NEUROBIOLOGICAL MODELS OF PSYCHOTHERAPY: HOW PSYCHOTHERAPY CHANGES THE BRAIN

EDITED BY: Arash Javanbakht and Cristina Maria Alberini
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NEUROBIOLOGICAL MODELS OF PSYCHOTHERAPY: HOW PSYCHOTHERAPY CHANGES THE BRAIN

Topic Editors:
Arash Javanbakht, Wayne State University, United States
Cristina Maria Alberini, New York University, United States

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EDITORIAL
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Editorial: Neurobiological Models of Psychotherapy

Arash Javanbakht[1]* *and Cristina Maria Alberini*[2]

[1] *Stress, Trauma, and Anxiety Research Clinic (STARC), Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI, United States,* [2] *Center for Neural Science, New York University, New York, NY, United States*

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Editorial on the Research Topic

Neurobiological Models of Psychotherapy

The last decade has witnessed an exponentially growing interest in integrating neuroscience into psychotherapy. While neuroscience addresses the mechanistic understanding of brain functions by framing specific questions, psychotherapy examines the richness of complex clinical and individual behavior and history. Understanding the biological bases of complex behavior, human brain-mind functions, as well as their maladaptive responses, and identifying scientific approaches to assess how psychotherapy can help psychopathologies would significantly transform the approaches to mental health and diseases.

Psychotherapy is an individualized yet comprehensive biological treatment; it does not target one receptor, one or two neurotransmitters, or single modulators; it taps into all the biological regulations underlying complex brain responses. The end result of this type of intervention is a re-elaboration of the whole sense of self and others, through new learning and new experiences that encompass cognitive, emotional, and internal regulation processes. Successful therapies produce comprehensive, lasting, measurable physical changes in the brain.

In the past few decades, the progress in neuroscience research has provided a much deeper understanding of the brain structures and functions; applying this understanding and neuroscientific methodology to psychopathologies and therapeutic interventions can be transformative for advancing mental health. Neuroscience research is now, in fact, able to identify the genetic, epigenetic, anatomical, circuitry, and functional bases of behavioral manifestations. Studies in non-human animal models have provided important knowledge for testing hypotheses in humans in both healthy conditions and diseases and have unraveled a number of mysteries of many diseases. Psychotherapy, on the other hand, offers years of clinical experience and a rich understanding of human behavior, but still lacks empirical assessments and methodologies. Therefore, integrating knowledge and methods of neuroscience and psychotherapy will exponentially advance the formulation of new hypotheses, and therefore the comprehension and treatments of mental states and diseases. Given the complexity and variety of human mental functions and diseases, both disciplines, but especially their integration, are still in their infancy, and will require a great amount of work and investment in order to advance relatively rapidly.

One major question that can be readily investigated is whether, how and what types of changes are produced by psychotherapy. The answer to this question will inspire and promote the development of more effective, long-lasting, and integrated therapeutic methods.

This Research Topic "*Neurobiological Models of Psychotherapy*" brings together basic, clinical, and translational neuroscience research with psychotherapy theories, knowledge and clinical approaches to discuss evidence that psychotherapy changes the brain. The discussions in this research topic suggest new integrated knowledge to understand mental health and treat diseases.

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Nuno Sousa,
University of Minho, Portugal

***Correspondence:**
Arash Javanbakht
ajavanba@med.wayne.edu

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Firstly, Solms (University of Cape Town, Cape Town, South Africa), discusses the neurobiological underpinning of the psychoanalytic theory, particularly focusing on the claims concerning innate emotional needs, learning from experience, and unconscious mental processing. On the basis of these claims, he also presents the neurobiological underpinnings of the mechanisms of psychoanalytic treatment, and, finally, he provides a review of the available empirical evidence of psychoanalytic therapeutic efficacy. Cabaniss (Columbia University, New York, NY, USA) underlines the importance and impact of teaching neuroscience to psychotherapy trainees and presents the crucial contributions of five papers that she uses in her teaching of psychotherapy. Radulovic et al. (Northwestern University and the University of Chicago, Chicago, IL, USA) discuss the importance of clinical, cognitive, and neurobiological perspectives on memory research relevant to dissociative amnesia. Zilcha-Mano et al. (University of Haifa, Israel, and Columbia University, New York, USA) review the literature regarding the neurobiological underpinnings of therapeutic alliance and expectancy and emphasize the importance of neurobiological studies to understand these effects. Scult et al. (Duke, Cornell, Kent State, Case Western, Arizona, CUNY, Columbia Universities, USA) report evidence that Emotion Regulation Therapy (ERT) change brain resting-state functional connectivity. Brockman (Columbia University, New York, NY, USA) describes his personal experience as an example to critically discuss what he believes psychoanalysis is lacking, and suggests ideas about how psychoanalysis needs to be integrated with the evidence-based neuroscientific approach.

Two articles discuss behavioral therapies of posttraumatic stress disorder (PTSD): Stojek et al. (Emory University and VA, Atlanta, GA, USA) present the current knowledge on how prolonged exposure therapy impacts the neural circuits related to PTSD, and discuss neurobiological enhancements that have been or may be used in conjunction with prolonged exposure therapy to enhance its effectiveness. Watkins et al. (Emory University, Atlanta, GA, USA) review and discuss the methodological guidelines indicated by the Veterans Health Administration and Department of Defense (VA/DoD) and the American Psychological Association (APA) in 2017 for PTSD treatment.

Finally, pointing at the robust overlaps of the phenomenology, neurobiology, and therapies of anxiety and trauma related disorders, Javanbakht (Wayne State University, Detroit, MI, USA) proposes potential overlapping neurobiology of seemingly different therapies of these disorders including psychoanalysis, cognitive, and behavioral therapies.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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HYPOTHESIS AND THEORY
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The Neurobiological Underpinnings of Psychoanalytic Theory and Therapy

*Mark Leonard Solms**

Psychology, University of Cape Town, Cape Town, South Africa

This paper sets out the neurobiological underpinnings of the core theoretical claims of psychoanalysis. These claims concern (1) innate emotional needs, (2) learning from experience, and (3) unconscious mental processing. The paper also considers the neurobiological underpinnings of the mechanisms of psychoanalytic treatment—a treatment which is based on the aforementioned claims. Lastly, it reviews the available empirical evidence concerning the therapeutic efficacy of this form of treatment.

Keywords: psychoanalysis, neurobiology, basic emotions, unconscious, repression, efficacy

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Edited by:
Arash Javanbakht,
Wayne State University, United States

Reviewed by:
James L. Abelson,
University of Michigan Health System, United States
Oliver Hugh Turnbull,
Bangor University, United Kingdom

***Correspondence:**
Mark Leonard Solms
mark.solms@uct.ac.za

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I recently published a short article in the *British Journal of Psychiatry* (international edition; Solms, 2018a) concerning the scientific standing of psychoanalysis. Implicit in that article were numerous neurobiological assumptions and hypotheses, which I would like to unpack here. This article also builds upon two other partial attempts to explicate these hypotheses (Solms, 2017b; Smith and Solms, 2018), in the *Annals of the New York Academy of Sciences* and *Neuropsychoanalysis*, respectively. There is some overlap between the present article and these previous articles, but the present effort attempts to go further and reveal an overarching picture.

My aim in the first article mentioned above was to set out what psychoanalysts may consider to be *the core scientific claims of their discipline*. Such scientific stock-taking is necessary at this stage in the history of psychoanalysis, due to widespread misconceptions among the public and neighboring disciplines, and disagreements among psychoanalysts themselves regarding specialist details, which obscure a bigger picture upon which most of us can agree.

I addressed three questions in the first article cited above (Solms, 2018a), namely: (A) How does the emotional mind work, in health and disease? (B) On this basis, what does psychoanalytic treatment aim to achieve? (C) How effective is it? My arguments in relation to these questions were:

(A) Psychoanalysis rests upon three core claims about the emotional mind that were once considered controversial but which are now widely accepted in neighboring disciplines (here, I am referring principally to neurobiology).
(B) The clinical methods that psychoanalysts use to relieve mental suffering flow directly from these core claims, and are consistent with current scientific understanding of how the brain changes.
(C) It is therefore not surprising that psychoanalytic therapy achieves good outcomes—at least as good as, and in some important respects better than, other evidence-based treatments in psychiatry today.

Now I will unpack these arguments, spelling out the neurobiological underpinnings which were partially explicated in the other two articles cited above (Solms, 2017b; Smith and Solms, 2018).

These underpinnings pertain especially to the first argument, much less so to the second, and least to the third. This is because questions about how and whether psychoanalytic therapy works are necessarily predicated upon claims about how the emotional mind works. The three sections of this article will, accordingly, be of unequal length.

I submit that the core claims of psychoanalysis regarding the emotional mind are the following:

(1) The human infant is not a blank slate; *like all other species, we are born with a set of innate needs*.
(2) *The main task of mental development is to learn how to meet these needs in the world*, which implies that mental disorder arises from failures to achieve this task.
(3) *Most of our methods of meeting our emotional needs are executed unconsciously*, which requires us to return them to consciousness in order to change them.

These core claims could also be described as foundational *premises*, but it is important to recognize that they are *scientific* premises, because they are testable and falsifiable. As I proceed, I will elaborate the core claims, adding details, but I want to distinguish between the core claims themselves and the specifying details. The details are empirical. Whether they are ultimately upheld or not does not affect the premises. Detailed knowledge develops over time, but premises are foundational.

For example, by analogy: a core claim of evolutionary biology is that species evolve by means of natural selection (Darwin, 1859). If this claim were disproven, then the whole theory of evolution would be rejected. With the early twentieth century integration into evolutionary theory of Mendel's laws of inheritance—about which Darwin knew nothing—the modern science of genetics was established. The same applied to the mid twentieth century discovery of DNA—the actual medium of inheritance, about which Darwin likewise had no inkling. This established the modern science of molecular biology. Molecular biology in turn led to the discovery in the late twentieth century of epigenetic regulatory programmes, revealing a whole new domain called evolutionary developmental biology—some of the findings of which directly contradict aspects of Darwin's thinking. All of these developments have elaborated the empirical *contents* of evolutionary theory—they have not shaken its *foundations*.

The same applies to psychoanalysis. Everything psychoanalysts do is predicated upon the above three claims. If *they* are disproven, the core scientific presuppositions upon which psychoanalysis (as we know it) rests will have been rejected. But as things stand currently, they are eminently defensible, supported by accumulating and converging lines of evidence in neurobiology. This justifies the assertion that "Psychoanalysis still represents the most coherent and intellectually satisfying view of the mind (Kandel, 1999)." However, in this article, I will also draw attention to some crucial errors in the contents (as opposed to foundations) of Freud's classical conception of the mind.

I turn now to the three identified core claims.

CLAIM 1

The human infant is not a blank slate; like all other species, we are born with a set of innate needs.[1] The innate needs of the human organism are regulated autonomically up to a point. But beyond that point they make "demands upon the mind to perform work," as Freud (1915a) put it. Once bodily demands become mental, they constitute what Freud called the "id."

Freud recognized that drive demands are ultimately felt as affects. This fact alone (i.e., the fact that the *fundamental needs of the organism* are felt in the pleasure-unpleasure series) explains why affect is so important in psychoanalysis (cf. Freud's "pleasure principle"). But what Freud did not realize is that such demands are actually felt at their *source*. In other words, there is evidence to suggest that drives, which Freud (1905) located at "the frontier between the mental and the somatic" become mental *when they are felt*, prior to which they are not drives but rather autonomic regulatory mechanisms (for summaries of this evidence, see Panksepp, 1998; Solms, 2013; Damasio, 2018).

Freud imagined that id demands take the form of unconscious drive "energies" which operate within the mind and only become conscious when they are registered by the superficial "system Pcpt-Cs," which he located in the cerebral cortex.[2] The mistaken

[1] Before readers exclaim "who ever doubted *that*?", let us recall: academic psychology departments were dominated during much of the twentieth century by a theory which questioned precisely that. The rival theory was called "behaviorism." The Wikipedia entry for "instinct," for example, states that "Instinct as a concept fell out of favor in the 1920s with the rise of behaviorism and such thinkers as B. F. Skinner, which held that most significant behavior is learned."

[2] Freud's localization of consciousness underwent many vicissitudes. Initially he made no distinction between perceptual and affective consciousness (Freud, 1894). Rather he distinguished between *memory traces of perception* ("ideas") and the *energy that activates them*. This distinction coincided with the conventional assumptions of British empiricist philosophy, but Freud interestingly described the activating energy as "quotas of affect," which are "spread over the memory-traces of ideas somewhat as an electric charge is spread over the surface of a body" (Freud, 1894, p. 60). Strachey (1962, p. 63) described this as the "most fundamental of all [Freud's] hypotheses." There is every reason to believe that Freud envisaged such activated memory traces of "ideas" as *cortical* processes. In his more elaborated Freud (1950 [1895-96]) "Project" model, he explicitly attributed consciousness to a subsystem of cortical neurons (the ω system), which he located at the *motor* end of the forebrain. This location enabled consciousness to register discharge (or lack thereof) of the energy that accumulated over the memory traces (the ψ system) from both endogenous and sensory sources (Please note: from 1895 onward Freud described mental energy as being unconscious in itself; it was no longer described as a "quota of affect"). Consciousness, which Freud now divided into two forms, arose from the manner in which mental energy excited the ω neurons. It gave rise to *affective* consciousness when differences in the quantitative level of energy in the ψ system (caused by degrees of motor discharge) was registered in ω as pleasure-unpleasure; and it gave rise to *perceptual* consciousness when differences in qualitative aspects of exogenous energies (e.g., wavelength or frequency) derived from the different sense organs were transmitted, via perceptual (ϕ) neurons, through the memory traces of ideas (ψ), onto ω. In an 1896 revision of this "Project" model, Freud moved the ω neurons to a position between ϕ and ψ, and simultaneously acknowledged that all energy in the mental apparatus was endogenously generated; energy did not literally enter the apparatus through the perceptual system. (Freud seemed to forget this later; e.g., 1920.) In *The Interpretation of Dreams* 1900, however, Freud reverted to the "Project" arrangement, and again located the perceptual and consciousness systems at opposite ends of the mental apparatus. His indecision in this respect seems to have derived mainly from the fact that the cortical perceptual (sensory) and consciousness (motor) systems form an integrated functional unit, since motor discharge necessarily produces perceptual information (Cf. the contiguous location

assumption underlying this theory, namely that consciousness is an intrinsic property of cortex, was first revealed in the 1940s, i.e., shortly after Freud died. The critical experiments were performed by Moruzzi and Magoun (1949), who showed that consciousness in cats is generated not in the cortex but rather in the upper brainstem, in a region now known as the "extended reticulothalamic activating system" (ERTAS). Confirmation that the same applied to humans was quickly forthcoming, for example from Penfield and Jasper (1954), who observed that consciousness is only lost during seizures when epileptogenic activity spreads to what they called the "centrencephalic" region. These observations have stood the test of time, although the role (in the generation of consciousness) of some non-ERTAS upper-brainstem structures, such as the PAG, and even higher (limbic) circuits, has gradually been recognized (Panksepp, 1998; Merker, 2007).

The whole situation I am addressing is summed up in the following statement by Freud (1920, p. 24)—who, incidentally, started his scientific life as a neuroanatomist:

> What consciousness yields consists essentially of perceptions of excitations coming from the external world and of feelings of pleasure and unpleasure which can only arise from within the mental apparatus; it is therefore possible to assign to the system *Pcpt.-Cs*. a position in space. It must lie on the borderline between outside and inside; it must be turned toward the external world and must envelop the other psychical systems. It will be seen that there is nothing daringly new in these assumptions; *we have merely adopted the views on localization held by cerebral anatomy, which locates the "seat" of consciousness in the cerebral cortex*—the outermost, enveloping layer of the central organ. Cerebral anatomy has no need to consider why, speaking anatomically, consciousness should be lodged on the surface of the brain instead of being safely housed somewhere in its inmost interior (emphasis added).

Ironically, it turns out that consciousness *is* lodged in the brain's inmost interior. Consciousness is an *endogenous* property of the brain; it does not stream in through the senses.

The full implications of this discovery were slow to emerge, and they are only now being fully digested (see Panksepp et al., 2017). Initially, Moruzzi and Magoun—and just about everybody else—tried to save the old theory by drawing a distinction between the "contents" of consciousness (which they assigned to the cortex) and its "level" (which they assigned to the ERTAS). The so-called level of consciousness (or "wakefulness") was therefore measured *quantitatively*—on a 15-point scale—while its (perceptual and cognitive) contents were assessed *qualitatively*. But evidence that "arousal" possesses qualities of its own is easily demonstrated. The supposed "level" of consciousness really consists in a variety of *states* of consciousness (cf. Mesulam, 2000). It *feels like something* to be awake. That is why the ERTAS and PAG are not a concern of anesthetists alone (or of neurosurgeons alone); they are of equal concern to psychiatrists. The neuromodulatory systems that are the targets of the best known psychoactive medications have their source cells in the ERTAS (Consider for example, serotonin, noradrenaline and dopamine.). Thus, it turns out that the contents of consciousness do not consist only in the sensory qualia of our classical exteroceptive modalities; the ERTAS generates endogenous qualia of its own. These contents or qualia are known as *affects*.

To be sure, affect is a *more fundamental* form of consciousness than the cortical form of it which attaches to the classical sensory modalities. The relationship between the two forms is hierarchical: *cortical consciousness (conscious perception and cognition) is dependent upon ERTAS arousal*. Thus, whereas even a small amount of damage to the ERTAS causes coma (Parvizi and Damasio, 2003), damage to large swathes of cortex results merely in a loss of "certain forms of information" (Merker, 2007, p. 65). The smallest area of brain tissue whose destruction causes total loss of consciousness is located just below the PAG, stimulation of which—importantly— produces the most extreme states of affective arousal known to man (both pleasurable and unpleasurable, depending on the precise site which is stimulated; see Panksepp, 1998; Merker, 2007).

That is why decorticate animals are conscious (Huston and Borbely, 1974), as are children born without cortex (Shewmon et al., 1999). These animals and children are totally devoid of cortical representations, yet they are awake and alert and display a wide range of emotional responses to adequate stimuli. This decisively contradicts the notion that emotions only become conscious if they are registered in (prefrontal or insular) cortex (cf. LeDoux, 1999; Craig, 2012). There is absolutely no evidence for this. In fact, decorticate animals are *excessively* emotional (Huston and Borbely, 1974), as are human beings with damaged prefrontal lobes (Harlow, 1868). Preserved—indeed enhanced—emotional consciousness can likewise be demonstrated in patients whose insular cortex is totally destroyed (Damasio et al., 2013).

But Freud shared the cortico-centric view of emotion. Thus, he (Freud, 1940, pp. 161–2) wrote:

> The process of something becoming conscious is above all linked with the perceptions which our sense organs receive from the external world. From the topographical point of view, therefore, it is a phenomenon which takes place in the outermost cortex of the ego. It is true that we also receive conscious information from the inside of the body—the feelings, which actually exercise

of the somatosensory and motor homunculi). Freud accordingly settled (in 1917) on a hybrid localization of the perceptual and consciousness systems. In this final arrangement, ϕ (renamed "Pcpt" in 1900) and ω ('Cs') were combined into a single functional unit, the system "Pcpt-Cs." At this point Freud clarified that the Pcpt-Cs system is really a single system which is *excitable from two directions*: exogenous stimuli generate perceptual consciousness, endogenous stimuli generate affective consciousness. Freud also retreated from the notion that affective consciousness registers the quantitative "level" of excitation within the ψ system, and suggested instead that it—like perceptual consciousness—registers something qualitative, like wavelength (i.e., fluctuations in the level of energy within the Pcs system over a unit of time; see Freud, 1920). The main thing to notice in this brief history of Freud's localization of consciousness is that it was from first to last conceptualized as a *cortical* process (Although Freud did seem to have fleeting doubts about this at times; e.g., 1923, p. 21). See (Freud, 1940) (quoted in the text below) for explicit confirmation that his cortical localization of consciousness applied to both perceptual *and* affective consciousness. See Solms (1997) for a first intimation that something was wrong with Freud's superficial localization of the internal (affective) surface of the system Pcpt-Cs.

> a more peremptory influence on our mental life than external perceptions; moreover, in certain circumstances the sense organs themselves transmit feelings, sensations of pain, in addition to the perceptions specific to them. Since, however, these sensations (as we call them in contrast to conscious perceptions) also emanate from the terminal organs and since *we regard all these as prolongations or offshoots of the cortical layer*, we are still able to maintain the assertion made above [at the beginning of this paragraph]. The only distinction would be that, as regards the terminal organs of sensation and feeling, the body itself would take the place of the external world (emphasis added).

So, for Freud, affects were only felt once they were "read out" in cortex, even though there was no evidence for the view that they are transmitted from terminal organs in the interior of the body to cortex via "prolongations or offshoots of the cortical layer."[3] There is, however, growing support for the view that affects emanate from the visceral interior of the body (see Damasio, 1994, 2018). Freud thought that affects register "oscillations in the tensions of drive needs" (1940, p. 198), and he defined "drive" as "the psychical representative of the stimuli originating from within the organism and reaching the mind, as a measure of the demand made upon the mind for work in consequence of its connection with the body" (Freud, 1915a, p. 122). In other words, *bodily "demands made upon the mind for work" are felt as affects.* On this basis, Damasio wrote that "Freud's insights on the nature of affect are consonant with the most advanced contemporary neuroscience views" (1999, p. 38).

