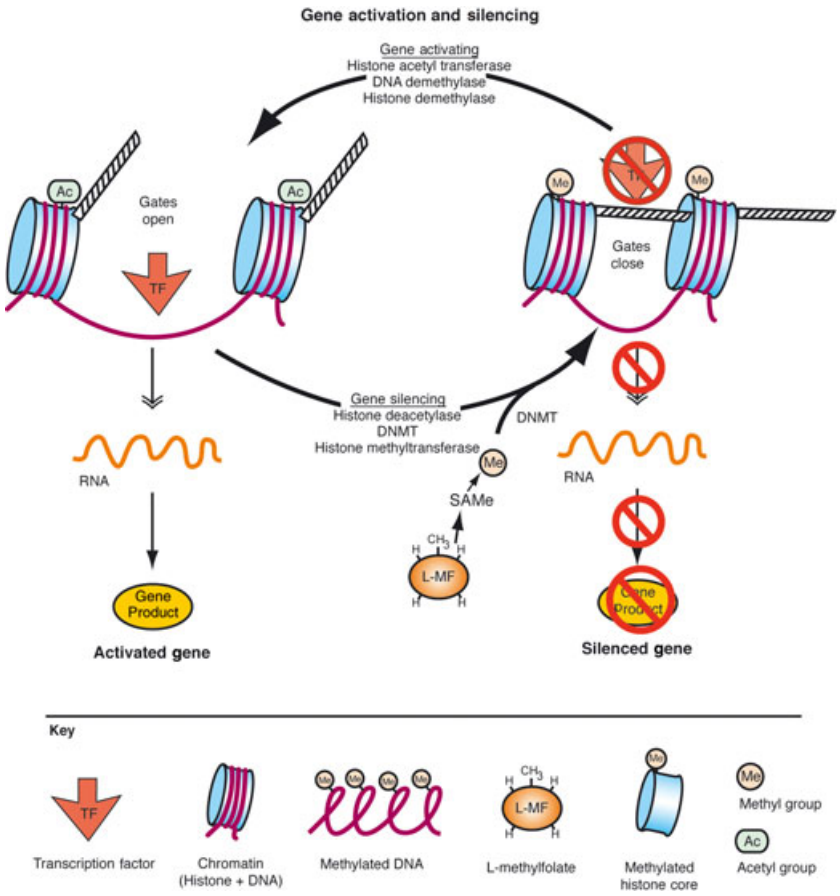

Fig. 3. Gene activation and silencing.

that inhibits the first one.[1–5] This requires long-term potentiation and glutamate neurotransmission at *N*-methyl-D-aspartate (NMDA) glutamate receptors, and behaviours and drugs can both facilitate the formation of these new synapses that block memories of fear or reward. Here is an obvious explanation not only of how psychotherapy can hypothetically change symptoms by altering neuronal circuits but also how combining drugs that facilitate NMDA neurotransmission could potentially enhance the efficacy of psychotherapy in changing neuronal circuits, and thus reduce symptoms.

If both psychotropic drugs and psychotherapy converge upon brain circuits, maybe, their combination can be harnessed for enhanced efficacy and better outcomes for patients with psychiatric disorders. Instead of an either or situation, both sides in the psychotherapy vs. drugs debate might best surrender, declare victory and work together. Now the questions seem to be what is the best way to move forward with this, which psychotherapies to combine with which drugs and for which disorders.

Psychotherapy as an epigenetic 'drug'

Psychotherapy can now be conceptualized not only by its classical psychodynamic principles but also, indeed, as a neurobiological probe capable of inducing epigenetic changes in brain circuits (Fig. 3), not unlike the ultimate actions of psychotropic drugs. The question is how to harness the potential of this approach and direct it most effectively to the relief of psychiatric symptoms. What are the techniques, what is the role of the therapist, what training is needed, how can this be standardized and made the most efficient over time with the fastest onset of action, how to measure the neurobiological and symptomatic results of this approach, how to assure that any progress is preserved? These and many more questions will form the research agenda for moving this approach forward as a central aspect of clinical therapeutics in psychiatry.

Combining psychotherapy with psychotropic drugs

Already, many studies and publications are appearing on this combination approach. For example, cognitive behavioural therapy combined with SSRIs has been reported to be more effective than medication alone for adolescents with SSRI-resistant depression[7] and also more effective than medication alone for adult inpatients with depression.[8] Psychotherapy may be particularly important to add to antidepressants in depressed patients with a history of childhood trauma.[9] Many of the studies of combining cognitive behavioural therapy with medications have been reviewed in a recent book.[10] We still do not know when to expect greater benefits of psychotherapy alone, medications alone or their combination, but at least now, we have a conceptual basis for using both of them and even for combining them, as both approaches converge neurobiologically.