It is certainly true that arousal states are *felt*; and many states of arousal are generated by drive needs. In short, *we become aware of our needs via feelings.* Consider hunger and thirst, for example. According to Damasio (1994), that is what feelings are *for*—which implies that is what *consciousness* is for, in its most basic form (Damasio, 2010, 2018). Affect is a value system, in terms of which pleasurable feelings signal states of the body that enhance the chances of survival and reproductive success, and unpleasurable feelings signal the opposite.

Significantly, as I have stated already, the mechanisms underpinning this—the most fundamental form of consciousness—are located in the upper brainstem and diencephalon. There, bodily "need detectors" (located principally but not exclusively in the medial hypothalamus) activate the basic arousal states that Panksepp (1998) calls "homeostatic affects."

But there are also more complex types of affect, the source cells and circuits for which are located slightly higher in the brain. These "emotional" affects (such as fear and attachment bonding) and "sensory" affects (such as surprise and disgust) are no less crucial for survival and reproductive success than the homeostatic ones; but they do not simply register the current state of the body. These circuits, which release complex behavioral stereotypes like grooming, fighting, and copulating (and the feelings associated with them), are intrinsic to the brain itself. (This transcends the James-Lange theory of emotion). Emotional circuits, too, arise mainly in the upper brainstem but they also extend higher into the limbic system (see Panksepp, 1998). A useful way of distinguishing the types of affect—following Panksepp—is to differentiate between three broad levels: drives (*homeostatic* affects), instincts (*emotional* affects), and reflexes (*sensory* affects).

The important thing for present purposes, however, is this: all three types of affect are generated by the brain mechanisms which perform the functions that Freud assigned to the id—see Solms (2013) for detailed evidence—and they are all *conscious*. In fact, Freud himself always insisted that the notion of unconscious affect was an oxymoron (thereby contradicting his own theory that the id is simultaneously unconscious *and* regulated by the pleasure principle).

To sum up so far: consciousness registers the state of the *subject*, not (in the first instance) of the object world. The sentient subject is first and foremost an *affective* subject. Only then can we (consciously) experience perceptual and cognitive representations. That is why—to state the obvious—there can be no objects of consciousness without a subject of consciousness "being there" to experience them. The subject of consciousness is primary. The secondary (perceptual and cognitive) form of consciousness is achieved only when the subject of consciousness *feels* its way into its perceptions and cognitions, which are unconscious in themselves. The pseudopodia of an amoeba, palpating the world, come to mind (see Solms, 2017a for the empirical details behind these arguments).[4]

However, this is not the place to rehearse all the arguments in favor of the view that affects are felt at their source, in the upper brainstem, diencephalon, and limbic system. I have repeatedly summarized the evidence for this view elsewhere (e.g., Solms, 2013, 2017a,b; Solms and Friston, 2018). Such questions are not what matter most in the present context, where I am laying out the *core claims* of psychoanalysis. The core claim in this respect remains: The human infant is not a blank slate; like all other species, we are born with a set of innate needs, *and these needs are (ultimately) felt as affects.* Few neurobiologists today would dispute this core claim.

Now we can move on. Each affect which promotes—i.e., broadcasts the presence of—a need releases driven or instinctive or reflexive *behaviors*. These innate behavioral tendencies—of which there are a great many—consist in hard-wired *predictions* (i.e., stereotyped action plans; I am following Friston's terminology here; see Friston, 2010). Both Panksepp and LeDoux conceptualize these action tendencies as hereditary "tools for survival" (and therefore, of course, by extension, for reproductive

[3]If affective consciousness truly was a property of cortex, Freud's "pleasure principle" would be a top-down regulatory principle, which it is not (see e.g., Freud, 1911).

[4]Cf. Freud's description of the process: "Cathectic innervations are sent out and withdrawn in rapid periodic impulses from within [the id] into the completely pervious system *Pcpt.-Cs.* So long as that system is cathected in this manner it receives perceptions (which are accompanied by consciousness) and passes the excitation onwards to the unconscious mnemic systems; but as soon as the cathexis is withdrawn, consciousness is extinguished and the functioning of the system comes to a standstill. It is as though the unconscious stretches out feelers, through the medium of the system *Pcpt.-Cs.*, toward the external world and hastily withdraws them as soon as they have sampled the excitations coming from it" (Freud, 1925, p. 231). Note that Freud's "feelers" are *unconscious* until they reach the cortical system *Pcpt.-Cs*. To reconcile his conception with contemporary knowledge, we should say "the id [not the unconscious] stretches out feelers."

success). In short, we execute these actions because they are designed to meet our (inescapable) biological needs—e.g., we cry, search, freeze, flee, attack, copulate.

These two concepts—innate *needs* and their associated *predictions*—underpin everything else I am going to say in this section.

Universal agreement about the number of such needs (and the associated innate behavioral predictions) in the human brain has not been achieved,[5] but most mainstream taxonomies include at least a subset of the following *emotional* ones:

- We need to engage with the world—since all our biological appetites (including bodily needs like hunger and thirst) can only be met there.[6] This is a *foraging* or seeking instinct. It is felt as interest, curiosity and the like. (It coincides roughly but not completely with Freud's concept of "libido;" see Solms, 2012).
- We need to find sexual partners. This is felt as *lust*. This instinct is sexually dimorphic (on average) but male and female inclinations exist in both genders. (Like all other biological appetites, lust is channeled through seeking)[7].
- We need to escape dangerous situations. This is *fear*.[8]
- We need to attack and get rid of frustrating objects (things that come between us and satisfaction of our needs). This is *rage*.
- We need to attach to caregivers (those who look after us). Separation from attachment figures is felt not as fear but as *panic*, and loss of them is felt as *despair*. (The whole of "attachment theory" relates to this need, and the next one).[9]
- We need to care for and *nurture* others, especially our offspring. This is the so-called maternal instinct, but it exists (to varying degrees) in both genders.[10]
- We need to *play*. This is not as frivolous as it appears; play is the medium through which social hierarchies are formed ("pecking order"), in-group and out-group boundaries are maintained, and territory is won and defended.

Please remember: as previously stated, Panksepp (1998) distinguishes between *bodily*, *emotional,* and *sensory* needs, which correspond roughly with current usage of the terms "drive," "instinct," and "reflex." Here I have listed only the *emotional* needs—which are felt as separation distress, rage, fear, etc.—not the *bodily* ones—which are felt as hunger, thirst, sleepiness, etc.—or *sensory* ones—which are felt as pain, disgust, surprise, etc. This focus is somewhat arbitrary, but I am highlighting the category of *emotional* needs because these most commonly give rise to psychopathology. In saying this, I do not wish to deny that *bodily* needs, too, can be enlisted in psychopathology (e.g., consider hunger in anorexia nervosa), and the same applies to *sensory* needs (e.g., consider pain in masochism). But, typically, these needs are only secondarily implicated in the psychological troubles that arise primarily from the patient's inability to meet their *emotional* needs (see next section).

I do not want to make too much of these taxonomic issues. The same applies to the disagreements between Panksepp and Ekman, say, regarding which emotions are (or are not) the truly *basic* ones. For example, Ekman considers disgust to be a basic emotion, whereas Panksepp considers it to be a *sensory* affect. (Either way, it is certainly true that disgust, like hunger and pain, can readily be enlisted in psychopathology). I say again, here we are dealing mainly with matters of principle, not with empirical details. The principle remains: *human beings—no less than other species of animal—have innate biological needs* (some of which may be described as bodily drives and some of which may be described as emotional instincts and some of which may be described as sensory reflexes). All of these needs are (ultimately) felt as effects. And all of them have to be *acted* upon. This last point leads us to the second core claim of psychoanalysis.

CLAIM 2

The main task of mental development is to learn how to meet our needs in the world. We do not learn for its own sake; we do so in order to establish optimal *predictions* (see above) as to how we may meet our needs in a given environment. This is what Freud (1923) called "ego" development.

Learning is necessary because even innate predictions have to be reconciled with lived experience. Evolution predicts how we should behave in, say, dangerous situations in general, but it cannot predict all possible dangers; each individual has to learn *what* to fear and *how best* to respond to the variety of actual dangers they are confronted with. The most crucial lessons are learned during critical periods, mainly in early childhood, when we are—unfortunately—not best equipped to deal with the fact that our innate predictions often *conflict* with one another (e.g., attachment vs. rage, curiosity vs. fear).[11] We therefore need to learn *compromises*, and we must find *indirect* ways of meeting our needs. This often involves *substitute-formation*. Humans also have a large capacity for *delaying* gratification and for (temporarily) satisfying their needs in *imaginary* and *symbolic* ways. This capacity is of course bound up with our large cortico-thalamic mantle, and in particular with its prefrontal component.

I now move to something fundamental. It is crucial to recognize that *successful predictions entail successful affect*

[5]The taxonomy of innate needs is an empirical question, of the kind I mentioned earlier; it does not alter the basic claim that *we are born with a set of innate needs*, which are felt as affects and which trigger stereotyped predictions. I am well aware that the taxonomy I cite here differs from Freud's. Unlike many of his followers, Freud (1920) accepted that biology might well "blow away the artificial fabric of our hypotheses [about the nature and number of instincts]."

[6]The fact that we can only meet our needs by engaging with others is why life is difficult. You cannot successfully copulate with yourself, attach to yourself, etc., although this does not stop us from trying (The psychoanalytic theory of "narcissism" arises from these simple facts)!

[7]For this easily-understandable reason, Freud conflated them.

[8]The relationship between (fear) anxiety and libido has a long history in Freud's work. Suffice it to say that they—like all of the instincts enumerated here—turn out to have distinctly separable brain circuits and chemistries.

[9]Here too, the evidence ultimately favored those psychoanalysts (like Fairbairn and Bowlby) who asserted that attachment and lust are two independent biological needs.

[10]Notwithstanding what I say above, it is interesting how closely intertwined is this brain system with the circuitry for female lust.

[11]This is why childhood, and the quality of parental guidance, are so important in psychoanalysis.

regulation, and vice-versa. This is because our needs are *felt*. Thus, successful avoidance of attack reduces fear, successful reunion after separation reduces panic, etc., whereas unsuccessful attempts at avoidance or reunion result in *persistence* of the fear or panic, etc.

Please note that this formulation implies that only *unmet* needs are felt. Indeed, the meeting of a need is heralded precisely by the *disappearance* of the relevant feeling (satiation). Increasing hunger is felt as unpleasurable and decreasing hunger (relieving hunger through eating) is felt as pleasurable. These affects indicate the *direction of change* in the underlying demand (see Solms and Friston, 2018). But once the demand disappears, the feeling (both unpleasurable and pleasurable) likewise disappears. Satiation removes feelings from the radar of consciousness.

Importantly, this implies that *lack of affectivity is the ideal state of the organism*. This is what Freud (1920) called the "Nirvana principle."[12] We should note in passing that Freud made another important error here. He equated his Nirvana principle (i.e., aspiring to feel nothing) with a drive toward *death*. There is an inherent contradiction in the view that removing all needs (i.e., satisfying them perfectly)—which is an *ideal* biological state, the most likely to maintain and produce *life*—corresponds to a drive toward death.

This is not the place to go into all the complexities of this arcane issue. However, it seems that the source of Freud's error was his assumption that the "pleasure" and "Nirvana" principles were two *different* principles (see Solms, 2018b). Hence the phrase "*beyond* the pleasure principle" (Freud, 1920). He did not realize that feelings of pleasure and unpleasure are in fact servants of the Nirvana principle (i.e., part of the *same* principle). They merely indicate whether one is heading *further from or closer toward* the desired Nirvana (i.e., from or toward the homeostatic settling point of the need in question).

This does not mean that the clinical phenomena which Freud tried to explain with reference to a "death drive" do not exist (e.g., suicidality, anorexia nervosa, addiction, negative therapeutic reaction). It just means they are not expressions of an elemental drive. In my view the clinical phenomena in question are just that—clinical—i.e., they are *aberrations*, not biological goals. What is "deathly" about these states is their implicit failure to accept that our needs can only *really* be made to go away through *work*—i.e., through an effortful engagement *with reality*. Thus, for example, the heroin addict achieves the *illusion* of meeting their attachment needs (which are mu opioid mediated) by artificially achieving the desired affect that occurs with the presence of the caregiver without actually undertaking the work of really finding her, and what is more, without working out how to make her stay. This failure (i.e., failure to engage with the reality of the absent caregiver) is an *ego* aberration, not an id drive. Such aberrations are bound to end badly; because, in reality, we mammals need actual caregivers, not illusions of care.

Returning to the central point: *the main task of mental development is to learn how to meet our needs in the world*. As explained above, learning is necessary because even innate predictions have to be reconciled with lived experience. This is a fact. Now we can add some theory. Having established the relationship between needs and the pleasure/Nirvana principles, we may speculate (following Damasio) that learning from experience literally requires *experience*—that is, it requires *consciousness*. This statement is predicated on the above facts about the affective basis of consciousness. Conscious experience is *felt* experience. The reason why feeling must be extended outwards, onto the lived exteroceptive world, is so that the organism can determine *whether things are going better or worse there*—in the environment in which it finds itself—within our biological scale of values (in terms of which survival and reproductive success are "good" and the opposite are "bad"). As noted previously, the biological good and bad here correspond to pleasurable vs. unpleasurable feelings. In short, *exteroceptive* consciousness takes the form: I feel this *about that*.

Without feeling, therefore, there could be no *choice*. And without choice there could be no surviving in unpredicted environments, and therefore no learning from experience.[13] *Feeling* one's way through problems (through situations not predicted by innate "survival tools"), during one's own lifetime, therefore, bestows an enormous adaptive advantage. This (feeling one's way through problems), I submit, is the essence of what we do with our "working memory." That is what working memory is for.

Of crucial importance here is the fact that we are talking mainly about *prospective* experience. There is little biological point in learning about the likely consequences of jumping in front of a moving train by *actually trying it out*. Working memory mainly entails virtual action, not physical action. (In the life of the mind, we are—for the most part—dealing with potential energies, not kinetic energies; which has some interesting implications for the mind/body problem).

The short-term-memory process that we nowadays call working memory is what Freud called "thinking." The essence of thinking for Freud was the fact that it is *interposed* between drives (or instincts) and action. Thinking is a process of deliberation which arises *instead of (and prior to) action*. This is crucial. This is how we supplement our innate priors (the rough-and-ready prior predictions we are born with) without actually having to commit ourselves to life-threatening courses of action, in conditions of uncertainty. This, in my view, is the only reason why cognition *needs* to become conscious. As we know, cognition typically remains unconscious (for the classical reviews, see Kihlstrom, 1996; Bargh and Chartrand, 1999). In short: our cognitions become conscious only to the extent that we need to feel them. Later we shall see that, since thinking necessarily requires inhibition of action—i.e., a *delay* function—it underwrites what Freud called the "secondary process."

To be clear: I am not saying that thinking entails unconscious cognition plus affect (two things); I am saying it entails *conscious*

[12]Which can in turn be traced back to his "principle of neuronal inertia" (Freud, 1950 [1895-96]).

[13]This type of learning literally saves lives. The alternative is learning through natural selection, over generations; i.e., what works was selected (and became an innate prediction) because it facilitated the survival and therefore reproductive success of our ancestors. Pity about all the others, who made the wrong random "choices."

cognition (one thing), which is something quite different. Through conscious cognition, raw feeling (what Friston (2010) calls variational "free energy;" see Solms and Friston, 2018) is *bound*—and this process actually changes it from the affective to the cognitive state (cf. Freud's concept of "cathexis," which comes in two forms: bound and freely mobile). In thermodynamic terms, this (binding) means that the state of the driving energy in the mind is *transformed* through useful mental work (see Carhart-Harris and Friston, 2010).

But here comes another crucial point. Working memory (cognitive consciousness) is *a very limited resource*; so, it has to be used sparingly. This fact is well-established. It is generally referred to as Miller's law (in terms of which we are only able to hold about seven units of information in consciousness simultaneously), which in turn may be explained physiologically by way of neurotransmitter depletion.[14] This means that the (predictive) products of thinking must be transferred from STM to LTM as rapidly as possible.[15] In other words, to put it teleologically, STM (conscious predictive-work-in-progress) "aspires" to the LTM condition (to unconscious prediction).

This distinction between STM consciousness and LTM automatism brings to mind a famous aphorism of Freud's which may be paraphrased as "a memory trace arises instead of consciousness" (cf. Freud, 1920). The process by which this happens is, as we now know, "consolidation." The opposite process ("consciousness arises instead of a memory trace") is called "reconsolidation" (Nader et al., 2000; Sara, 2000; Tronson and Taylor, 2007). By "opposite process" I mean the *reversal* of consolidation; the *dissolution* of the trace: i.e., an activated trace (a salient prediction) becomes labile once more, and can therefore be revised, before it is reconsolidated.

Due to the constraints on working memory capacity just mentioned, reconsolidation is generally *resisted*. By this, I do not mean the physiological process of reconsolidation itself confronts a physiological counter-process; rather, I mean that there are biological constraints on how much uncertainty an organism can sustain. That is why roughly 95% of our goal-directed activities are executed unconsciously (Bargh and Chartrand, 1999), which means that only 5% are *not* automatized and are subject to review. To put this psychoanalytically, *the ego prefers problems to remain in the solved condition rather than the unsolved one*. Freud called this "resistance," which gives rise to "defense." Stated differently, and in more familiar terms: we prefer to *confirm* our predictions rather than to *disconfirm* them (cf. the "self-serving bias," Campbell and Sedikides, 1999). Every scientist knows this bias!

The LTM predictions arising from working memory are thus stored in the corticothalamic "preconscious" and *unthinkingly* enacted, unless and until *prediction error* arises. This (prediction error, i.e., "surprise," or falsification of the hypothesis implicit in the LTM prediction) releases "free energy" (see above). That is, surprise increases *entropy*. In terms of information theory, increased entropy implies increased *uncertainty*; and in physiological terms it implies increased *arousal* (see Pfaff, 2006; Solms and Friston, 2018). *Prediction error therefore triggers arousal, which renders the relevant preconscious prediction salient again*. It is important to notice that the "arousal" in question is not merely quantitative; as stated at the outset, it entails affective *quality*. And the quality of an affect always *means* something. Affective arousal broadcasts the presence of an *unmet need* (and the "flavor" of the affect in question identifies the *specific* need that is unmet).[16] Stated differently: prediction error means that a prediction that was meant to meet a need did not achieve its purpose. An unmet need is thus what activates ("hypercathects," in Freudian terms) the memory-traces that were meant to satisfy it.

On this view, only *upper brainstem and limbic arousal* can provide the activation process that is necessary for reconsolidation of a corticothalamic LTM trace to take place through working memory.[17] (The hippocampus is, of course, part of the limbic system; it enables us to *feel* our long-term memories). For the computationally-minded, this entails the adjustment of *precision weighting* within the LTM predictive model, by the action of the core modulatory systems, which in turn—over slower time scales—drive plasticity (see Solms and Friston, 2018). Physiologically, increased precision means increased post-synaptic gain. On my view, this (precision regulation) is *the* function of the ERTAS.

So, what Friston calls *prior* predictions (what Freud called "wishes;" see below) are subjected—reluctantly—to the reality principle, whereby, through what is known as empirical Bayesian processing, they are updated (to become *posterior* predictions).

It is very important to recognize that what I have described so far involves only *cortical* memory systems. *Only cortical memory systems generate virtual realities* (consciously thinkable images, so-called "declarative" representations). These systems coincide exactly with what Freud called the "preconscious."

Typically, the processes I have just described involve *iterative* transfers of predictive traces between three memory systems: short-term "working memory" (Freud's system Cs.) on the one hand and long-term "episodic memory" and "semantic memory" (which together constitute Freud's system Pcs.) on the other. Semantic memory is the deepest (most abstracted) of the three declarative systems.

[14]STM traces decay rapidly as a consequence of neurotransmitter reuptake mechanisms that restore presynaptic neurons to the state that existed prior to the formation of each trace; thereby enabling them rapidly to form further traces. See Mongillo et al. (2008).

[15]Another, closely related, reason for this is that a complex organism has to *set priorities*. In order to determine "what to do next," problems must be prioritized. This is because, generally, it is not possible to do two things at once (e.g., one must eat first, drink second; defeat the rival first, copulate second). The capacities of the motor system, no less than those of working memory, establish an executive "bottleneck" (see Merker, 2007).

[16]I am of the view that this "flavoring" (or "color coding") of different needs via affect is an important facilitator of the *prioritizing* processes discussed above. It enables the brain to identify and compartmentalize computations requiring updating from those that do not, and thus to reduce computational complexity and save on processing power. This is an important part of the causal contribution of qualia to neural information processing (see Solms and Friston, 2018).

[17]See Puryear and Mizumori (2008). Cf. the "global workspace" theory of consciousness. See also Haubrich et al. (2015).

In this respect, therefore, what Freud called "word presentations"—to the extent that language relies upon semantic memory, and vice-versa—are actually *more deeply* encoded than what he called "thing presentations" (i.e., episodic memory). Please note that "thing presentations" occur in the preconscious; they are not exclusive to the system unconscious—as even Freud (1923) himself acknowledged. However, we will have to go further than Freud on this point. Below I will claim that the unconscious (i.e., non-declarative memory) is *devoid* of "thing presentations." On this basis I will claim that *there are no images in the unconscious* (as opposed to the preconscious). In fact, this appears to be the defining distinction between declarative and non-declarative memory. Images are the (almost) exclusive preserve of the cortex. (I say almost because crude, rough and ready "images" do exist in some brainstem structures, such as the tectum. But I use scare quotes, for the reason that these subcortical "images" never enter consciousness, which makes them curious images indeed. Who ever heard of an image that you cannot imagine?).

Now we can turn our attention to the *subcortical* memory systems.

CLAIM 3

Most of our predictions are executed unconsciously. As we saw above, cognitive consciousness (short-term "working memory") is an extremely limited resource, so there is enormous pressure to consolidate our solutions to life's problems into long-term memory, and then ultimately to *automatize* them. Innate predictions—of the kind discussed above[18]–are effected automatically from the outset, as are those acquired in the first 2–3 years of life, before the preconscious ("declarative") memory systems mature (cf. infantile amnesia, which applies only to episodic and semantic memory). Multiple unconscious (non-declarative) memory systems exist, but the ones that are most relevant to psychopathology are "procedural" and "emotional" memory, which operate according to different rules. These stereotyped systems bypass thinking (cf. Freud's "repetition compulsion") and define the mode of functioning of the system unconscious (see below).

The ultimate aim of learning is to *permanently* solve our problems (i.e., to learn how to meet our needs in the world *reliably*). To the extent that this goal is achieved, preconscious predictions are iteratively consolidated and reconsolidated *ever more deeply*. The consolidation of such *automatized* predictions centrally involves transferring them from cortical to subcortical memory systems (principally but not exclusively located in the basal ganglia and cerebellum). The crucial thing to note about these latter systems is that they entail non-representational (sometimes called "model free") *action* programmes. Here I am using the term "representation" in the sense in which I used it above—namely to refer to *images*. That is why non-declarative memories simply cannot be retrieved into working memory; they are *non-thinkable* executive programmes.

All of this implies that truly unconscious (as opposed to preconscious) memories are *not subject to updating in working memory*. This is of crucial importance. They are, therefore, in a sense, indelible (LeDoux, 1995). But they are also highly efficient. LeDoux (1995) calls them "quick and dirty." This is the neural basis of what Freud (1911) called the "primary process." Via these circuits, stimulus X simply triggers response Y, with nothing in between (no delay, no thinking, no "secondary process").[19]

This does not mean that non-declarative memories are not subject to reconsolidation. What it means is that they are not subject to reconsolidation via *thinking* (via conscious cognition, via working memory); they are only subject to reconsolidation through action. Non-declarative memories can only be activated (and thereby consolidated/reconsolidated) through embodied *enactment*.

Of course, not all automatized memories start out as declarative memories. The multiple memory systems operate both successively *and simultaneously*. Some (especially emotional memories, which arise from purely subcortical associations) are therefore automatized from the outset. This applies also to innate emotional predictions. (Instinct is just another word for innate predictions). Instinctual executive programmes are all subcortical. But—as we have seen above—they need to be *supplemented by learning*. Fear conditioning is an excellent example. Here we speak of "single-exposure learning;" e.g., we cannot afford to learn twice what happens when we stick our fingers into an electrical socket.

Learning in each of the different instinctual-emotional systems follows somewhat different rules. For example, early sexual experiences, as with fear conditioning, appear to entail single-exposure learning and to leave indelible impressions. Attachment bonds, by contrast, are established slowly during the first 6 months of life, but they become extremely difficult to change after that (cf. the difference between acute "protest" and chronic "despair" with experiences of separation and loss).

Procedural memories, similarly, are "hard to learn and hard to forget." What these two non-declarative memory systems have in common is that *they by-pass thinking*. But this does not mean that they by-pass *affective* consciousness. Just because we cannot "declare" our automatized predictions does not mean we cannot *feel* their causes and their consequences. (The conflation of consciousness with conscious cognition—i.e., excluding affect—has often led cognitive science astray).

Now we come to the heart of the matter. I have localized Freud's system "preconscious" in the cortex and his system "unconscious" in the non-declarative memory systems located beneath the cortex, primarily in the basal ganglia, and cerebellum (Solms, 2017b). But the unconscious memory systems I have just described are conventionally called "the *cognitive* unconscious," which is contrasted with "the *dynamic* unconscious." Psychoanalysts acknowledge the existence of a cognitive unconscious (they call it the "unconscious ego") but they point out that it excludes the dynamic processes that Freud discovered (which they call the "repressed").

[18] Please note: there probably are no innate *cortical* predictions. See Ellis and Solms (2018).

[19] See footnote below for further discussion of what Freud (1915b) called "the special characteristics of the system Ucs."

Freud thought the repressed unconscious was part of the id. This was one of his biggest mistakes, as I discussed above. I do not mean that the repressed unconscious does not exist. I mean only that *the system unconscious and the id are two different things*, located in two different parts of the brain.

The repressed is derived from cognitive (representational) processes, from learning, whereas the id consists in affective (non-representational) processes, and it is innate. The parts of the brain that perform the functions which Freud called "id" are located mainly in the upper brainstem and limbic system; whereas the parts that perform the functions he attributed to "the repressed" (or the "system unconscious") are located mainly in the basal ganglia and cerebellum (There are, of course, multiple interactions between these systems. For example: the amygdala and nucleus accumbens straddle the tail and head of the caudate nucleus, respectively; and the basal ganglia, in turn, interact constantly with the prefrontal lobes).

In my opinion the difference between the cognitive and the dynamic unconscious is simply this. The cognitive unconscious consists in predictions that are *legitimately* automatized. That is, they are deeply automatized because they work so well; they reliably meet the underlying needs that they are aimed at. The repressed, by contrast, is *illegitimately* (or prematurely) automatized. Illegitimate automatization occurs *when the ego is overwhelmed by its problems*; that is, when it *cannot* work out how to satisfy id demands in the world. This happens a lot in childhood, when the ego is feeble.

The infamous Oedipus complex provides an excellent example of an insoluble problem: it is an almost-inevitable constellation of compulsive (innate) emotional needs, arising simultaneously, which are beyond the reach of the child, and irreconcilable with each other. ("Conflict" is just another word for "insoluble problem"). In such situations, *the child has no other choice but to cut its losses*. It is doomed either (1) to obsess endlessly over a problem that it cannot solve, thereby wasting precious working memory resources which could be more usefully deployed for problems that it *can* solve—such as how to read, write, and calculate—or (2) to make the best of a bad job and automatize the least-bad childish prediction it can come up with, *even though it does not work so well*.[20]

Repression (through the adjustment of precision weighting) has the inevitable implication that a deeply automatized prediction does *not* manage the feelings it is aimed at, but there is nothing the subject can do about this; since the essence of repression consists in the fact that the prediction is treated as if it *does* work well, and it is therefore *immune to reconsolidation*.[21] The resultant prediction error is the constant pressure that Freud theorized as the threat of "the return of the repressed" (This, in turn, leads to secondary defenses—i.e., to what Freud called "after-pressure").

Where I differ from Freud in this regard is that *I do not believe the repressed ever returns*; it is only the *affect* (which it fails to regulate) that returns. How many patients actually remember their Oedipal strivings, even in psychoanalysis, for example? This is because *non-declarative memories are just that: non-declarative*. Non-declarative memories are purely associative (and permanently unconscious) action tendencies of the kind described by LeDoux, as with Pavlov's dogs. No thinking occurs, not even implicitly. This has major implications for how psychoanalytic treatment works.

Before moving on to that topic (of how this type of treatment works), I want to restate the concluding point of this section, because it is of utmost importance: *Not only successful predictions are automatized*. With this simple observation, we have overcome the unfortunate distinction between the "cognitive" and "dynamic" unconscious. Sometimes a child has to make the best of a bad job in order to focus on the problems that it *can* solve. Such illegitimately or prematurely automatized predictions (i.e., *wishes* as opposed to realistic *solutions*) are called "the repressed." Normally, in order for predictions to be updated in light of experience, they need to be reconsolidated; that is, they need to enter consciousness again, in order for the long-term traces to become *labile* once more. This is impossible to achieve for repressed predictions, because *the essential mechanism of repression entails immunity from (declarative) reconsolidation, despite prediction errors*.

My second argument is that the *clinical methods that psychoanalysts use to relieve mental suffering flow from the above core claims*, which are consistent with current understanding of how the brain changes. The argument unfolds over three steps:

(a) *Psychological patients suffer mainly from feelings*. The essential difference between psychoanalytic and psychopharmacological methods of treatment is that we believe feelings *mean something*. Specifically, feelings represent unsatisfied needs. (Thus, a patient suffering from panic is afraid of losing something, a patient suffering from rage is frustrated by something, etc.). This truism applies regardless of etiological factors; even if one person is constitutionally more fearful, say, than the next, or cognitively less capable of updating predictions, their fear still means something. To be clear: *emotional disorders entail unsuccessful attempts to satisfy needs*. That is, psychological symptoms (unlike physiological ones) involve *intentionality*.

(b) The main purpose of psychological treatment, then, is to *help patients learn better ways of meeting their emotional needs*. This, in turn, leads to *better emotion regulation*. The psychopharmacological approach, by contrast, suppresses unwanted feelings. We do not believe that drugs which treat feelings directly can *cure* emotional disorders; drugs are symptomatic (not causal) treatments. To cure an emotional disorder, the patient's failure to meet their underlying needs must be addressed, since this is what is *causing* the symptoms. However, symptomatic relief is sometimes necessary before patients become accessible to

[20] Please note: on this view, the Oedipus complex is derived from experience (Here I am differentiating the Oedipus complex itself from the needs which give rise to it).

[21] This is why the system Ucs is *timeless*. This is also why it *tolerates mutual contradiction*; which simply means that it tolerates unsolved problems. The same applies to the another "special characteristic" of the system Ucs, namely its preference of *psychical vs. material reality*; which simply means that it is impervious to evidence. The fourth special characteristic of the Ucs is *primary process* mobility of cathexes, which I have already discussed in the text above.

psychological treatment, since most forms of psychotherapy require collaborative work between patient and therapist (see below). It is also true that some patients *never* become accessible to psychotherapy. We must also concede that patients just want to feel better: they do not want to work for it.

(c) *Psychoanalytical* therapy differs from other forms of psychotherapy in that it *aims to change deeply automatized predictions*, which—to the extent that they are consolidated into non-declarative memory—*cannot be reconsolidated in working memory*. Non-declarative predictions are *permanently* unconscious. Psychoanalytic technique[22] therefore focuses on:

- Identifying the *dominant emotions* (which are consciously felt but not always recognized as arising from specific needs and their associated predictions).
- These emotions reveal the *meaning* of the symptom. That is, they lead the way to the particular *automatized predictions* that gave rise to the symptom.
- The pathogenic predictions *cannot be remembered directly* for the very reason that they are automatized (i.e., non-declarative). Therefore, the analyst identifies them *indirectly*, by bringing to awareness the *repetitive patterns of behavior* derived from them.
- Reconsolidation is thus achieved through activation of non-declarative traces via their *derivatives in the present* (this is called "transference" interpretation). As stated above, non-declarative predictions cannot be retrieved into working memory; but patients *can* be made aware of the here-and-now *enactments* of those predictions. This is the essence of psychoanalytical cure.
- Such reconsolidation is nevertheless *difficult to achieve*, mainly due to the ways in which non-declarative memory systems work (they are "hard to learn, hard to forget" and in some respects "indelible") but also because repression entails intense resistance to the reactivation of insoluble problems (see also my comments above regarding the "self-serving bias").
- For all these reasons, psychoanalytic treatment takes time—i.e., *numerous and frequent sessions*—to facilitate "working through." Working through entails numerous repetitions of transference interpretations in relation to ongoing derivates of repressed predictions, while new (and crucially, *better*) predictions are slowly consolidated.

To say the same thing in different words: repression leads to endless, mindless *repetition*; which is why "transference" is so important in psychoanalytic treatment. Patients cannot re-think the repressed (since non-declarative memories cannot be retrieved into working memory), but they can think about what they are doing now, *in consequence* of the repressed. What patients *can* think about—i.e., can re-problematize, if it is brought to their attention—are the repetitive *derivatives* of the repressed, which involve *cortical* representations (of current experiences), which can therefore enter working memory and declarative (and reflective; i.e., prefrontal) thinking. This in turn allows their (derivative) predictions to be *reconnected with the affects that belong to them*, which enables the ego to *come up with better predictions,* with more realistic action plans, with the help of an adult brain (and that of the analyst) in adult circumstances.

After transference interpretation comes the harder work of "working through," since the establishment of new procedural memories is a *slow* process. Those who want shorter treatments, and less frequent sessions, will have to learn how non-declarative memory actually works. (Funders of psychological treatments need to learn how learning works.).

From all I have said, I hope it is clear why *our patients suffer mainly from feelings*. They don't come to us saying, "Doctor, there is something I'm unconscious of; could you please tell me what it is?" What they say is, "Doctor, I've got this [all-too-conscious] feeling that I don't want; will you please take it away." Psychopharmacologists try to oblige patients on that score. The psychoanalytic approach, by contrast, is to help patients instead to *understand* their unwelcome feelings, i.e., to discern the errant predictions that *cause* them—i.e., the unconscious, repressed predictions—which our patients are invalidly (and unknowingly) using to meeting their emotional needs.

The analytic task is to bring these predictions back to consciousness—to re-problematize them in working memory. This is achieved by re-directing the feelings which the patient suffers from to the repressed predictions that are causing them. But, as I have said, this cannot be done *directly* in the case of non-declarative memories. It can only be done via *derivatives* of the repressed—via what is being repeated in the present moment and can therefore be "declared" and thought about. The unconscious is just that: it is *unconscious*, for ever more. Although we can infer it, we can never experience it. Such inferences (called "reconstructions" in psychoanalysis) help us to better understand the here-and-now transference. On the basis of this understanding, all that we can hope to achieve is new and better predictions; which must be *consolidated alongside the old ones*.[23] But since the new ones are better at meeting the underlying needs, they are (gradually) deployed more readily by the patient, and thus consolidated, ever more deeply, even after the treatment ends. This last point explains the well-established "sleeper effect," whereby symptoms continue to improve after the termination of psychoanalytic treatments (see below).

There are many other things I would have liked to discuss here, such as how we use affects in the so-called "countertransference;" but that is not my focus in this article (for a more clinically oriented discussion, see Smith and Solms, 2018).

My third and final argument is that *psychoanalytic therapy achieves good outcomes*—at least as good as, and in some respects better than, other evidence-based treatments in psychiatry today (see Shedler, 2015). This argument unfolds over four stages:

(a) *Psychotherapy in general is a highly effective form of treatment*. Meta-analyses of psychotherapy outcome studies typically reveal effect sizes of between 0.73 and 0.85. (An

[22] See Blagys and Hilsenroth (2000) and Smith and Solms (2018).

[23] The persistence of the old predictions is why patients can sometimes get worse (regress) during times of stress—revert to their old ways.

effect size of 1.0 means that the average treated patient is one standard deviation healthier than the average untreated patient). An effect size of 0.8 is considered a large effect in psychiatric research, 0.5 is considered moderate, and 0.2 is considered small. To put the efficacy of psychotherapy into perspective, recent antidepressant medications achieve effect sizes of between 0.24 (tricyclics) and 0.31 (SSRIs).[24] The changes brought about by psychotherapy, no less than drug therapy, are of course visualizable with brain imaging (see Beauregard, 2014).

(b) *Psychoanalytic psychotherapy is equally effective* as other forms of psychotherapy (e.g., CBT). This has recently been demonstrated conclusively by comparative meta-analysis (Steinert et al., 2017). However, there is evidence to suggest that *the effects last longer—and even increase—after the end of the treatment*. (Shedler, 2010) authoritative review of all randomized control trials to date reported effect sizes of between 0.78 and 1.46, even for diluted and truncated forms of psychoanalytic therapy.[25] An especially methodologically rigorous meta-analysis (Abbass et al., 2006) yielded an overall effect size of 0.97 for general symptom improvement with psychoanalytic therapy. The effect size increased to 1.51 when the patients were assessed at follow-up. A more recent meta-analysis by Abbass et al. (2014) yielded an overall effect size of 0.71 and the finding of maintained and increased effects at follow-up was reconfirmed.

This was for *short-term* psychoanalytic treatment. According to the meta-analysis of de Maat et al. (2009), which was less methodologically rigorous than the Abbass studies, *longer-term* psychoanalytic psychotherapy yields an effect size of 0.78 at termination and 0.94 at follow-up, and *psychoanalysis* proper achieves a mean effect size of 0.87 at termination and 1.18 at follow-up. This is the overall effect; the effect size that she found for symptom improvement (as opposed to personality change) at termination was 1.03 for long-term therapy, and for psychoanalysis it was 1.38. A subsequent study by Leuzinger-Bohleber et al. (2018, in press) shows even bigger effect sizes: between 1.62 and 1.89 after 3 years of treatment. These are enormous effects. Follow-up data are of course not yet available from this ongoing study. The consistent trend toward *larger effect sizes at follow-up* (where the effects of other forms of psychotherapy, like CBT, tend to *decay*) suggests that psychoanalytic therapy sets in motion processes of change that continue even after therapy has ended (cf. "working through," discussed above). This is called the "sleeper effect."

It is important to recognize that these findings concern symptom improvement only. Psychoanalytic treatments are not directed primarily at symptomatic relief but rather at what might be called personality change. Not surprisingly, therefore, psychoanalytic treatments achieve much better results than other treatments on *this* outcome measure. In Leuzinger et al.'s ongoing study, for example, almost twice as many patients receiving psychoanalytic treatment vs. CBT reached their criteria for "structural change" after 3 years (60 vs. 36%).

(c) The therapeutic techniques that predict best treatment outcomes *make good sense in relation to the psychodynamic mechanisms outlined above*. These techniques are (Blagys and Hilsenroth, 2000):

- *unstructured*, open-ended dialogue between patient and therapist.
- identifying *recurring themes* in the patient's experience.
- linking the patient's *feelings* and perceptions to *past experiences.*
- drawing attention to *feelings* regarded by the patient as *unacceptable.*
- pointing out ways in which the patient *avoids* feelings.
- focusing on the here-and-now therapy relationship.
- drawing connections between the therapy relationship and other relationships.

It is highly instructive to note that these techniques lead to the best treatment outcomes, *regardless of the "brand" of therapy the clinician espouses*. In other words, these same techniques (or at least a subset of them; see Hayes et al., 1996) predict optimal treatment outcomes in CBT too, even if the therapist believes they are doing something else.

(d) It is therefore perhaps not surprising that psychotherapists, irrespective of their stated theoretical orientation, tend to choose psychoanalytic psychotherapy for themselves (Norcross, 2005)!

CONCLUSION

I am aware that the neurobiological assumptions and hypotheses outlined in this article are synthesized in a highly abstracted way. My aim has been only to sketch the bigger picture, in broad brushstrokes, so that the wood emerges from the trees. I hope that this rough sketch has served its essential purpose, which is to provide in simple terms a neurobiological understanding of psychoanalytic theory and therapy, as things stand today. I do not mean to assert, of course, that psychoanalysis was *based upon* these underpinnings. Rather, I hope to have shown that the core theoretical claims and technical practices of psychoanalysis have gradually *acquired* neurobiological support.

I am also well aware that the claims I have summarized here do not do justice to the full complexity and variety of views in psychoanalysis, both as a theory and a therapy. I am saying only that these are the *core* claims, which underpin all the details, including some of those upon which psychoanalysts are yet to reach agreement. I believe that these claims are increasingly supportable, in light of current scientific evidence, and that they make simple good sense.

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The author confirms being the sole contributor of this work and has approved it for publication.

[24] See Turner et al. (2008) and Kirsch et al. (2008).

[25] I would like to thank Jonathan Shedler for his generous help with this section of my paper, which is based on Solms (2018a).

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OPINION
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Psychoanalysis and Neuroscience – A Disclosure

*Richard Brockman**

Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY, United States

Keywords: neuroscience, Freud, metapsychology, data collection, hypothesis

Disclosure.

I'm staring at the ceiling. I don't like this office. It's always felt small. It's always felt white. I stare at a shoe, polished and brown, dangling to my right.

"What are you thinking?"

He takes a drag on the cigarette.

Smoke. I'm thinking about smoke.

He sits in a chair as dark as his shoe.

"I had this dream. I'm skiing down a double black diamond. Six inches of powder. I cut a series of perfect turns. There is a crowd of people watching. They are impressed with my skill."

I say, not so much to Dr. P. as to the wall on my left, that I miss the thrill of competitive skiing. I was once a really good skier -

"Six inches?" he asks.

- I still am. "Yeah, just enough to lay perfect tracks."

The windows face onto the park. The room could be light and airy. Instead he keeps it dark and claustrophobic. I once met my once high school sweetheart in the waiting room. She was in treatment with Dr. P's colleague on the other side of the waiting room wall, a bald psychoanalyst, named Dr. Q.

"What are you thinking?"

I'm thinking about the waiting room meeting with my once high school sweetheart with whom I had shared an awkward silence, each of us thinking, "Oh God what are you doing here?" My once high school sweetheart's name is/was Vivian. Vivian K.

In the dream, the wind picks up, blowing snow in my eyes.