One practical implication of the movement to combine psychotherapy with medications by psychiatrists, who have mostly

used medications and consider themselves psychopharmacologists, is that many of us have been out of touch with conducting psychotherapy for a while and perhaps never received training or supervision on some of the newer 'manualized' (i.e. out of a manual), brief and programmed techniques of psychotherapy, and thus may require some retooling or new training. Given ever increasing pressures on payments and provider time, these new psychotherapies must be efficient to be realistically adapted in a clinical psychopharmacologist's practice setting; that is one of the reasons that the new 'trial-based therapy' described by De Oliveira *et al*.[11] is so interesting because it is intuitive, readily adapted by psychiatrists who are not necessarily sophisticated cognitive behavioural therapists and it is even fun.

Psychotherapies that are manualized, brief, goal directed and prescriptive: trial-based therapy

The best psychotherapy candidates to combine with drugs are cognitive behavioural therapy and interpersonal therapy, which are often conducted by therapists who have read a training manual, been supervised administering it to patients and who use a 12- to 24-week approach that follows a progression with a beginning, a middle and an end.[10–12]

Trial-based therapy. Popular culture is obsessed today with police stories, crime scene investigations and courtroom dramas. Even modern psychopharmacology can be seen through the prism of crime scene investigation: instead of crime scene investigators, then maybe central nervous system investigators with DNA testing and functional magnetic resonance imaging of the scene of the 'crime,' namely the circuits of the brain of a patient with a psychiatric illness. Now comes a novel idea about using this same popular trend to organize and conduct cognitive behavioural therapy, a technique called trial-based therapy, where the patient literally puts his psychiatric symptoms and core beliefs on trial.[11] This idea is based on the universal principle portrayed in Franz Kafka's 'The Trial' that human beings by their very nature are self accusatory, and this can lead to confusion, anxiety and existential suffering. In fact, the central character of this novel, Joseph K, was arrested, put on trial and convicted without ever knowing the crime for which he was accused.[13] De Oliveira *et al*.[11] take this universal truth and fit it into a modern courtroom paradigm.[14] Here, during outpatient psychotherapy, a patient's self accusations are put on trial as distorted schemas and core beliefs that have been developed about the self by the patient's 'inner prosecutor' who convinces the patient that these beliefs are true, and because of this the patient suffers.[14] Trial-based therapy seeks to point out to the patient that his symptoms and suffering are because of core beliefs that can be countered by activating his/her 'inner defence attorney' to see things in a more balanced and realistic way, and thereby relieve symptoms.[11–14] One could hypothesize that when successful, this approach is forming a second synapse of the new perspective of the 'inner defence attorney' to counter and inhibit the circuit mediating the activation of the first learning, namely the distorted core belief of the 'inner prosecutor.'

De Oliveira *et al*.[11] test this technique against traditional cognitive therapy in patients with social phobia and show that it results in comparable or better improvement in symptoms. This is an interesting first step and merits attempts to replicate it in social phobia and to extend it to major depressive disorder, as well as to test whether it can augment the efficacy of psychotropic drugs for these conditions when given in combination. It is brief (10–12 weeks), intuitive and easy to learn, so it is a good candidate for a psychotherapy technique for psychiatrists wishing to re-enter the practice of psychotherapy and add it to their therapeutic armamentarium.

WHAT IS NEW AND CONCLUSION

Synergy and the art of practising bad math

Successful psychotherapy may activate epigenetic mechanisms in brain circuits to reduce psychiatric symptoms by improving the efficiency of information processing in these circuits, just like effective drug therapy is thought to do. Given the limits of psychotropic drugs alone, and the slowing of the pace of innovation in psychopharmacology, one of the most promising therapeutic advances to get us beyond the current plateau of pharmacotherapy is to combine drugs with psychotherapy. This development has the potential of making the entire outcome greater than the sum of the parts, or 1 + 1 = 3, the delightful 'bad math' of therapeutic synergy.

DISCLOSURES OF CONFLICT OF INTEREST

Dr Stahl has served as a consultant to Abbott, Advent, Alkermes, Arena, Astra Zeneca, BioMarin, Boehringer Ingelheim, BristolMyers Squibb, Cypress Bioscience, Lilly, Forest, Genomind, Janssen, Jazz, LaboPharm, Lundbeck, Merck, Neuronetics, Novartis, ONO, Orexigen, Otsuka, PamLabs, Pfizer, Rexahn, Royalty Pharma, Servier, Shire, Sunovion, Valeant and Vivus. He has served on speakers bureaus for Merck, PamLabs, Sunovion, Lilly and has received research and/or grant support from Astra Zeneca, Biomarin, Sunovion, Lilly, Forest, Genomind, Merck, PamLabs, Pfizer, Servier, Shire and Torrent.

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