"Dreams are never concerned with trivia," I remember reading somewhere in *The Interpretation of Dreams* (Freud, 1900).

"What are you thinking?", he asks interrupting my thinking.

"I'm thinking about dreams," I say. And then add, "And what they mean."

"Dreams satisfy wishes," again somewhere in *The Interpretation of Dreams*. Analysts I would learn, refer to the *Interpretation of Dreams* as "Chapter 7." It's code.

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Edited by:
Nuno Sousa,
Instituto de Pesquisa em Ciências da Vida e da Saúde (ICVS), Portugal

Reviewed by:
Arash Javanbakht,
Wayne State University School of Medicine, United States

***Correspondence:**
Richard Brockman
rb37@columbia.edu

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Dr. P. clears his throat, then in his soft, strangely uncomforting tone, "The dream is about your desire to lay perfect tracks, a metaphor for sex, and the thought that your 'tracks' are better than your father's."

My father was raised on a shtetl in Poland. There was no skiing in or near the shtetl where he lived.

"What are you thinking?"

I'm thinking about dreams, perfect tracks, metaphors for sex.

On November 29th, 1895, Freud wrote to his friend and fellow physician, Wilhelm Fliess, "I no longer understand the state of mind in which I hatched the psychology; cannot conceive how I could have inflicted it on you." He was referring to a manuscript, *The Project for a Scientific Psychology*, that he had sent to Fliess. By abandoning *The Project,* Freud was opening the door to Chapter 7. "It appears to have been a kind of madness," again in that letter to Fliess (Freud, 1887–1905/1985, p. 152).

"What are you thinking?" he asks as he takes another drag on his cigarette.

The smoke drifts over my head.

He coughs.

I sit up.

"The hour is not over," he says.

I swing my feet to the floor.

"Please lie back down."

I don't say a word and then stand. "The hour is not over," I hear again as I walk past Dr. P. who stays seated in his dark as shoe leather chair. I open the double inner doors, pass through the waiting room where I had once seen my once high school sweetheart Vivian, Vivian K (perhaps she had changed the hour of her appointment to avoid ever again overlapping with mine), out the outer door to the hall, down the elevator where the elevator operator always hummed one song or another as he took me up and down, this time down, a song by a reggae composer whose name I can't quite recall. To the ground. Out the building's door. Into air. City air.

What are you thinking?

"Gentlemen," Freud began in a report he gave to the Medical Society of Vienna in April of 1896, "when we set out to form an opinion about the causation of a pathological state…"

In that report, Freud revealed that of 18 patients whom he had treated for "hysteria," all 18 were found to have suffered from some form of sexual abuse during childhood, sometimes during the earliest years of childhood. From this data, Freud developed a therapeutic technique, "When we set out to form an opinion about the causation of a pathological state such as hysteria, we begin by adopting the method of anamnestic investigation" (Freud, 1896b, p.191).

He was describing a technique that he had learned from a mentor, Josef Breuer, that followed the path from symptoms to memory to treatment -

"Where shall we get if we follow the chains of associated memories which the analysis has uncovered? How far do they extend? Do they anywhere come to a natural end?"

From this beginning, the idea emerged that neurological illness ("hysteria" was then considered neurologic) could be caused by childhood sexual trauma that would not manifest itself until the victim had matured to such time as she would be able to more fully understand what had been done to her. The ultimate union of memory with affect, against the force of resistance, was this "natural end,"

"One only succeeds in awakening the psychical trace of a precocious sexual event under the most energetic pressure of the analytic procedure, and against the most enormous resistance," (Freud, 1887–1905/1985, p. 153).

Everything about this was revolutionary. That psychological events could cause physical symptoms. That current symptoms could be related back to sexual assaults. That these assaults had occurred when the victim was a child. That these events were most often only partially understood and retained as fragments of memory. And that by following the chain of associations back from the inciting event that brought on the illness to the true etiologic event that had occurred to the child, a psychological method (psychoanalysis) was devised that could bring the fragments of memory and affect together into a coherent narrative and effect a cure. "Traveling backwards into the patient's past, step by step…I finally reached the starting-point of the pathological process" (Freud, 1896a, p.151). Everything about this was revolutionary.

Yet all of this would be abandoned on September 21st, 1897, when Freud wrote in another letter to Fliess, "I no longer believe in my *neurotica*" (Freud, 1887–1905/1985, p. 264). As of the date of this letter (actually somewhat before), Freud stopped believing that actual childhood seduction was the primary cause of hysteria.

A great deal has been made of this reversal.

It has been argued that Freud's abandonment of the "seduction theory" was a "failure of courage" (Masson, 1984, p. 19). That it reflected his desire to get back into the good graces of the Vienna Medical Society that had received his seduction theory with disapproving silence –

"A void is forming around me….my consulting room is empty" (Freud, 1887–1905/1985, p.185). That it reflected Freud's desire to protect his friend Wilhelm Fliess from accusations of incompetence after Fliess' operation on the nasal turbinates of Emma Eckstein nearly killed her (Freud would write to Fliess that the patient's post-operative near fatal hemorrhages were due to psychological factors, thus shifting blame from Fliess's malpractice to the patient's neurosis: "There is no doubt that her hemorrhages were due to wishes," Freud wrote [Freud, 1887–1905/1985, p. 191]).

I do not believe that any of these really explain why Freud abandoned his *neurotica*. Rather I believe that Freud abandoned

his theory of childhood seduction because he was not looking for the cause of a neurosis. Rather he was looking for the cause underlying all neurosis. He was looking for something he had sought in *The Project*. "The intention is to furnish a psychology that shall be a natural science" (Freud, 1895/1950, p. 295). But when he realized that he could not find the unifying principle in the brain, he sought to find the unifying principle in the mind. And he was confident he would.

"For I am actually not at all a man of science…I am by temperament nothing but a conquistador – an adventurer, if you want it translated – with all the curiosity, daring, and tenacity characteristic of a man of this sort. Such people are customarily esteemed only if they have been successful, have really discovered something" (Freud, 1887–1905/1985, p. 398).

Freud abandoned the seduction theory not because he felt it wasn't valid, but because he realized it wasn't universal. He made this discovery when he uncovered an error in his formulation, "…that in all cases, the *father*, not excluding my own, had to be accused of being perverse…." (Freud, 1887–1905/1985, p. 264). From this error, Freud was lead to another more subtle error: "I attributed to the aetiological factor of seduction a significance and universality which it does not possess" (Freud, 1896c, p. 168 footnote 1, 1924). And from this realization, he knew he had to look elsewhere for the universal. And to find it, he turned to a normal mind, to his own—"My self-analysis is in fact the most essential thing…." (Freud, 1887–1905/1985, p.270).

From that point, it did not take Freud long to discover the universal that he had sought. Indeed 3 weeks after writing to Fliess exclaiming that he was lost (September 21st, 1897), he wrote that he was found (October 15, 1897).

"A single idea of general value dawned on me. I have found, in my case too, being in love with my mother and jealous of my father, and I now consider it a universal event in early childhood…" (Freud, 1887–1905/1985, p. 272).

By studying his own mind, Freud discovered that the universal factor was not actual seduction of the child. The universal factor was the child's desire to be seduced. And thus, less than a year after having discovered what he came to regard as a false source of a neurosis in particular—"*one or more occurrences of premature sexual experience*" (Freud, 1896b, p. 203)—he discovered the source of neurosis in general—*infantile sexual phantasy*. And like the image of the conquistador he so admired, Freud was now certain he had "really discovered something," something that was common to every man, woman and child –

"We can understand the gripping power of *Oedipus Rex*…Everyone in the audience was a budding Oedipus in fantasy and each recoils in horror from the dream fulfillment here transplanted into reality, with the full quantity of repression which separates his infantile state from his present one" (Freud, 1887–1905/1985, p. 272).

Some have argued, including his daughter, Anna, that Freud had to sacrifice the seduction theory in order for psychoanalysis to be born,

"Keeping up the seduction theory would mean to abandon the Oedipus complex, and with it the whole importance of phantasy life, conscious or unconscious phantasy. In fact, I think there would have been no psychoanalysis afterwards" (September 10, 1981 in Malcolm, 1983, p. 63).

And thus the universal agent at the heart of neurosis, was revealed –

"If hysterical subjects trace back their symptoms to traumas that are fictitious, then the new fact which emerges is precisely that they create such scenes in *phantasy*." (Freud, 1914, p. 17).

- the universal agent that would be at the very foundation of psychoanalysis.

But there was a hurdle. If a child's fantasies of seduction were at least as powerful as actual experiences of childhood seduction, rape, and/or violence, then the newly discovered power of fantasy would have to be explained. And it was, by another fact:

"It remains a fact that the patient has created these phantasies for himself, and this fact is of scarcely less importance for his neurosis than if he had really experienced what the phantasies contain. The phantasies possess *psychical* as contrasted with *material* reality, and we gradually learn to understand that *in the world of the neuroses it is psychical reality which is the decisive kind*" (Freud, 1916–1917, p. 368, italics in original).

This new fact established fantasy to be as powerful as reality because in the world of the neuroses it is psychical reality which is the decisive kind.

Freud needed to make this leap in order to explain the power of fantasy. It was with this leap that he was able to explain how fantasy could create illness. It was with this leap that he established the science of psychoanalysis. And it was with this leap where things between me and Freud got personal -

"What are you thinking?"

- because several months after beginning treatment with Dr. P., I encountered my once high school sweetheart in the shared waiting room of Drs. P and Q. I don't know what my once high school sweetheart said to Dr. Q. I don't know what Dr. Q. said to her because I never saw her again. I just know that 5 years after seeing my once high school sweetheart that one time in that shared waiting room, she committed suicide.
- because when I was a boy, my mother was sent to see a psychoanalyst, Dr. S. I don't know why she was sent to see Dr. S. I don't know what she said to Dr. S. I don't know what Dr. S. said to her. I just know that when I was seven years, 2 months and 2 days old, my mother walked down the stairs to the basement of our house in the Sheepshead Bay section of Brooklyn and hung herself.

Part of me always thought that my one encounter with my once high school sweetheart in the waiting room of Drs. P. and Q. had in some way contributed to her death. Even though it was 5 years later when she killed herself. Even though it was she who broke up with me. Even though my once high school sweetheart and I had never had sex. Even though I still wanted to when I saw her in the waiting room of Drs. P. and Q. Even though I never mentioned any of this. Not to her. Not to him. Maybe that's what the dream was about. Sex and love and a once high school sweetheart and death.

Part of me always felt responsible for the death of my mother. Part of me always felt that her death was my fault. Part of me always felt I should have saved her. Even though I had no idea that anything had been wrong. Even though I was seven years, 2 months, and 2 days old. Even though I loved her as deeply as any child could and still do.

"What are you thinking?"

I'm thinking it was Freud, not me, who contributed to the death of my once high school sweetheart. I'm thinking it was Freud, not me, who contributed to the death of my mother. I'm thinking is was Freud not me who caused harm to people I loved. I'm thinking it was Freud—that's what I've been thinking. And I've been thinking that I'm not sure it's fair to blame any or all of this on Freud. Or on myself. But I do.

Is it fair to blame psychoanalysis for their suicides?

Is it fair to blame myself for their suicides?

I don't know.

I just know this is personal.

I became a physician to become a psychiatrist. I became a psychiatrist to become a psychoanalyst. I went to analytic school. I felt the only way for me to save my mother and my once high school sweetheart was to become one of those who in my mind, had killed them. It was a fantasy of rescue. It was a fantasy of revenge. The fantasy was "overdetermined" in the parlance of psychoanalysis. But I never became a psychoanalyst. I quit psychoanalytic school the way I quit Dr. P. I just left.

But I studied psychoanalysis. I learned its teachings. I learned its codes. And thus this paper, this confession, this disclosure is an "inside job."

If psychoanalysis is to survive, it must accomplish what Freud set out to do when he started *The Project*. If psychoanalysis is to survive it must rid itself of every hypothesis founded on antecedent hypothesis. If psychoanalysis is to survive, it must never allow one of its own to say to someone like me, that the dream reflects a desire to lay "sexual" tracks better than my father's or some other blurred Oedipal crap. If psychoanalysis is to survive, it must never allow anyone to repeat what was done to my once high school sweetheart. If psychoanalysis is to survive, it must never allow anyone to repeat what was done to my mother. If psychoanalysis is to survive, it must never describe anything Freud wrote after 1897 (or anything derived from what he wrote after 1897) as "science." If psychoanalysis is to survive it must never call on neuroscience to justify its "facts." If psychoanalysis is to survive it must be honest with itself.

And if psychoanalysis can't be honest with itself, then it shouldn't survive. If psychoanalysis can't be honest with itself, then I will do everything in my power to destroy it.

But if psychoanalysis is to survive, then it must sacrifice many if not most of its most cherished "facts" because almost all of psychoanalysis after 1897 was derived from a core hypothesis that had incubated in Freud's mind from sometime in early 1896 when he abandoned the *Project*, until that day in September 1897 when new insight dawned. It was a hypothesis that was brilliant, compelling, persuasive—the insight of a conquistador, the kind of insight that comes "but once in a lifetime." And it was wrong. Dead wrong.

This key insight, "The certain conviction of the existence and importance of infantile sexuality…" (Freud, 1914, p. 18) lead Freud to the awareness of repression: "We have learnt from psycho-analysis that the essence of the process of repression lies, not in putting an end to…the idea which represents an instinct, but in preventing it from becoming conscious." From this he was lead to discover the unconscious, "When this happens, we say of the idea that it is in a state of being 'unconscious'" (Freud, 1915, p. 166). And thus Freud established the fact of *infantile sexual phantasy* by explaining that it was buried deep in the unconscious and kept there by the force of repression. Because of repression, the only way to become aware of *infantile sexual phantasy*, is via the method that Freud had developed, "The certain conviction of the existence and importance of infantile sexuality, can, however, only be obtained by the method of analysis …" (Freud, 1914, p. 18).

The implication, of course, is that if one has failed to uncover *infantile sexual phantasy* in one's analysis, it is not because such fantasies were not there, rather it is because the analysis itself failed or because the repression was too powerful. Either way, there was never any doubt of the existence of these factors, "There are two positions which I have never repudiated or abandoned – the importance of sexuality and of infantilism." (Freud, 1906, p. 278).

"This is probably not intelligible without an explanation" (Freud, 1887–1905/1985, p. 264) Freud wrote in that September letter.

Between early 1896, when he abandoned *The Project*, and September 21st, 1897 when he abandoned his *neurotica,* Freud's thinking went through a gradual but ultimately radical change. His thinking went from the hypothesis that childhood sexual trauma was the basis for hysterical illness in particular, to the hypothesis that childhood fantasy was the basis for neurotic illness in general. It wasn't that trauma wasn't a factor for some. It was that fantasy was a factor for all. It was a shift from external reality to internal instinct. It was a shift from the biology of brain to the psychology of mind. And it was a shift from the methods of science to the methods of psychoanalysis.

And because all data was now the data of psychoanalytic observation, Freud treated his clinical observations as though they had the rigor of science. Plausible speculation became fact. Persuasive argument, proof. The posing of a question established the assumptions that underlay the question. And so when Freud asked, "Whence comes the need for these phantasies and the material for them?"—it was as if the question had transformed a clinical hypothesis into a scientific fact—as if the question about infantile sexual fantasy had established the fact of *infantile sexuality phantasy*. And so from the question—"Whence comes the need for these

phantasies and the material for them?"—came a response that not only explained but also confirmed their existence: "There can be no doubt that their sources lie in the instincts…"

And having established their existence as derived from an "instinct," Freud then went on to provide the history of their origin, "I am prepared with an answer which I know will seem daring to you. I believe these *primal phantasies*…are a phylogenetic endowment. In them the individual reaches beyond his own experience into primeval experience at points where his own experience has been too rudimentary."

And having established this origin, Freud then needed to explain just how *infantile sexual phantasies* of violence and seduction that are recreated in psychoanalytic transference and dream, have the power of actual violence and seduction. They have this power, he explained, because even if they are fantasies now, they were once real.

"It seems to me quite possible that all the things that are told to us to-day in analysis as phantasy – the seduction of children, the inflaming of sexual excitement by observing parental intercourse, the threat of castration (or rather castration itself) - were once real occurrences in the primeval times of the human family, and that children in their phantasies are simply filling in gaps in individual truth with prehistoric truth" (Freud, 1916–1917p. 370–371).

And so not only is the existence of infantile sexual fantasy established, but the incredible power of infantile sexual fantasy is also established by this "phylogenic endowment." Fantasy thus has the power of reality because it once was real. And so a hypothesis about the power of *infantile sexual phantasy* has become fact. As has the instinct. As has the endowment. And because of these facts, fantasy has the force of reality.

"When I had pulled myself together I was able to draw the right conclusions from my discovery: namely that the neurotic symptoms were not related directly to actual events but to wishful phantasies, and that as far as the neurosis was concerned psychical reality was of more importance than material reality" (Freud, 1925, p. 34).

Once Freud had made his discovery, no data was needed to establish the validity of *infantile sexual phantasy*. Phylogenic endowment established fantasies in the infant's mind. Repression kept them out of awareness in the unconscious. Psychoanalysis demonstrated this fact.

Freud was so convinced of the validity of *infantile sexual phantasy* (a fact that he confirmed in his self-analysis) that his actual observation of an infant was unnecessary. "Why do I not go into the nursery and experiment with Annerl?" he asked in a letter to Fliess referring to his then 2-year-old daughter, Anna.

Darwin, unlike Freud, had spent quite a bit of time playing with and observing his children. "I attended to this point in my first-born infant…I was convinced that he understood a smile and received pleasure from seeing one, answering it by another, at much too early an age to have learnt anything by experience" (Darwin, 1872/1965, p. 358). Darwin had thus observed that his son was instinctively responsive to his environment pretty much from birth. Freud wrote in the margins of his copy of the *Expression of the Emotions in Man and Animals*, the book from which this quote of Darwin's is taken. So there is no question but that Freud was aware of Darwin's observations. But Freud was apparently not impressed. He did not feel observations in the nursery were necessary. Or at least, he wrote, "I have no time for it" (Freud, 1887–1905/1985, p. 230).

And so Freud extended his argument. He theorized that an infant is born with *infantile sexual phantasy* active at the very moment of birth. For this reason, the neonate does not seek his/her mother. The neonate instead seeks pleasure from *auto-eroticism*. Only after the failure of *auto-eroticism* (the failure of the Freudian primary process) does the neonate realize that fantasy is failing to provide pleasure (nourishment), and then seeks a remedy (the mother). "The process of arriving at an *object*…takes place alongside of the organization of the libido." The mother is not the neonate's first choice. Because it is only "After the stage of *auto-eroticism,* (that) the first love-object in the case of both sexes is the mother; and it seems probable that to begin with a child does not distinguish its mother's organ of nutrition from its own body" (Freud, 1925, p. 36). Thus, *auto-eroticism* (another expression for *infantile sexual phantasy*) is our first consciousness. Only after the neonate realizes that in order to find nutrition it must find another, does *auto-eroticism* and the pleasure principle give way to the search for the mother and the reality principle.

Freud's response as to why he didn't spend some more time with his daughter, Annerl, may have been less a fact, than that in order for Freud to maintain the idea that he had discovered the universal principle of neurosis, he needed to argue that not only was repression the corner stone of psychoanalysis ("The theory of repression is the corner-stone on which the whole structure of psycho-analysis rests" [Freud, 1914, p. 16]), but most critically that *infantile sexual phantasy* was the first content of mind. In other words, once Freud had established *infantile sexual phantasy* as universal, then everything had to follow from that.

Looking to the future, Freud had two quite different takes on how his ideas would be viewed. In (Freud, 1914), he wrote: "Science would ignore me entirely during my lifetime; some decades later, someone else would infallibly come upon the same things…would achieve recognition for them and bring me honor as a forerunner whose failure had been inevitable" (p. 22).

Six years later in 1920, his sense of how he would 1 day be received had changed. It was as if he were returning to the bolder, scientific vision he had when he began to write *The Project*,

"Biology is truly a land of unlimited possibilities. We may expect it to give us the most surprising information, and we cannot guess what answers it will return in a few dozen years to the questions we have put to it. They may be of a kind which will blow away the whole of our artificial structure of hypotheses" (p. 60).

If neuroscience seeks to answer some of the questions raised by psychoanalysis, then it should take this (Freud, 1920) statement of Freud's as his "wish" and "blow away the whole

of (his) artificial structure of hypotheses." Because his artificial structure of hypotheses is beautiful, compelling, convincing, and dangerous. It contributed to the deaths of two people I loved.
Disclosure:

I blame Freud. (I am not the first to find fault with Freud's a-scientific theories. Jeffrey Masson, Janet Malcom, John Bowlby—there are of course many more).
Disclosure:

I was never analyzed. I got up off the couch that last time, opened inner doors, walked through the waiting room where I had once encountered my once high school sweetheart, moved through the hall to the elevator where the elevator man was humming a song by a reggae composer whose name I just can't quite –

Marley.

He was humming a song by Robert Marley.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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frontiers in Behavioral Neuroscience

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Teaching Neuroscience: A Primer for Psychotherapists

*Deborah L. Cabaniss**

Department of Psychiatry, Columbia University, New York City, NY, United States

From the beginning of their psychotherapy training, students need to think about how talking changes the brain, how development is encoded in the body, and how connecting neuroscience and psychotherapy can help us improve psychosocial interventions to optimally help patients. But teaching neuroscience doesn't come naturally to many psychotherapy educators—myself included. We were trained as clinicians, not as researchers, so for many of us, reading and searching the neuroscience literature is challenging. Over many years, and with the help of wonderful colleagues, I am learning to read neuroscience papers and to incorporate what I learn into my psychotherapy teaching.

When I teach neuroscience in a psychotherapy course, I do it with great humility. I make it very clear to my students that I'm not a neuroscientist and that I'm not an expert in the field. Instead, I learn *with* my students, as together we try to understand the science and what it can tell us about the mind, development, and psychotherapy.

I also make it very clear that I'm not presenting this material as if it proves something about psychotherapy. We don't know enough about the neuroscience of psychotherapy to do that. Rather, I'm trying to get my students as excited as I am about what neuroscience can teach us about psychotherapy. My hope is that it will stimulate them to think about connections between neuroscience and psychotherapy when they are talking to patients, thinking about formulation, conceptualizing experiments and choosing their careers.

Over the years, I've found that using carefully chosen neuroscience papers that *I* can understand really helps me to get the neuroscience/psychotherapy conversation going in a classroom. To that end, I offer five papers that I use when I teach psychotherapy. They are all written by top researchers and published in the nation's premiere scientific journals. Each one provides interesting potential insights into a different aspect of psychotherapy.

Keywords: psychotherapy education, psychotherapy training, psychoanalysis, unconscious, epigenetics

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Arash Javanbakht,
Wayne State University, United States

Reviewed by:
Douglas Ingram,
New York Medical College, United States
Jonathan Sugar,
University of Michigan, United States

***Correspondence:**
Deborah L. Cabaniss
Deborah.Cabaniss@nyspi.columbia.edu

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PSYCHOTHERAPY CHANGES THE BRAIN

Eric Kandel—Psychotherapy and the Single Synapse

The first paper I give my second-year residents to read in their Introduction to Psychodynamic Psychotherapy Course isn't by Freud, Kohut, or even Kernberg. It's by Eric Kandel and it's called "Psychotherapy and the Single Synapse" (Kandel, 1979). It was published in the *New England Journal of Medicine* in 1979. When I first read this paper as a resident, it blew my mind. Here was Eric Kandel, who had taught me neuroscience in medical school, written the neuroscience textbook I had read, and was soon to win the Nobel Prize in Physiology or Medicine, writing about

psychotherapy. Who knew that he had any interest in that? As I later learned from reading his award-winning memoir, "In Search of Memory" (Kandel, 2006), Dr. Kandel was born in Vienna and has had a longstanding interest in psychoanalysis. The very fact that the most famous neuroscientist in my department was writing about psychotherapy was significant to me. And it wasn't even published in a psychiatry journal—it was published in the *New England Journal of Medicine*! Even at that first reading, I could feel the concepts of mind and brain coming together, and the artificial dichotomy between functional and organic dissolving. And today, in 2018, it still has that effect on my residents.

In this brilliant, prescient, paper, Kandel talks about himself as a young psychiatry resident at the Massachusetts Mental Health Center in 1960 (it's an added extra that he identifies as a clinician), grappling with his colleagues about whether neuroscience was important for understanding psychiatric illness. In his characteristic clear, persuasive style, he takes the reader through his argument that, in fact, it is. Reviewing studies by Rene Spitz, Harry Harlowe, and Hubel and Wiesel, as well as his own work on the physiologic underpinnings of learning, he argues that since both early sensory deprivation and later learning have been shown to have longstanding, lasting effects on the brain, the same must be true of psychotherapy. "Ultimately, all psychologic disturbances reflect specific alterations in neuronal and synaptic function," he writes. "And insofar as psychotherapy works, it works by acting on brain functions, not on single synapses, but on synapses nevertheless." He goes on to say:

. . . when I speak to someone and he or she listens to me, we not only make eye contact and voice contact but the action of the neuronal machinery in my brain is having a direct and, I hope, long-lasting effect on the neuronal machinery in his or her brain. . . Indeed, I would argue it is only insofar as our words produce changes in each other's brains that psychotherapeutic intervention produces changes in patients' minds.

Bottom line: psychotherapy is a brain-changer. That's the message I want to convey to my students as they begin to learn psychotherapy, and there's nothing like this classic paper to help me do that.

THE UNCONSCIOUS IS IN THE BRAIN

Antoine Bechara et al—Deciding Advantageously Before Knowing the Advantageous Strategy

In 1895, Sigmund Freud, wrote his "Project for a Scientific Psychology" at white heat, eager to explain his new psychological findings as having their basis in the substrate of the nervous system (Freud, 1950). But he abandoned it unfinished, moving forward with a psychology unrooted in the brain. Why? Was it because he thought he was wrong? Hard to imagine that this young physician, trained in physiology and neurology, was truly leaving behind the newly described neuron. As Kandel explains in "Single Synapse," until recently, neurobiology was not mature enough to shed light on "higher order" psychological functions (Kandel, 1979). But that's not necessarily true anymore.

Since psychodynamic psychotherapy is based on the idea that unconscious elements and processes affect conscious function, there's no better entry point to discussing the way that psychoanalytic functions could be produced by the brain than the concept of the unconscious. And there's no better paper to facilitate that conversation than "Deciding Advantageously Before Knowing the Advantageous Strategy," written by Antoine Bechara, Hanna Damasio, Daniel Tranel and Antonio Damasio and published in *Science* in 1997 (Bechara et al., 1997).

Again, this isn't just any paper, it's a paper from Damasio's lab published in *Science*. In it, the investigators describe an experiment in which they ask two groups of subjects—one with normal brain function and one with prefontal damage and decision-making deficits—to play a gambling game in which they choose randomly from 4 decks of cards with the goal of making as much (play) money as possible. Decks A and B have cards marked with high rewards and high penalties, and Decks C and D have cards marked with lower rewards but similarly lower penalties. Winning requires choosing from Decks C and D. The subjects were given no information about the decks and were instructed to choose cards randomly. As the game went on, subjects were periodically asked what they understood about the game and were also monitored for anticipatory skin-conductance responses. Normal subjects began choosing advantageously before they understood why, suggesting that their choices were guided by what the authors call non-conscious biases (aka unconscious processes). In addition, only normals developed these "hunches," suggesting that these non-conscious biases are generated in the prefrontal cortex.

This is a terrific paper to use in a psychotherapy course for many reasons. It has neuroscientists investigating properties of the unconscious and suggests some type of localization for at least this unconscious function. It's also a classic cognitive neuroscience paper, insofar as it uses patients with a localized deficit to demonstrate something about the function of a brain area. You don't need to be able to read scans to understand it. It's also great to teach using the cognitive neuroscience literature, since, at this point, studies conducted by cognitive neuroscientists connect to psychotherapy more readily than most circuit, synaptic, cellular, or molecular level studies. The need to translate from "non-conscious bias" to "unconscious" is also helpful, in that it will help students decode this in other papers. Plus, it's two pages long, well-written, and about gambling—perfect for your psychotherapy syllabus.

PSYCHOTHERAPY AND MEMORY

Daniella Schiller et al—Preventing the return of fear in humans using reconsolidation update mechanisms

"*Hysterics suffer mainly from reminiscences*," wrote Freud and Breuer in 1893 (Breuer and Freud, 1893). That finding led the two men to their discovery of psychotherapy—the talking cure—designed to help people alleviate symptoms by talking about repressed memories. Although we now know that it's more complicated than that, memory and talking about memories is at the heart of psychodynamic psychotherapy—and it seems

clear that something about talking about memories in therapy is therapeutic. But why? Although we don't yet know, scientists are actively working to understand how memory works and how retrieving memories can be therapeutic.

I often introduce this topic with the paper, "Preventing the return of fear in humans using reconsolidation update mechanisms," featuring experiments from the NYU lab of Elizabeth Phelps and published in *Nature* in 2010 (Schiller et al., 2010). In this paper, lead author Daniella Schiller describes an experiment on humans, based on the concept of memory reconsolidation. Although memory was originally thought to be a one-time process, scientists working with animal models have shown that memories change every time they are remembered, and that this process requires protein synthesis (Alberini, 2011). The idea is that, during the reconsolidation, the memory is "labile" and thus potentially vulnerable to change. To test this, Schiller and her colleagues created a fear memory in three groups of people—a mild shock connected to a color—then brought them back a day later to try to extinguish the memory. For two of the groups, they preceded the extinction with a reminder of the fear memory (the color), presenting this reminder 10 min prior to extinction in one group and 6 h prior to extinction in the other. The group that received the reminder 10 min before did the best—and the extinction lasted up to a year.

To me, this paper offers a great entrée into a discussion of how talking about memories might alter them. This happens in all types of psychotherapy, from CBT to psychoanalysis. This paper helps to foster discussion of what actually happens when we talk about memories in psychotherapy. The idea that we stir up a memory and then work with it during a period of lability could shed light on the way that psychotherapy helps people think differently about a parent, or revise their sense of self. Students often ask me why we recommend that patients in psychodynamic psychotherapy come more than once a week—this paper actually makes me think that it might be better to see someone in the morning and then again after lunch!

HOW IS EARLY ENVIRONMENTAL EXPERIENCE ENCODED IN THE BODY?

Michael Meaney—Maternal Care, Gene Expression and the Transmission of Individual Differences in Stress Reactivity Across Generations

Sabine Herpertz and Katja Bertch—A New Perspective on the Pathophysiology of Borderline Personality Disorder: A Model of the Role of Oxytocin

As a psychoanalyst, there's nothing more exciting than studies investigating how early environmental experiences are encoded in the body. Learning about these alongside psychodynamic developmental theories enriches students' ideas about formulation and deepens their understanding of their patients. A great place to start this conversation is with epigenetics –the study of gene modification that occurs due to factors other than direct modification of the genetic code. In his paper, "Maternal Care, Gene Expression and the Transmission of Individual Differences in Stress Reactivity Across Generations," published in the *Annual Review of Neuroscience* (Meaney, 2001), Michael Meaney reviews the findings of his lab and others that, rat pups who receive more nurturing from their mothers (which translates into more licking and grooming) have decreased stress reactivity than pups who receive less. The really exciting finding is that this seems to be mediated by differential methylation of histones—the proteins around which DNA is wound in the cell nucleus. Thus, early parenting directly translates into histone methylation, which mediates gene expression—and when the gene is for the glucocorticoid receptor, the connection between good parenting and later life stress response becomes strikingly clear.

A second paper on this topic is Sabine Herpertz and Katja Bertch's 2015 "A New Perspective on the Pathophysiology of Borderine Personality Disorder: A Model of the Role of Oxytocin," published in the *American Journal of Psychiatry* (Herpertz and Bertch, 2015). Like Meaney, Herpertz and Bertch are hypothesizing about how early experience affects later behavior—here, specifically, characteristics of borderline personality disorder (BPD). They discuss the cycle in which oxytocin levels predict parental physical affection (touching and cuddling), parental care predicts childhood oxytocin levels, and childhood oxytocin levels predicts capacity for social interactions. They then review the evidence that oxytocin may mediate the triad of affect dysregulation, behavior dyscontrol, and interpersonal hypersensitivity, suggesting that oxytocin levels could be the biological mediator that translates early trauma and neglect into characteristics of BPD.

Both of these reviews are clear and seem to have been written with the clinician in mind. They are well-suited to classes on formulation and discussions of "how are patients came to be the way they are."

BRINGING THESE PAPERS TO LIFE IN PSYCHOTHERAPY CLASS

The findings covered in these papers are exciting and directly relevant to discussions about development, formulation, and psychotherapy. They don't have answers; rather, they spark questions. That's the spirit in which I use them with students. I choose them carefully—no more than one per class—and assign them alongside psychotherapy readings. For example, we might read the article about oxytocin alongside one by Kernberg when studying BPD. In a 1 h seminar, I don't spend a lot of time reviewing the article—either I do a brief review or I ask a student to do this—and then we ask the central question:

How do the findings in this article affect the way that you think about your patients and your work with them?

This is really what I want my students to consider. It's difficult to change the behavior of a borderline patient—could that be because we're having to reverse the methylation of histones? Should we decrease the time between sessions in order to facilitate memory recall? How should our psychotherapeutic work change when working with patients with prefrontal deficits?

How could psychotherapists work with neuroscientists to learn more about the mind and how to optimize psychotherapeutic interventions?

Including neuroscience in a psychotherapy curriculum helps to break down silos by modeling that psychotherapists are interested neuroscience, actively teaching these disciplines side by side, and fostering future collaboration. So, psychotherapy educators—be brave! Stick your toe in the neuroscience literature and bring your students with you. It's easier than you might imagine, fascinating, and might even contribute to the future of psychotherapy.

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The author confirms being the sole contributor of this work and approved it for publication.

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REVIEW
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State-Dependent Memory: Neurobiological Advances and Prospects for Translation to Dissociative Amnesia

Jelena Radulovic[1], Royce Lee[2] and Andrew Ortony[3]*

[1]Department of Psychiatry and Behavioral Sciences, Northwestern University, Chicago, IL, United States, [2]Department of Psychiatry and Behavioral Neuroscience, The University of Chicago, Chicago, IL, United States, [3]Department of Psychology, Northwestern University, Evanston, IL, United States

In susceptible individuals, overwhelming traumatic stress often results in severe abnormalities of memory processing, manifested either as the uncontrollable emergence of memories (flashbacks) or as an inability to remember events (dissociative amnesia, DA) that are usually, but not necessarily, related to the stressful experience. These memory abnormalities are often the source of debilitating psychopathologies such as anxiety, depression and social dysfunction. The question of why memory for some traumatic experiences is compromised while other comparably traumatic experiences are remembered perfectly well, both within and across individuals, has puzzled clinicians for decades. In this article, we present clinical, cognitive, and neurobiological perspectives on memory research relevant to DA. In particular, we examine the role of state dependent memory (wherein memories are difficult to recall unless the conditions at encoding and recall are similar), and discuss how advances in the neurobiology of state-dependent memory (SDM) gleaned from animal studies might be translated to humans.

Keywords: dissociative amnesia, state-dependent memory, episodic memory, neuronal oscillations, neuronal connectivity, animal models, excitation/inhibition dynamics, stress

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****Correspondence:***
Jelena Radulovic
j-radulovic@northwestern.edu

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INTRODUCTION

Normal states of consciousness involve an ongoing awareness of oneself and one's environment. Nevertheless, many everyday experiences such as daydreaming, losing track of time, being submerged in a play, a novel, or a movie, are manifestations of temporary dissociation from normal states of consciousness. Getting into, and especially getting out of these states is typically relatively easy, so they are usually considered to be normal. However, in some individuals, particularly those who have been exposed to psychological trauma, dissociation occurs unconsciously and cannot be controlled. In such pathological cases, dissociation is viewed as a "disruption of and/or discontinuity in the subjective integration of one or more aspects of psychological functioning, including—but not limited to—memory, identity, consciousness, perception and motor control" (Spiegel et al., 2011b). Some researchers believe that by compartmentalizing these psychobiological functions, trauma-related threats and distress can be separated from conscious awareness, preventing the experience of pain, discomfort and anxiety, and promoting coping and survival in the face of overwhelming traumatic stressors (Putnam, 1989; Herman, 1992). From this perspective, dissociation can be viewed as adaptive. However, dissociation is maladaptive when it persists and is used to cope with everyday stressors that do not pose a significant threat (Haugaard, 2004;

Schimmenti and Caretti, 2016; Choi et al., 2017). Under these conditions, dissociation can disrupt the development of self-regulatory processes in stress response systems and can lead to the development of persistent self-dysregulation and dissociative disorders (Curtois and Ford, 2009).

Based on the most prevalent symptomatology, dissociative disorders include dissociative amnesia (DA, inability to access important autobiographical and other memories), dissociative identity disorder (fragmentation of identity and formation of multiple personalities), and depersonalization-derealization disorder (detachment from self or the environment; Spiegel et al., 2011a). DA, which used to be called memory repression, is a manifestation of dissociative disorders that predominantly affects memory systems and enables individuals to detach from the past. The earliest theoretical accounts of such memory failures proposed that overwhelming stress prevents the adequate integration of traumatic and normal conscious experiences (Janet, 1889). Importantly, it was also recognized that although the trauma-related memories were inaccessible their continued existence was manifested through affective and behavioral symptoms (Janet, 1889; Breuer and Freud, 1955). Newer accounts similarly define DA as a process whereby individuals automatically lose access to (dissociate from) memories of an entire traumatic event or details of that event, resulting in significant memory gaps or in no memory at all (Wolf and Nochajski, 2013). DA can also generalize to identity and life history, causing clinically significant distress or impairment in social, occupational, affective and other important areas of functioning. Consistent with the view that dissociation is maladaptive, peritraumatic dissociation is seen as a strong risk factor for the development of PTSD (Briere et al., 2005). However, in some cases DA can also be protective, as evidenced in survivors of childhood sexual abuse suffering from DA who had less depression and anxiety than survivors without it (Coifman et al., 2007).

While improving memory access in the case of generalized DA is an important therapeutic goal, accessing specific traumatic memories can have unpredictable consequences. For some patients, it delays recovery and worsens symptoms. For example, although survivors of childhood sexual abuse suffering from DA tend to suffer less from depression and anxiety, if their memories of the traumatic event surface, these individuals are at increased risk of experiencing higher levels of traumatic symptoms compared to survivors who have never experienced DA (Bonanno et al., 2003). Similarly, the successful recall of traumatic memories can sometimes be highly stressful and can cause symptoms of PTSD or suicidal urges (Fetkewicz et al., 2000). In contrast to these observations, in other individuals, regaining access to trauma-related memories results in positive outcomes because once the memories have been accessed, psychotherapy can help such individuals understand how trauma caused their amnesia, how it disrupted their lives, and how their issues can be resolved so as to help prevent further trauma-related symptoms in the future (Staniloiu and Markowitsch, 2014; Sharma et al., 2015; Cassel and Humphreys, 2016; Markowitsch and Staniloiu, 2016).

Several mechanisms have been proposed to explain restricted access to unwanted traumatic memories. Historically, the idea was that such memories are voluntarily repressed (Breuer and Freud, 1955)—a view that has recently been re-conceptualized as executive control of memory access (Anderson and Green, 2001; Anderson et al., 2004). An alternative view proposes an automatic process wherein such memories are state-dependent in that their accessibility is critically dependent on the congruence between the encoding and retrieval conditions (Putnam, 1989; Eich, 1995; Harrison et al., 2017). Although both mechanisms might be playing a role, here we will focus on the relationship between state-dependent memory (SDM) and DA because of recent progress in the understanding of the neurobiology of SDM. The remainder of this article is divided into four main sections. First, we present a case study of an individual, which provides a vivid example of DA ("A Case Study" Section). We then, in Section "SDM as a Gateway to DA—the Human Cognitive Perspective", move on to a discussion of the cognitive foundations of SDM and, especially, of episodic memory, and lay out their relation to DA. Findings from animal and human research emphasizing neurobiological aspects of SDM are reviewed in Section Memory and SDM—a Neurobiological Perspective. In Section Implications of Neurobiological Research for Human DA", we return to the human level and present a brief discussion of the implications of our current understanding of current neurobiological knowledge for DA, after which, in Section "Revisiting Skepticism Concerning DA", we conclude with a discussion of some standard objections to the concept of DA itself.

A CASE STUDY

The complexity of stress-related disorders can best be illustrated by an example of a clinical case that demonstrates the impact of psychological trauma. The case we have chosen illustrates several common features of DA including high comorbidity with other mental disorders, an inability to recall a life-threatening traumatic memory that was readily recalled by family members, the occurrence of flashbacks after withdrawal from a hypnotic drug (clonazepam) treatment, and full recovery of the memory accompanied by significant clinical improvement following prolonged exposure (PE) psychotherapy.

"Patient *X* is a 60-year-old male who presented with new onset symptoms consistent with PTSD with dissociative symptoms, delayed expression (309.81 (F43.10)). The index trauma was a house fire 15 years ago, in which he evacuated his granddaughter and sister-in-law while suffering from smoke inhalation. Symptoms included nightmares of the fire, recurrent and involuntary memories of the event, dissociative symptoms including flashbacks, DA in the form of an inability to readily recall details about the fire, avoidance of talking about the fire, profound guilt, severe insomnia and hyperarousal. Of interest, the re-experiencing symptoms did not begin until the present time, a decade and a half after the fire, although hyperarousal symptoms have been chronic. The recent *onset of nightmares, re-experiencing and dissociative flashbacks was temporally correlated*

with a reduction and elimination of clonazepam, used to treat a longstanding severe insomnia that was resistant to Cognitive Behavioral Therapy (CBT) for insomnia. His medical history is significant for a history of childhood epilepsy and remote, pre-trauma history of left middle cerebral artery with sparing of the medial temporal lobes but damage to the left parietal lobes. His Montreal Cognitive Assessment (MoCA) score is 29, with no deficits in declarative or procedural memory, but a mild dysarthria. There is an additional adult history of psychogenic non-epileptic seizures, confirmed by inpatient video EEG recordings of grand mal and partial seizures without correlated EEG activity. He has been on long term anti-epileptic treatment that has remained stable through the period from the fire to the present, including phenobarbital 120 mg qHS and gabapentin 600 mg TID. His psychiatric history is extensive, with a diagnosis of borderline personality disorder since adolescence, with multiple inpatient psychiatric hospitalizations for suicidal ideation and at least three suicide attempts.

Chart review reveals prominent DA regarding the fire. About 1 week after the fire, he was hospitalized at two different hospitals, for nearly 2 months for intractable seizures. It was only during the second hospitalization that the diagnosis of psychogenic non-epileptic seizures was made. Extraordinarily, *no mention was made during this 2-month period of the fire by the patient nor the medical chart*, despite psychiatric consultations for suicidality. The patient retrospectively reports that from the beginning of the neurological hospitalization to the present day, he has not thought about the fire and has not discussed it with any of his health providers. His subjective experience of that time is of "waking up" in the hospital after a period of sedation in a state of shock, but *without memory, or awareness of memory, of the fire*. Interestingly, the family corroborates the account of the fire by the patient. His PTSD Checklist-Civilian Version (PCL-C) score was 64, exceeding proposed thresholds for clinically significant PTSD severity. A course of weekly PE psychotherapy was initiated. PE is an evidenced based treatment for PTSD with established efficacy (reviewed in Foa, 2006). During initial imaginal exposure sessions, the level of fear-related arousal was relatively low. The predominant source of distress was shame at not being able to prevent the fire. After six sessions, *during imaginal exposure, the levels of distress related to fear increased, to subjectively maximal levels of intensity (100% of experienced fear intensity)*. Simultaneously, the PCL-C scores began to decrease to 55. During session seven, he had a short seizure during imaginal exposure, coinciding with peak subjectively experienced fear. The seizure was consistent with previous psychogenic non-epileptic seizures. During session eight, he revealed that in the previous week, practicing imaginal exposure at home resulted in psychogenic non-epileptic seizures about 50% of time with prolonged periods of dissociative state. In session eight, session imaginal exposure was modified to be conducted with eyes open rather than closed. Additionally, when dissociative symptoms started, verbal reorienting was provided, followed by resumption of imaginal exposure. He was to practice imaginal exposure at home with his lapdog present, who has been trained to lick the patients face at signs of dissociation or seizure. At session nine, the PCL-C score for the previous week decreased further to 41, with a marked reduction in frequency of nightmares. He was able to complete PE over the course of six more sessions, without a return of seizures during session, and a final PCL-C score of 21.

In summary, this was case of delayed onset of PTSD, with onset of symptoms occurring a decade and a half after the trauma. In the interim, there was documented evidence of DA, which is relatively common in patients suffering from borderline personality disorder (Sar et al., 2014). Family members confirmed the severity of the fire and involvement of the patient. The trigger for the onset of PTSD symptoms was the elimination of a nighttime dose of clonazepam. During a course of PE, there was further reduction of DA, specifically of emotional numbing, which had previously blocked access to the subjective experience of fear of dying due to smoke inhalation and heat exposure. Although access to intense feelings of fear and distress when retrieving of details of the traumatic experience led to transient states of dissociation and even non-epileptic seizures during a session, continuing PE therapy resulted in habituation and reduction of fear and distress. The dissociative states and non-epileptic seizures did not return.

Even though in some cases, as in this one, therapy seems to be successful, in general there is disappointingly little evidence-based research to inform successful approaches to the treatment of DA. This might be due in part to a bitter controversy in the field that arose in the 1990's as to whether DA is a real phenomenon. The controversy, which came to be known as the "Memory Wars" (after the widely publicized book by Crews, 1995), was largely a reaction to psychodynamic approaches to DA (in particular those arising from cases of alleged childhood sexual abuse). Issues of central concern related to "repression" as a specific mechanism of memory inaccessibility (Breuer and Freud, 1955), as well as to the problem of distinguishing false from veridical memories (Loftus and Davis, 2006) and dissociated from non-dissociated memories (McNally, 2007). Fortunately, advances in both human and animal research in the neurobiology of memory are providing new insights in light of which many such questions can be newly addressed.

STATE-DEPENDENT MEMORY AS A GATEWAY TO DA—THE HUMAN COGNITIVE PERSPECTIVE

In seminal work on the relationship between stress and memory, Brewin et al. (1996) proposed that traumatic experiences give rise to two types of memory representations. One type results from the conscious processing of the trauma and includes accessible memories that can be expressed verbally, while the other results from the unconscious processing of the trauma. Brewin et al. (1996) referred to the result of this latter type of memorial representation as "situationally accessible knowledge," which they argued is automatically retrieved when a person is in a situation that is similar to the one in which the trauma was experienced, a view supported by many others (Eich, 1995; van der Kolk and Fisler, 1995; Whitfield, 1995).

This account of "situationally accessible knowledge" fits well the definition of the phenomenon of SDM that we discuss in depth below. However, before doing so, we need to set the stage by briefly reviewing some key concepts in human memory.

Memory Systems

Understanding the basic issues relating to memory ought to be simple: through experience and learning, we *acquire information*, we *encode* it, *retain* it for later use, and when we need it, we *retrieve* it. But, of course, it isn't that simple, in part because memory is not a unitary concept and such a bare-bones account inevitably neglects its rich complexity. Cognitive psychologists have identified all manner of different kinds of memory—iconic, haptic, echoic, short-term, working, long-term, declarative, non-declarative, procedural, semantic, episodic, implicit, explicit and more. These different kinds of memory, or memory systems, can be thought of as (collections of) different kinds of specific memories, and they are distinguished in terms of the nature of their content, their durability, and the way in which they are acquired and accessed.

The most relevant top-level aspect of the human memory system is long-term memory, which comprises information that is retained for a long time—days, weeks, months, or years, rather than seconds, minutes, or hours. Long-term memory is comprised of non-declarative and declarative memory (Squire, 1992), a distinction which is reminiscent of the classic partitioning of knowledge into *knowing how* and *knowing that* (Ryle, 1945). The brain has the capacity to store vast amounts of information that is used to organize behavior and make decisions, and much of this information is part of the non-declarative memory system, which means that it can be accessed and used automatically without the need to voluntarily retrieve it. Non-declarative memory includes procedural memory (or knowledge) such as one's knowledge of how to ride a bicycle, as well as the results of simple classical conditioning, of perceptual learning, and of non associative learning (e.g., habituation).

By contrast, declarative memories are records of specific facts and events that can normally be intentionally recalled. Memories of facts and events can be talked about, they can be articulated in language, they can be reported; hence, "declarative." The declarative memory system consists of episodic memory, with which this article is primarily concerned, and semantic memory. Individual episodic memories are representations of actual experiences that generally incorporate the spatial, sensory, and temporal information associated with those experiences, integrated into a unitary whole. In its original formulation (Tulving, 1972), the episodic memory system was characterized as the totality of a person's encoded personal experiences—an autobiographical record of experienced events and their temporal and spatial contexts. Subsequently, Tulving (1985) modified the idea, tying it more explicitly to the conscious act of remembering a past experience. On the revised view, for something to count as an episodic memory it was not sufficient that the remember merely know (or believe) that something happened to him or her. That kind of factual knowledge, even though it is knowledge about the self, is better thought of as belonging to semantic memory. Rather, Tulving proposed that the construct of episodic memory capture the awareness—the autonoetic consciousness—associated with the actual act of remembering, for it is this that bestows the "special phenomenal flavor to the remembering of past events" (p. 3). On this view, what matters is the *remembering of the experience itself* rather than the remembering of the fact of the experience (Markowitsch and Staniloiu, 2016).

The (in)fidelity of Episodic Memories

An important aspect of individual memories is their degree of fidelity. Fidelity has to do with the relation between what was experienced and what was encoded, and between what was encoded and what was retrieved, and thus concerns the integrity of the information encoded or retrieved. It is well-established that memories of meaningful information are rarely exact records of what was seen or heard (Bartlett, 1932; Bransford and Franks, 1971; Anderson and Ortony, 1975). In general, there is very little information that is encoded and retained verbatim. Instead, even at the time of encoding, what is encountered routinely contains omitted as well as elaborated and even intruded information, often the result of unconscious inferences. Thus, what is encoded is not the raw sensory or semantic input, but a representation constructed from that input. Furthermore, just as encoding is a constructive process, so is retrieval. The most celebrated early exponent of this (re)constructive view of memory is Frederick Bartlett who undertook detailed experimental work on memory for drawings and stories. Bartlett's work, and that of many after him, established conclusively that memory for meaningful material normally involves the unconscious elaboration of stored fragments of that material enhanced with general world knowledge, associations and conventional ideas and schemas. In addition, memory for such material is also influenced by subsequent exposure to relevant related information as well as by subsequent successful or unsuccessful attempts to recall it.

The basic principles relating to the constructive nature of memory encoding and retrieval mean that the fidelity of the relation between what was encountered and what is encoded can in no way be guaranteed, nor can the fidelity of the relation between what was encoded and what is or can be retrieved. Thus, even under normal conditions, memory distortions, memory failures, and even false memories are routine psychological phenomena.

Sources of Problems in Accessing Episodic Memories

The concepts of *retrieval* and *forgetting* are, of course, central to any discussion of memory and memory-related disorders. Assuming that forgetting is some sort of failure of retrieval, we can start by asking what retrieval is. One might think that retrieval is simply the process of recovering or locating information stored in memory (VandenBos, 2015). However, this kind of definition is too course-grained to be useful, not

least because it fails to acknowledge two crucially different processes, namely, *intentional* vs. *unintentional access* to stored information—the willful effort to retrieve, also called recall, vs. the incidental, unintended activation of such information, as happens in many cases of recognition and reminding where, material comes to mind unbidden. In our discussion of memory processes in humans, we shall primarily be concerned with the intentional process of *retrieval* rather than with unintentional processes, and with the nature and consequences of failures of retrieval (i.e., the forgetting) of episodic memories.

Forgetting can occur for one of two general reasons: either the to-be-remembered material itself is compromised, or access to that material is compromised. When the memory itself is compromised, forgetting can occur because its contents have degraded so that only fragments of the original memory remain, or in some cases because the memory is degraded to such an extent that there is nothing coherent to access at all. But, forgetting can also result from a failure of the retrieval mechanism to access an intact memory. In such cases, access to the to-be-recalled representation is for one reason or another, temporarily (or even permanently) blocked, as in the case of patient X, described in the case study, who for 15 years was unable to retrieve his traumatic involvement in a frightening house fire.

Of particular interest in the present context is the kind of retrieval failure that occurs when the conditions at time of retrieval differ from those that pertained at the time of encoding. Although known as SDM, this phenomenon might be thought of as a special case of blocked-access forgetting, because state-dependency could be a feature of the access mechanism rather than (or in addition to) a feature of the memory itself. This kind of state-dependent forgetting is particularly important because of its potential relevance to DA. We will therefore now discuss it in greater detail, although referring to it by its more conventional name of SDM.

Formal definitions of SDM hone in on the psychological, biological, or physical states of the rememberer. For example, dictionaries of psychology define SDM as "the tendency for information that was learnt in a particular *mental or physical state* to be most easily remembered in a similar state" (Colman, 2009 italics added), or as "a condition in which memory for a past event is improved when the person is in the same *biological or psychological state* as when the memory was initially formed" (VandenBos, 2015, italics added). State dependence is a quite general phenomenon which to some degree is characteristic of many kinds of memories. An interesting anecdotal example of its relevance to cases other than episodic memory, and which is also of some historical interest, is mentioned by Godden and Baddeley (1975). They noted that John Locke, the 17th century British philosopher, wrote of a man who, having learned to dance "to great perfection" in a room in which there was a wooden trunk, could then only perform well what he had learned in that or a similar room, and one in which was situated a similarly placed trunk. This would be an example of state-dependent procedural memory. State-dependency can also arise in simple conditioning. Indeed, the first documented experiment demonstrating SDM (Girden and Culler, 1937) was in the context of a conditioned reflex in dogs, with learning taking place under conditions quite different from normal states of consciousness. These authors showed that a conditioned reflex induced under curare could not be induced at all when the dogs were awake, there being a complete amnestic barrier between the normal and curare-induced states.

Even though it is important to recognize that state dependence is a phenomenon that occurs in the context of other kinds of memory, its occurrence in the context of episodic memories is particularly interesting because episodic memories, reflecting as they do personal experiences, are by definition the kind of memories that can be consciously recalled. In their classic experiment, Godden and Baddeley (1975), referring to their particular case of SDM as context-dependent memory, demonstrated that the recall of word lists that scuba divers had learned under water was superior when the divers were again under water than when they were on dry land. The phenomenon has also been demonstrated when acquisition of the to-be-remembered information occurred under the influence of psychoactive drugs such as alcohol (Weingartner et al., 1976) and marihuana (Hill et al., 1973); and essentially the same phenomenon, but under the label of *encoding specificity* (Thomson and Tulving, 1970; Tulving and Thomson, 1973) was demonstrated by showing that retrieval of items from episodic memory was optimal when the conditions at the time of retrieval, such as context or available cues, were the same as those at the time of encoding.

It should be noted that the fact that state-dependency is about the optimal conditions for accessing items stored in episodic memory does not mean that absent those conditions, memory access will necessarily fail. In fact, state-dependence is perhaps best be thought of as a variable that can affect the ease of access, ranging from minimal if any influence at one end of the continuum to substantial influence at the other. It might be that cases of SDM in which access to a memory is highly restricted, representing the extreme (high-influence) end of the continuum, are qualitatively different from other cases. These would be the cases of most relevance for DA.

MEMORY AND SDM—A NEUROBIOLOGICAL PERSPECTIVE

DA, flashbacks and other dissociative phenomena have frequently been observed not only as a result of traumatic stress, but also as a result of the use of dissociative drugs such as PCP, ketamine, or LSD (Brna and Wilson, 1990). However, due to ethical and regulatory issues, such drugs cannot be used in human SDM research. For this reason, most of our current knowledge on the neurobiology of SDM is based on animal studies. Using tools for visualizing and manipulating neurons directly involved in memory processing in animals (Gradinaru et al., 2010; Zhu and Roth, 2014), it is now possible to study the memory circuits that process veridical memories, false memories and SDMs (Garner et al., 2012; Ramirez et al., 2013; Liu et al.,

2014; Jovasevic et al., 2015). We are thus in an unprecedented position to explore the connection between state-dependency and memory access in DA. In fact, animal models allow us to examine extreme cases of SDM, in which memories cannot be retrieved at all under normal conditions ("complete amnestic barrier" Overton, 1991). Below, we discuss the strengths and limitations of animal approaches to episodic-like memories including SDM, highlighting the relevance of emerging findings to our understanding of DA and possibly other memory-related psychopathologies.

Modeling Episodic-Like Memories and SDM in Rodents

Robust memories of stressful experiences that persist over months or years (Gale et al., 2004) can be readily induced in experimental animals. This is typically done using contextual fear conditioning or passive avoidance learning in which animals—most often, rodents—learn to associate multisensory environmental contexts with aversive foot shocks. As evidence that such learning has occurred, upon re-exposure to the conditioning context, rodents express either freezing behavior (contextual fear conditioning if the animals cannot escape) or avoidance behavior (passive avoidance if they can escape). Such memories resemble human episodic memories in that they require the integration of spatial, multisensory, and temporal information into memory, and this integrated representation has to be accessed for freezing or avoidance behavior to occur (Fanselow, 1990; McGaugh and Roozendaal, 2002). Both in rodents and humans, these memories depend on neuroanatomical mechanisms which differ from those required for conditioning to simple cues (Kim and Fanselow, 1992; Phillips and LeDoux, 1992). The only aspect of human episodic memory that we cannot test in animal models is the subjective re-experiencing of the encoded event, for which reason we use the expression *episodic-like memory* when discussing animal research. Despite this limitation, the neurobiological basis of the processing of episodic-like memories in animals is known to be surprisingly similar to that in humans (Grillon, 2002; Milad et al., 2006; Rauch et al., 2006) and can thus be successfully used to develop mechanistic hypotheses related to memory processes.

From a neurobiological point of view, memories are most likely encoded and retrieved as sequences of neuronal activity (Eichenbaum, 2000; Hasselmo, 2005; Pastalkova et al., 2008; Carr and Frank, 2012) bound and ordered by neuronal oscillations (Lisman and Jensen, 2013). These patterns of activity vary with neuronal connectivity and other properties, such as strength of synaptic connections and responsiveness to excitatory and inhibitory input, which are determined by the genetic and molecular profile of each neuron. These features change in different brain states, sometimes resulting in state-dependent encoding of memories, as reviewed recently (Radulovic, 2017; Radulovic et al., 2017). Furthermore, it appears that even initially accessible memories can be rendered state-dependent if the brain states are manipulated at the time of retrieval (Sierra et al., 2013; Gisquet-Verrier et al., 2015). Such memories are no longer accessible under the conditions present at encoding, but instead, under the conditions present at retrieval. Thus, there is much evidence that the efficient encoding of memories, but with only limited subsequent access, is possible.

Mechanisms of SDM: the Role of Excitatory/Inhibitory Balance and Stress

The standard approach to studying SDM is to manipulate the brain states of animals by using various drugs (Netto et al., 1987; Overton, 1991; Colpaert et al., 2001; Rezayof et al., 2003). Such pharmacological approaches have unique advantages such as allowing for rigorous control over the experimental conditions (e.g., dose, injection site, memory phase), and enabling the determination of the role of individual neurotransmitter systems. This means that we can investigate mechanisms that causally contribute to memory processing in different brain states and characterize these states at different scales of neuronal function. Moreover, animal models can be easily designed to test extreme cases of SDM that completely restrict memory access, which could be particularly relevant to DA.

At the level of neurotransmission, the encoding and retrieval of episodic memories depend on the dynamics between neuronal excitation (mediated by glutamate) and inhibition (mediated by GABA; Froemke, 2015). Whereas excitatory neuronal networks are believed to play a key role in memory encoding and retrieval, inhibitory networks have been typically viewed as memory impairing (Rudolph and Möhler, 2006). However, this stance has been challenged by recent evidence indicating that while inhibitory networks do make memories quiescent, those memories nevertheless remain available for activation under particular conditions (Barron et al., 2016, 2017). Consistent with this view, many drugs used to generate SDM in animal models increase the inhibitory tone in the hippocampus (Radulovic et al., 2017). SDM can also be seen at the other extreme, namely under conditions of enhanced excitatory transmission, for example in response to psychostimulants and noradrenaline (Overton, 1991; Berridge and Waterhouse, 2003).

Just as drugs alter the local or global excitatory/inhibitory dynamics, so too do stressful experiences. In some cases, acute stress predominantly triggers release of glutamate (Popoli et al., 2011). In other stress paradigms, there are important individual variations, with some animals responding with low GABA/glutamate release (indicating relatively high excitation vs. inhibition) and others with high GABA/glutamate release (indicating relatively high inhibition vs. excitation) in the prefrontal cortex (Drouet et al., 2015). High inhibition has also been found after chronic stress in both adult (McKlveen et al., 2016) and juvenile (Albrecht et al., 2016) rodents. Notably, the effects of juvenile stress persisted throughout adulthood in a population of hippocampal neurons (dentate granule cells). These findings suggest that under some circumstances, and when stress is particularly severe (Drouet et al., 2015), the excitatory/inhibitory balance can shift towards inhibition or excessive excitation, both of which are more likely to result in SDMs than in easily accessible memories. A shift

in excitatory/inhibitory balance in the direction of increased excitation could underlie the finding in patient X described in the case study, whose loss of memory of the fire was alleviated during clonazepam withdrawal, which typically results in overexcitation.

Although the similarities between stress-induced and drug-induced SDM are suggestive, it is important to note that reliable models of stress-induced SDM have yet to be developed and validated. To date, the field has mainly focused on stress-enhanced and extinction-resistant memories (Rau et al., 2005; Tronson et al., 2010) rather than inaccessible memories. Given the advances in our understanding of memory impairing effects of stress (Todorovic et al., 2007; Maras et al., 2014; Moreira et al., 2016), studying inaccessible memories is now feasible. The development of reliable animal models of stress-induced SDM is an important future challenge for the identification of a translational link between fundamental mechanisms identified in animals and psychopathologies in humans.

Brain States That Subserve SDM

At first glance, the finding that susceptibility to SDM processing increases with the excitation/inhibition balance might suggest that SDM is a quantitative rather than a qualitative phenomenon. However, analyses at the level of network activity and connectivity indicate otherwise. Changes in the hippocampus, which is known to play important roles in processing both conscious and unconscious memories (Henke, 2010; Hannula and Greene, 2012; Shohamy and Turk-Browne, 2013), may be particularly relevant. A notable change within the hippocampus and cortex during SDM encoding under heightened tonic inhibition (using systemic infusion of the drug gaboxadol) is the increase in power of slow, delta oscillations, along with a decrease of theta and gamma oscillations (Meyer et al., 2017). At the same time, at the circuit level, the connectivity between the hippocampus and neocortical areas (retrosplenial, entorhinal and anterior cingulate cortex) is significantly reduced (Jovasevic et al., 2015; Meyer et al., 2017). Consistent with these observations, it was recently found that enhanced cortical delta oscillations causally contribute to the formation of state-dependent fear-inducing context memories during states of reduced excitation (using systemic administration of the NMDA receptor antagonist MK-801; Jiang et al., 2018).

Changes of network activity and connectivity have at least three important implications. First, they are consistent with the suggestion of Jacobs and Nadel (1998) that traumatic levels of stress lead to disconnections between memory processing brain areas. This view has been supported by recent imaging studies in patients with DA (Staniloiu and Markowitsch, 2012; Harrison et al., 2017; Thomas-Antérion, 2017). For example, patients show alterations of functional MRI imaging signals in frontal and temporal lobes (Hennig-Fast et al., 2008) with increased prefrontal and decreased hippocampal metabolic activity during testing for memory recall (Kikuchi et al., 2010). After treatment for DA, the pattern of brain activation normalized in a patient whose memories were recovered, whereas it remained unchanged in the patient whose memories were not recovered. Although these initial findings need to be confirmed in larger cohorts, they suggest a direct relationship between alterations of hippocampal and cortical activity and DA. Thus, as in other cases of memory inhibition (Anderson et al., 2004; Benoit et al., 2015), DA is often accompanied by increased activation in the dorso- and ventral-lateral prefrontal cortex, with associated deactivation in medial temporal structures, such as the hippocampus.

Second, the role of slow oscillations in SDM could explain an apparently paradoxical observation, namely, that access to traumatic memories can be facilitated not only under conditions of elevated stress, as seen in patient X during PE therapy, but also during therapies carried out while in hypnotic or relaxed states (Li et al., 2017). We know that the power of delta waves increases both during elevated arousal associated with severe stress (Kolassa et al., 2007; Ahnaou and Drinkenburg, 2016; Marshall and Cooper, 2017) and during states of sleep and relaxation (Knyazev, 2012). For example, a study of memories acquired under severe stress (near death experiences) found that the power of delta oscillations was positively correlated with memory details recalled during hypnosis, particularly with regard to the resolution, reliving, and spatiotemporal organization aspects of those memories (Palmieri et al., 2014).

Third, the findings pertaining to the relationship between delta oscillations and SDM could further our understanding of the relationship between brain oscillations and memory processes more generally. Both empirical data and computational modeling suggest that at the level of the hippocampus, memories are encoded as sequences (patterns) of neuronal activity that are combined into "chunks" of memories at the level of the cortex (Levy and Wu, 1996; Kesner and Rolls, 2015). Importantly, the size of these sequences depends on the balance between excitatory and inhibitory synaptic connections (Levy and Wu, 1996). Typically, theta oscillations are highly effective in binding components of episodic memories, however, this does not seem to be the case in human DA or extreme cases of SDM in animals. It is possible that traumatic memories and SDMs are particularly fragmented (van der Kolk and Fisler, 1995; Nadel and Jacobs, 1998) in which case slower delta oscillations might bind them more effectively than theta oscillations. However, this speculation would need to be tested experimentally.

All in all, neuroscience research in rodents demonstrates that depending on the conditions, stress-related experiences can be encoded either as robust memories or as impaired memories. According to our model, tress-related SDMs, as an example of the latter, would be particularly favored when the excitation/inhibition balance is shifted towards extremes, resulting in qualitatively different brain states in terms of brain oscillations and overall connectivity between hippocampal and cortical circuits, as illustrated in our recent work (Radulovic et al., 2017). We suggest that such states are likely to lead to the encoding of memories in more fragmented sequences that cannot be bound with high-frequency oscillations and therefore cannot be easily integrated in the hippocampal-cortical episodic memory circuits.

IMPLICATIONS OF NEUROBIOLOGICAL RESEARCH FOR HUMAN DA

Although the phenomenon of SDM has been recognized for a long time, our understanding of its underlying mechanisms is only in its early stages. Nevertheless, with advances in human neuroscience research, several findings from animal research can already be tested, and possibly translated to humans. The increasing sophistication of imaging techniques has paved the way for delineating the processing of real, imagined, and high-stress-induced memories (Palmieri et al., 2014). For example, by using dynamic causal models derived from data from EEG and fMRI studies (Legon et al., 2016), it is now possible to explore in great detail the excitatory/inhibitory balance across brain regions in humans, thus helping us to define the conditions for processing SDMs and contributing to our understanding of DA. Another line of research that could be translated to human patients deals with the potential role of neuronal oscillations in DA. To date, low frequency oscillations have been largely ignored, with most work focusing on theta, alpha, beta and gamma oscillations. However, focusing on delta oscillations could be more relevant for understanding SDM and its role in DA. Lastly, although we only touched on the role of microRNAs as regulators of cellular states, these molecules might show specific profiles in individuals with a history of traumatic stress associated with DA.

In our view, important remaining questions, both for animal and human researchers, relate to the mechanisms by which inaccessible stress-related memories might contribute to psychopathology. If consciously accessible (typically cortically processed) memories of trauma can have debilitating consequences for social behavior, affective behavior, and autonomic function, as they do for PTSD patients, there is no reason to believe that inaccessible memories (typically subcortically processed) would not have similar consequences in DA patients. In fact, one might expect inaccessible memories to have even stronger adverse effects, given the neuroanatomical proximity and connectivity to the amygdala, hypothalamus and other centers for socio-affective and autonomic regulation. Another important issue is under what conditions their successful retrieval might be beneficial or detrimental for patients. Lastly, we know little about extinction of affective (e.g., fear) and behavioral (e.g., avoidance) symptoms related to SDM or DA. More research in this area is needed, particularly in view of the fact that extinction processes themselves are sometimes state-dependent and even facilitated under increased stress levels (Self and Choi, 2004). From a basic science perspective, novel circuit approaches in neurobiology should be able to address these questions by determining the relationship between SDM and affective circuits, in the same way as they have already been applied to research with accessible memories (Ramirez et al., 2015). As already indicated, one of the challenges that we face in investigating these issues experimentally relates to the ethical problems associated with applying extreme stress to animals and humans. In animal research, this can, to some extent be circumvented by working with genetically susceptible individuals that are more likely to engage memory-suppressing mechanisms even when stress is not excessive. In the human domain, we suspect the best approach would be to invest more heavily in genetic, epigenetic, imaging and behavioral studies in patients as a way of providing additional support to existing psychotherapies.

REVISITING SKEPTICISM CONCERNING DA

In this final section, we shall make a few observations relating to skepticism surrounding the notion of DA itself (Pope et al., 1998; Piper and Merskey, 2004; McNally, 2007). In doing so, we will focus on issues pertaining to information processing and memory in general. Objections to the idea of DA can be summarized as follows: (1) encoding inaccessible memories is not a "natural capacity" of the brain; (2) there are no recovered memories because the memories in question were never lost or repressed—they were simply forgotten or not thought about in the ordinary way; (3) recovered memories are false memories; (4) there are no recovered memories because there never were any memories to lose or repress in the first place—they were never formed (e.g., due to infantile amnesia); (5) known biological mechanisms of memory show that stress can only enhance memory; and (6) if traumatic stress triggers DA, why is it found only in some traumatized individuals? We should note that whereas we are not convinced by some of the arguments adduced by DA skeptics, we nevertheless agree that raising such questions is a legitimate enterprise especially given the lack of rigorous analyses of DA in early reports.

With respect to objection (1) that encoding inaccessible memories is not a "natural capacity" of the brain (e.g., McNally, 2007), our response is unquestionably that it is, and our conviction is not based only on brain research. In fact, highly restricted state-dependent access to information is a cellular phenomenon, evolutionarily evident as early as in plants (Ku et al., 2015). Under extreme (abiotic) stress, plants completely shift their genetic expression program in such a way as to preclude access to mechanisms that regulate their normal behavior, instead allowing access to mechanisms that give rise to stress-specific adaptive behavior. Moreover, this massive reversal of information processing is regulated by microRNA molecules (Sunkar et al., 2012), which also play a prominent role in neurons and have been implicated in SDM by virtue of regulating GABA receptor levels (Jovasevic et al., 2015). Importantly, brain microRNAs can reach the blood, and can thus contribute to the assessment of processes taking place in the brain. Although more research is needed in this area, the field has already moved significantly towards understanding the relationship between blood microRNAs and psychopathologies such as schizophrenia and depression (Moreau et al., 2011). Similar studies in patients with DA could be helpful as an auxiliary diagnostic tool.

Of the remaining candidate objections two are particularly worth addressing—the "dissociated memories are merely forgotten memories" claim (2), and (3) the "recovered memories are false memories" claim. Defenders of DA as a bone fide condition claim that DA does not follow the rules of ordinary forgetting. In particular, they argue that DA is

more likely to occur after repeated episodes, which ordinarily improves remembering, and that unlike normal memory processes, dissociated memories are not sensitive to reminders (Spiegel et al., 2011b). Similarly, Waller et al. (1996) proposed that discontinuity in consciousness associated with DA is an extreme deviation from normality. They proposed that psychopathological dissociation is separate from the normative continuum of dissociation and that rather than a simple cluster of scores at the high end of a continuum, pathological DA is a completely separate construct. This position is taken by others as well (van der Kolk and Fisler, 1995; Harrison et al., 2017), and has received recent support from animal research on SDM. Nevertheless, critics of traumatic amnesia argue that there is nothing special about memories that cannot be accessed during DA (Shobe and Kihlstrom, 1997) and that in fact they represent nothing more than mere forgetting. Unfortunately, the issue of forgetting is difficult to adjudicate because the notions of "normal remembering and forgetting" remain vague. As discussed earlier, the term *forgetting* is ambiguous and quite generic because it can refer to both degraded and inaccessible memories. From a neurobiological perspective, there have been important advances in defining mechanistically different types of forgetting: neurogenesis-based forgetting, interference-based forgetting, and intrinsic forgetting (Davis and Zhong, 2017). However, all of these kinds of forgetting assume partial or complete memory loss. Regarding blocked access forgetting, other difficulties arise because there can be different causes of the memory deficits, including failure of retrieval mechanisms (Ouyang and Thomas, 2005), reactivation-induced memory modifications (Nader et al., 2000; Alberini et al., 2006), or state-dependence (Gisquet-Verrier et al., 2015; Radulovic et al., 2017). In any case, specifying the nature of normal forgetting seems to be essential for developing further the argument on forgetfulness in amnesia.

The objection (3) that recovered traumatic memories are false memories similarly suffers from vagueness as to what it is for a memory to be a false memory. Is the objection the strong, but implausible, claim that "recovered" memories are all complete fabrications, or is it the weaker claim that some (perhaps even many) of the details of such memories are erroneous? As indicated in the section on memory fidelity, there is nothing abnormal about memories being false, especially in the second sense. The problem of false memories is more serious as a societal and legal problem, but from the standpoint of memory research most of our memories are to a certain degree false. Although fragmented memories might indeed render trauma survivors more prone to form trauma-relevant false memories (Jacobs and Nadel, 1998) it is a bit puzzling why this becomes an issue only for memories that were forgotten and then remembered, as in DA, and not for all of our memories, especially given the ease with which false memories can be produced, even in the laboratory (Roediger and McDermott, 1995; Wade et al., 2007). To complicate matters further, in parallel with false memories, another, apparently very robust and quite opposite phenomenon becomes pronounced as we age. This is the "reminiscence bump" whereby in older people early memories start to be over-represented in what they spontaneously recall, resulting in remembering even those early life events to which access has long been denied (Koppel and Rubin, 2016). Thus, rather than taking sides in this debate, it might be more helpful to intensify research in psychology and neurobiology that attempts to differentiate false from veridical memories. A recent study suggests that this might be possible, by demonstrating discrete patterns of brain activity during processing of true, imagined, and high stress-related memories (Palmieri et al., 2014).

We believe that the objection (5) that stress only enhances memory can be rejected on the basis of neuroscientific evidence for memory suppressing effects of stress (recently reviewed, Moreira et al., 2016), and the objection (4) that there can be no recovered memories because such putative memories were never formed in the first place, is an untestable proposition and therefore devoid of empirical content. Neither we, nor the proponents of such a claim, can ever provide any evidence of the non-existence of something.

Finally, Piper and Merskey (2004) have expressed a general concern about the relationship between trauma and dissociative disorders because, among other things, (6) many individuals experience trauma but do not develop the disorder. Although a number of retrospective and prospective studies have identified the role of chronic childhood trauma in the development of dissociative disorders, trauma, although necessary, has never been considered to be sufficient for their emergence (Sanders and Giolas, 1991; Ogawa et al., 1997). We do not find this to be a compelling objection partly because it is now well established that there is no unitary response to traumatic stress. But more important, this kind of wholesale rejection of individual differences is inconsistent with the fact that many genetic, epigenetic and environmental factors confer susceptibility, resilience, or resistance to different psychopathologies.

To sum up, we believe that strong clinical evidence, compelling neurobiological evidence, and well-grounded theoretical arguments all lead to the conclusion that DA is a real phenomenon and that modern advances might enable us to distinguish between legitimate cases of DA on the one hand and contrived cases on the other. Furthermore, we believe that we have provided some convincing reasons for supposing that state dependence constitutes a good explanation of at least some of the mechanisms that underlie DA.

AUTHOR CONTRIBUTIONS

JR wrote parts of the overview, the section on neurobiological mechanism and conclusion. RL provided the case study and associated material, and AO wrote substantial parts of the overview and conclusion and the section on cognitive perspective. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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frontiers in Behavioral Neuroscience

REVIEW
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Not Just Nonspecific Factors: The Roles of Alliance and Expectancy in Treatment, and Their Neurobiological Underpinnings

Sigal Zilcha-Mano[1], Steven P. Roose[2], Patrick J. Brown[2] and Bret R. Rutherford[2]*

[1]Department of Psychology, University of Haifa, Haifa, Israel, [2]New York State Psychiatric Institute, Columbia University College of Physicians and Surgeons, New York, NY, United States

Therapeutic factors such as alliance and expectancy have been found to greatly affect treatment outcome in both psychotherapy and psychopharmacotherapy. Often, these factors are referred to as nonspecific because of their common roles across treatment modalities. Here we argue that conceptualizing such factors as nonspecific is not accurate at best, misleading at worst and may undermine treatment outcome across various modalities. We argue that alliance and expectancy contain both a trait-like common factor component and a state-like specific effect, and that it is clinically, conceptually and methodologically critical to disentangle the two. In other words, both alliance and expectancy may also function as active ingredients of treatment, leading to better outcome. We review the literature regarding the neurobiological underpinnings of alliance and of the expectancy effect, and suggest how future studies on the neurobiological basis of these effects can shed further light on the potentially distinct mechanisms of the trait-like and state-like components of each therapeutic factor.

Keywords: alliance, expectancy, common factor, nonspecific factors, psychotherapy, mechanisms of change, process research

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Arash Javanbakht,
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Jon-Kar Zubieta,
University of Michigan, United States
Anthony S. Joyce,
University of Alberta, Canada

****Correspondence:***
Sigal Zilcha-Mano
sigalzil@gmail.com

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One of the most debated questions in psychotherapy research is whether psychotherapies, psychopharmacotherapy and other treatments for mental health operate mainly through specific or nonspecific common factors (Mulder et al., 2017). The division of potential factors into specific and nonspecific has become a common framework for conceptualizing the factors affecting the process of therapeutic change. Theorists and researchers generally refer to specific effects as those factors that are described in treatment manuals and are considered specific to a psychotherapeutic orientation (e.g., cognitive restructuring in depression, exposure in anxiety disorders, or interpretations of transference) or the active chemical ingredients in a drug (e.g., increasing the extracellular level of the neurotransmitter serotonin by limiting its reabsorption into the presynaptic cell as with SSRIs). By contrast, nonspecific and common factors refer to those factors that are shared across most if not all forms of therapy. Typical examples of such factors are the therapeutic alliance between patients and their therapist or physician, and patients' levels of expectancy regarding the process and outcome of treatment (Rosenzweig, 1936; Laska et al., 2014).

The division of factors into one of the two categories generally positions specific factors as the ones that are under the therapist's control and need to be in the focus of therapist's attention when seeking to improve treatment outcome. Nonspecific or common factors, by contrast, are those that everyone agrees are part of successful treatment, but at the same time are often taken for granted or considered to be factors that are outside of the therapist's control. For example, the ability to form a strong alliance is often perceived strictly as a byproduct of the patients' ability

to form an adaptive relationship with others, and not something that the therapist can influence (DeRubeis et al., 2005). Given the division to specific vs. non-specific factors, it is not surprising that many psychotherapy research manuals describe techniques related to specific factors, and most therapist training focuses on such factors, and that in psychopharmacotherapy, most of the time and money allocated by pharmaceutical companies is to establish the mechanism of action of the drugs. Similarly, the knowledge derived from the division of factors into specific and nonspecific has produced few manuals that describe how to improve alliance, and little training has been devoted to this subject, especially in psychopharmacotherapy. Several notable exceptions in psychotherapy research include the work by Safran and Muran (2000) on training therapists in repairing alliance ruptures, and the work by Stiles and colleagues on therapists responsiveness to patient requirements and characteristics (Stiles, 2013; Kramer and Stiles, 2015). Similarly, despite the extensive knowledge produced by empirical studies regarding the important role of expectancy in treatment, no manual exists on techniques to boost expectancy. The scarce attention paid to the so-called nonspecific factors in manuals and training stands in contrast to the findings that they explain a significant amount of variance in treatment outcome. At least in the cases of alliance in psychotherapy and of expectancy in psychopharmacotherapy, meta-analyses and empirical studies suggest that they are stronger predictors of outcome than are specific psychotherapy techniques (Horvath et al., 2011 vs. Webb et al., 2010), and that they have a strong effect relative to the active effects of a drug (Rutherford and Roose, 2013).

We argue that treating therapeutic factors that have been found to be some of the stronger predictors of outcome as "nonspecific" greatly impairs the ability to fully understand their implications and realize their potential to bring about better therapeutic outcomes (Laska et al., 2014). We argue further that the distinction between common and specific factors is fundamentally problematic, and that each nonspecific factor may include both specific and nonspecific components. In other words, each such ingredient of the treatment may serve as a common facilitating environment and be deliberately used as an active ingredient of treatment, leading to better outcome. We support our argument using the cases of two factors commonly defined as nonspecific, alliance and expectancy, with examples from psychotherapy and psychopharmacotherapy. We present the available knowledge regarding the neurobiological basis of each, and suggest how the framework proposed here can be used to investigate potential distinct neurobiological mechanisms underpinning the specific and non-specific components of each therapeutic factor.

THE ROLES OF THE WORKING ALLIANCE IN TREATMENT

Common vs. Specific Roles of Alliance in Treatment

The relationship between the patient and the therapist or physician has been found to have a crucial effect on the success of any treatment, as has been demonstrated both indirectly, through meta-analyses testing the effect of the number of visits with the therapist or physician on outcome, and directly, focusing on explicit measures assessing the therapeutic relationships. Some of the indirect support for the importance of the therapeutic relationship is derived from studies and meta-analyses demonstrating that across psychotherapies (Falkenström et al., 2016), and even in antidepressant medication (ADM) treatment, the number of meetings with the therapist, which may represent opportunities for therapeutic interaction, affects treatment outcome. For example, meta-analyses suggest that in both placebo and ADM conditions more visits with the treating physician resulted in significantly greater symptom reduction (Rutherford et al., 2014). Although the effects were common across conditions, highlighting the common factor component of the interactions with the therapists, the effects also showed specificity, and were significantly more robust in the placebo condition. For example, it has been demonstrated that for patients receiving placebo, where no other active treatment is administered, the interactions with the physician may play a more active role than for patients receiving ADM. Among placebo recipients, between weeks 2 and 6, patients with weekly visits improved by 4.24 points on the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), whereas those with one fewer visit improved by 3.33 points, and those with two fewer visits improved by 2.49 points (Posternak and Zimmerman, 2007). Additional visits explained approximately 50% of the symptom change observed between weeks 2 and 6 in patients receiving placebo. The magnitude of this effect was about 50% lower for participants receiving active medication.

A more recent meta-analysis further suggests that intensifying supportive care from 6 to 10 visits over 12 weeks resulted in a reduction of the average medication vs. placebo difference from 12.2% to 0.4% (Rutherford et al., 2014). Additional support to the specificity of the effect of visit frequency in placebo vs. ADM comes from another recent meta-analysis, showing that the increase in visit frequency in randomized controlled trials (RCTs) over the decades may, at least partly, account for the rise in placebo response at an average rate of 7% per decade over the past 30 years (Furukawa et al., 2016). Thus, visit frequency shows an effect across treatment modalities, supporting the common factor component of alliance. Moreover, the specificity of the effect in the placebo vs. medication conditions supports the specific factor component of alliance. This specific effect may be explained by additional visits providing additional opportunities for supportive empathic interactions with the physician (Rutherford and Roose, 2013). Indeed, studies suggest that the placebo effect is larger in a group receiving acupuncture treatment by a warm, empathic practitioner than in a group receiving treatment by a neutral practitioner (Kaptchuk et al., 2008; Kelley et al., 2009).

Decades of empirical research provided additional direct support of the importance of a strong therapeutic relationship for the success of treatment, both as a common and as a specific factor. These studies assessed the associations between measures of the therapeutic relationship, most commonly

defined as the working alliance, and treatment outcome. The working alliance is commonly defined as the emotional bond established in the therapeutic dyad, and the agreement between the two about the goals of therapy and the tasks necessary to achieve them (Bordin, 1979; Hatcher and Barends, 2006). Meta-analyses have consistently demonstrated that stronger alliance is associated with better treatment outcome across treatment modalities, both in various psychotherapies (based on a data from more than 30,000 patients; Flückiger et al., 2018) and in psychopharmacotherapy (N = 1,065 patients; Totura et al., 2017).

Theoretical conceptualizations posit that the alliance plays a more active role in some treatments than in others (Safran and Muran, 2000; Castonguay et al., 2010), arguing, for example, that in cognitive behavioral treatments (CBTs) alliance serves the role of a nonspecific factor, enabling the effective use of various CBT techniques, whereas in alliance-focused treatment (AFT) it serves as a mechanism of change in itself. For decades, studies have failed to demonstrate that the extent to which alliance plays an active role in affecting treatment outcome differs by treatment modality. Only in recent years, with advances in trial design (notably, session-by-session measurement of the alliance) and in statistical methods to disentangle within- and between-patient variances (Wang and Maxwell, 2015)[1], has it become possible to thoroughly and systematically examine the distinct roles that alliance plays in treatment success, and to differentiate between the roles of alliance as a common and as a specific factor.

Recent studies demonstrate the importance of separating the trait-like and state-like components of the alliance, each of which play a distinct role in treatment (Zilcha-Mano, 2016, 2017). The trait-like component refers to the way in which trait-like characteristics of the patients, such as their ability to form satisfying relationships with others, affect their ability to create, with their therapist, the environment required to conduct any effective treatment. The trait-like component of alliance is a product of the patients' (and the therapists') trait-like characteristics, such as attachment orientation. Some individuals have better trait-like capacity to form strong and satisfying relationships with significant others. Empirical studies suggest that these capabilities affect their tendency to create a strong helping relationship with their therapist (Barber et al., 2002; Haggerty et al., 2009; Zilcha-Mano et al., 2014, 2015a), which is the environment facilitating the conduct of any effective treatment. Indeed, patients with such adaptive trait-like characteristics improve more following treatment than do patients without such characteristics (Hoffart et al., 2013; Zilcha-Mano and Errázuriz, 2015; Zilcha-Mano et al., 2015c). This component, however, is not sufficient in itself to induce change, and it is mainly a product of other trait-like characteristics of the patient.

By contrast, the state-like component of alliance serves as a mechanism of change in itself, such that changes in this component of the alliance are the cause of subsequent symptomatic change (Zilcha-Mano, 2017). The state-like component represents the role of alliance as an active ingredient, capable of inducing therapeutic change in itself. During the process of therapeutic change, the patient develops abilities to form a strong and satisfactory alliance with the therapist, resulting in better outcomes. Empirical studies suggest that state-like changes in alliance significantly predict subsequent treatment outcome over the course of treatment (Falkenström et al., 2013; Zilcha-Mano and Errázuriz, 2015; Zilcha-Mano et al., 2015c), supporting their role in bringing about therapeutic change. The state-like component may function as an active ingredient, whereas the trait-like component may act as a common/non-specific one.

Recent empirical studies have demonstrated that treatments differ in their state-like effect of alliance on outcome, but not in their trait-like effect (Zilcha-Mano, 2016, 2017), further supporting the distinction between the portion of the alliance that serves as a common factor across treatment, and the portion that has a specific effect in treatments in which the alliance is expected to be an active ingredient. In these studies, the state-like component was found to have a greater effect on outcome in treatments in which alliance is conceptualized as a mechanism of change, such as in AFT, as opposed to treatments in which it is conceptualized as a common factor, such as in CBT (Zilcha-Mano et al., 2016). The state-like component was also found to have a stronger effect on outcome in placebo than in the ADM condition (Zilcha-Mano et al., 2015b). Moreover, the state-like component was found to have a stronger effect for patients with relatively poor capabilities to form satisfying relationships with others (Zilcha-Mano and Errázuriz, 2017), such that the state-like alliance had a stronger effect on outcome for those with more vs. less interpersonal problem. Taken together, studies suggest that state-like alliance may have a specific effect for those who have more interpersonal problems, and in treatment in which the alliance is conceptualized as an active ingredient. Recent studies further suggest that the magnitude of the state-like effect of alliance on outcome can be manipulated by providing therapists with continual feedback on alliance, as rated by their patients, throughout the course of treatment (Zilcha-Mano and Errázuriz, 2015). Taken together, these studies support both a common factor component of alliance and a clear specific component, and they demonstrate that the state-like component is not merely a nonspecific factor, but rather can be manipulated and used for treatment success.

Neurobiological Underpinning of the Working Alliance

Studies are only now starting to illuminate the neurobiological basis of the effect of alliance. Most of this literature is still tentative, referring to neurobiological mechanisms that have the

[1]State-like and trait-like components can be disentangled by untangling between- and within-patient variance in the alliance and its effect on outcome. Several methods are available for disentangling between- and within-patient effects in longitudinal data, including centering and detrending of the variable. Centering is the statistical operation of subtracting from each individual's measurements the mean of that individual's measurements. Detrending is the statistical operation of removing the time trend, in addition to centering. Using detrending methods, it is possible to control for the effect of time while examining the relation between the dependent and independent variables. For more information about the two methods, see Wang and Maxwell (2015).

potential to serve as markers of the alliance, but were never explicitly tested as such. Some of the most promising paths include the literature on "mirror neurons", originally discovered in the premotor cortex of monkeys, which are activated when an individual observes an activity, in a similar way to when performing it (Gallese et al., 1996). Activation of these areas was found to be related to empathy, and deficits were linked to disorders characterized by interpersonal impairments, such as autism (Dapretto et al., 2006; Iacoboni and Dapretto, 2006; Cattaneo and Rizzolatti, 2009; Le Bel et al., 2009).

Another promising path involves the role of hormones, such as oxytocin and cortisol, as potential bio-markers. It has been suggested that the effects of comforting interactions with a therapist on outcome, and their role in regulating stress and inflammation, may be mediated in part by the release of oxytocin (Brown and Brown, 2015). Administration of oxytocin has been shown to regulate stress at a variety of levels, including decreasing blood pressure and the stress hormone cortisol, as well as increasing progesterone, a regulatory hormone that restores GABAergic tone following activation of the hypothalamic-pituitary-adrenal axis (Childs et al., 2010). To our knowledge, only one study to date has examined empirically the biomarkers of alliance (Zilcha-Mano et al., 2018b). The study focused on oxytocin and found converging associations between both self-reported alliance and behavioral coding of alliance by external coders, and changes in oxytocin during psychotherapy sessions throughout treatment. These associations were found only after disentangling state-like and trait-like effects, further supporting the importance of untangling the two components. Future studies can use the empirical data collected on the two distinct components of alliance, the state-like and the trait-like, to investigate potential distinct neurobiological markers of each component. It may be the case that the same neurobiological systems are involved in both but in different ways, or that different systems are active in each one. For example, greater increase in oxytocin during the sessions may be found in conditions in which the specific component of alliance is active. Similarly, other agents, such as cortisol, may be at work whenever the common factor component of alliance is dominant. For example, in sessions which include extinction-based interventions, superior therapeutic gains were found when cortisol levels where higher than lower (Meuret et al., 2015).

THE ROLES OF EXPECTANCY IN TREATMENT

Common vs. Specific Roles of Expectancy in Treatment

Expectancy refers to the patients' beliefs about whether and how much they expect to improve as the consequence of the treatment (Rutherford et al., 2017b). Expectancy can be conceptualized as including both a facilitating component, which is common across treatments, and an active therapeutic component (Zilcha-Mano et al., 2018a). The trait-like component refers to individual differences between patients in their general tendency to show high levels of expectancy, which is a product of the patients' other characteristics, such as degree of general optimism vs. pessimism, perceived locus of control, and other psychological factors. By contrast, the state-like component refers to the changes in expectancy within individual patients over the course of treatment, which may be related to events in the treatment process. The vast majority of studies have focused on the trait-like component of expectancy, arguing that it can serve as a common factor across therapeutic modalities (Kirsch, 1990; Rutherford and Roose, 2013). This claim has been supported by accumulating findings, demonstrating the effect of trait-like expectancy across treatment modalities (Constantino, 2012). For example, a secondary analysis based on data collected in the Treatment of Depression Collaborative Research Program showed that higher levels of expectancy at baseline were associated with higher likelihood of complete response, and lower level of depression post-treatment across all four treatment conditions: CBT, interpersonal psychotherapy (IPT), imipramine with clinical management (CM) and placebo with CM (Sotsky et al., 1991). A recent meta-analysis of the association between patients' expectancy and post-treatment outcome across a variety of psychotherapies and clinical contexts further supports the importance of expectancy across treatment modalities (Constantino et al., 2018): based on the data of 12,722 patients across 81 independent samples, a small but significant effect emerged, according to which higher levels of expectancy were associated with better treatment outcome.

Although most of the literature on expectancy has focused on the common factor role of trait-like expectancy, there are promising findings to support also a specific role for expectancy, especially in the above-mentioned meta-analysis and in the latest empirical literature on expectancy. In addition to demonstrating the role of expectancy as a common factor across treatment modalities, the meta-analysis also supports the specificity of the effect, such that some patients may benefit more than others from increased expectancy for the success of treatment (Constantino et al., 2018). Specifically, the effect of expectancy on outcome is weaker as patients age. Similar findings regarding the specificity of the expectancy effect in younger vs. older adults have been demonstrated in psychopharmacotherapy as well (Rutherford et al., 2017b; see also Rutherford et al., 2017a).

Studies further suggest that expectancy may increase during treatment and that such increases may affect treatment outcome. Higher levels of expectancy were found to follow more competent use of techniques (for example, in delivering CBT for generalized anxiety disorder), and the higher levels of expectancy were in turn associated with better post-treatment outcome (Westra et al., 2011). In another study, stronger early alliance was related to higher patient expectancy, which in turn was associated with fewer post-treatment interpersonal problems (Vîsla et al., 2018). Although these studies attest to the potential promising effect of state-like expectancy, they did not manipulate expectancy, nor did they examine how expectancy changes over treatment. Because expectancy is generally perceived as a common nonspecific factor and not as a factor that includes a state-like component that can be increased during treatment,

almost all studies on expectancy assessed it only at baseline or in early treatment (Constantino et al., 2018). Yet, several studies have focused directly on state-like expectancy and demonstrated its effect on treatment outcome. Recently, a prospective randomized trial manipulated expectancy and tested the effect of such manipulation on outcome. The study showed that increasing pre-treatment expectancy levels by manipulating patients' chances of receiving ADM vs. placebo (increasing it from 50% to 100% probability) resulted in greater reduction in symptoms (Rutherford et al., 2013, 2017b). These findings are further supported by a series of meta-analyses demonstrating that patients who know they are receiving medication, that is, those in comparator or open trials, show significantly greater medication response (mean of 15% higher) than those receiving medication as part of a placebo-controlled trial, who do not know whether they received medication or placebo (Rutherford et al., 2009, 2017b). Consistent with these results, in their meta-analysis, Papakostas and Fava (2009) reported that the probability of receiving placebo in a clinical trial was negatively correlated with antidepressant and placebo response, such that for each 10% increase in the probability of receiving placebo, the probability of antidepressant response decreased 1.8% and the probability of placebo response decreased 2.6%.

The studies on the effects of pre-treatment expectancy manipulation on outcome shed important light on the potential for augmenting expectancy as a tool for improving treatment efficacy. This literature, however, is limited to pre-treatment expectancy, and does not account for changes in expectancy during treatment. A recent study from our group focused on the state-like component of expectancy and showed that state-like changes in expectancy indeed occur during the course of treatment, both in the ADM and the placebo conditions (Zilcha-Mano et al., 2018a). The study further suggested that state-like changes in expectancy are not merely a byproduct of changes in symptoms, but rather predicted subsequent changes in symptoms. Taken together, the findings support significant effects of both a trait-like, non-specific common factor component and a state-like specific active ingredient component, of expectancy on outcome.

Neurobiological Underpinning of Expectancy

Similarly to the literature on alliance, studies are only now starting to cover the neurobiological basis of the effect of expectancy. Most of this literature refers to neurobiological mechanisms that have the potential to serve as markers of expectancy, based on their roles in emotional appraisal and in placebo analgesia. Accumulating studies have established that the prefrontal cortex (PFC) is critical to the cognitive regulation of emotion, particularly the dorsolateral, ventrolateral and ventromedial prefrontal cortices (DLPFC, VLPFC and VMPFC; Ochsner and Gross, 2005). PFC regions reciprocally connect with subcortical areas such as the amygdala, nucleus accumbens (NAcc) and insula, which are important for appraising the aversive or rewarding properties of stimuli (O'Doherty et al., 2002). Focusing on placebo effect in major depression, studies demonstrate the important roles of prefrontal and striatal regions as well as of the opioid system (e.g., Peciña et al., 2014).

It has been suggested that a PFC-amygdala pathway underlies a negative appraisal process, leading to the generation of negative emotional responses to stimuli (Wager et al., 2008). In studies of placebo analgesia, expecting pain relief before a painful stimulus leads to increased activation in the DLPFC/VMPFC, decreased activation of the amygdala and insular regions, and increases in NAcc activation (Wager et al., 2004). These findings suggest that expectancy may lead to improvement in depressive symptoms by reversing depressed patients' mood-congruent processing bias toward negative emotions, and ameliorating impaired reward functioning (Chiu and Deldin, 2007; Vallance, 2007). There is evidence to suggest that antidepressant treatments may indeed function by normalizing these pathological increases in limbic activity (Fu et al., 2004; Arce et al., 2008). Recent findings by our group suggest that that manipulation aimed at raising expectancy in patients with MDD reduced activation in the left amygdala, which in turn resulted in a more effective treatment.

An ongoing trial by our group seeks to disentangle the trait-like and state-like components of expectancy and to investigate their distinct potential neurobiological underpinnings. For example, based on the accumulating literature, it is possible to cautiously suggest that white matter hyperintensities (WMH) may underlie the effect of the state-like component of expectancy. WMH have been associated with poor response to antidepressants (Simpson et al., 1997; O'Brien et al., 1998). According to the vascular depression model, vascular lesions in deep white matter tracts disconnect prefrontal antidepressant response in depressed patients, so that WMH results obtained with serotonergic medications are less efficacious in the presence of this structural brain pathology. WMH burden was related to especially high limbic hyperactivity in response to emotional face stimuli (Aizenstein et al., 2011). WMH damage is assumed to interrupt the neural circuitry underlying expectancy-based placebo effects. Such damage is not expected to interfere with the formation of expectancies, therefore the common factor component is not expected to be affected. Rather, WMH damage is expected to be related to difficulty updating and maintaining appropriate treatment expectancies in response to new information regarding the treatment being received. The vascular damage to frontostriatal tracts may limit the top-down modulation of limbic and striatal structures necessary for depressive symptom change. Thus, the specificity of WMH as an underlying neurobiological mechanism for state-like but not trait-like expectancy can be expected.

Additional support for the state-like component of expectancy comes from studies demonstrating that the update of expectation over time may influence the response to placebo in the treatment for pain (Peciña et al., 2014; Schafer et al., 2018). Specifically, the discrepancy between expectations and subjectively rated effectiveness was found to be associated with placebo analgesic responses, and with the activation of regional m-opioid neurotransmission in a substantial number of regions implicated in opioid-mediated antinociception. The largest placebo responses were observed in those with low expectations and high subjective effectiveness (Peciña et al., 2014).

CONCLUDING REMARKS

The most recent studies on both expectancy and alliance suggest that these two central examples of common, nonspecific factors contain both common, trait-like effects across studies, and specific effects, which can be manipulated to affect treatment outcome. Separating trait-like and state-like components is of great importance for conceptual, clinical and methodological reasons. Conceptually, separating trait-like and state-like components is critical to move toward a comprehensive perspective that replaces the one-dimensional, partial understanding of common factors that is prevalent today. Clinically, the separation may provide additional tools for therapists to improve treatment outcome. Expanding the therapist's repertoire of tools is essential for moving toward personalized medicine, which endeavors to make use of the most beneficial individually-tailored tools in the treatment of each patient. For example, developing a manual to improve treatment expectancy may be beneficial across treatment modalities (the common factor expectancy component), and especially beneficial with certain populations (the state-like expectancy component). Such information can be particularly valuable in treatment selection processes with populations such as the elderly, which showed clear deficits in the ability to benefit from manipulations aimed at boosting expectancy (Rutherford et al., 2017a,b). The methodological literature also demonstrates how crucial it is to disentangle these two components if one seeks to explore causal relationships during treatment (Curran and Bauer, 2011; Wang and Maxwell, 2015). Our argument for disentangling the trait-like and state-like components of what was previously referred to as "nonspecific" factors is also consistent with progress toward identifying commonalities between treatments and at the same time identifying the uniqueness in each. For example, common patterns of symptom reduction (such as sudden gains) have been identified across treatment modalities, but their precursors were found to be unique and specific for each treatment (Tang and DeRubeis, 1999; Andrusyna et al., 2006).

As we demonstrated using the cases of expectancy and alliance, common factors are associated with therapeutic outcome across treatments. The strength of this effect, however, is not common (the effect may be greater in some treatments and in some populations than in others, such as in younger vs. older individuals), and can even be manipulated. Labeling these therapeutic ingredients as nonspecific may result in underestimating their role and treating them as a minor, unchangeable part of treatment. Although we based our arguments on the most central factors identified in the literature as common nonspecific factors, we believe that implementing the suggested framework for differentiating trait-like and state-like effects can be instrumental in revealing the components of many of the constructs that have been referred to as nonspecific factors. Note further that although we discussed alliance and expectancy separately, they are not unrelated but rather interdependent constructs (Vîsla et al., 2018). For example, it has been suggested that higher patient pre- or early-treatment expectancy is related to stronger alliance, which in turn correlates with better outcomes (Yoo et al., 2014; Vîsla et al., 2018).

It is of great importance to establish neurobiological signatures for the effects of therapeutic factors in treatments, especially to examine whether the state-like vs. trait-like components of each factor are based on distinct neurobiological signatures. Such signatures may help demonstrate the distinct effect of each component in treatment. Neurobiological markers have also the potential to complement and improve the accuracy of clinical assessment of the process and outcome of treatment. Future studies on state-like and trait-like components of therapeutic factors will be instrumental in designing therapeutic interventions that make use of the heterogeneity of expectancy and alliance effects. It is reasonable to expect that not all patients will derive the same benefits from each therapeutic factor. Therefore, such studies are critical for progress toward personalized treatment and for producing actionable, prescriptive information about which interventions are best suited for which patients.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the conceptualization of the idea and the writing of the manuscript.

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Changes in Functional Connectivity Following Treatment With Emotion Regulation Therapy

Matthew A. Scult[1,2], *David M. Fresco*[3,4]*, *Faith M. Gunning*[1], *Conor Liston*[1,5], *Saren H. Seeley*[6], *Emmanuel García*[7,8] *and Douglas S. Mennin*[9]

[1]Department of Psychiatry, Weill Cornell Medicine, New York, NY, United States, [2]Department of Psychology & Neuroscience, Duke University, Durham, NC, United States, [3]Department of Psychological Science, Kent State University, Kent, OH, United States, [4]Department of Psychiatry, School of Medicine, Case Western Reserve University, Cleveland, OH, United States, [5]Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY, United States, [6]Department of Psychology, University of Arizona, Tucson, AZ, United States, [7]The Graduate Center, City College of New York, City University of New York (CUNY), New York, NY, United States, [8]Hunter College, City University of New York, New York, NY, United States, [9]Department of Counseling and Clinical Psychology, Teachers College, Columbia University, New York, NY, United States

Emotion regulation therapy (ERT) is an efficacious treatment for distress disorders (i.e., depression and anxiety), predicated on a conceptual model wherein difficult to treat distress arises from intense emotionality (e.g., neuroticism, dispositional negativity) and is prolonged by negative self-referentiality (e.g., worry, rumination). Individuals with distress disorders exhibit disruptions in two corresponding brain networks including the salience network (SN) reflecting emotion/motivation and the default mode network (DMN) reflecting self-referentiality. Using resting-state functional connectivity (rsFC) analyses, seeded with primary regions in each of these networks, we investigated whether ERT was associated with theoretically consistent changes across nodes of these networks and whether these changes related to improvements in clinical outcomes. This study examined 21 generalized anxiety disorder (GAD) patients [with and without major depressive disorder (MDD)] drawn from a larger intervention trial (Renna et al., 2018a), who completed resting state fMRI scans before and after receiving 16 sessions of ERT. We utilized seed-based connectivity analysis with seeds in the posterior cingulate cortex (PCC), right anterior insula, and right posterior insula, to investigate whether ERT was associated with changes in connectivity of nodes of the DMN and SN networks to regions across the brain. Findings revealed statistically significant treatment linked changes in both the DMN and SN network nodes, and these changes were associated with clinical improvement corresponding to medium effect sizes. The results are discussed in light of a nuanced understanding of the role of connectivity changes in GAD and MDD, and begin to provide neural network support for the hypothesized treatment model predicated by ERT.

Keywords: generalized anxiety disorder, major depressive disorder, worry, decentering, reappraisal, emotion regulation, resting state functional connectivity

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***Correspondence:**
David M. Fresco
fresco@kent.edu

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INTRODUCTION

Major depressive disorder (MDD) and generalized anxiety disorder (GAD) are two prevalent disorders with lifetime prevalence estimates ranging from 17 to 41% for MDD and 6% to 14% for GAD (Kessler et al., 2005; Moffitt et al., 2010). These conditions are also highly comorbid with one another (Kessler et al., 2003) which may account for a sub-optimal treatment response with otherwise efficacious treatments (Farabaugh et al., 2010, 2012). Given these high rates of diagnostic comorbidity and shared surface level clinical features, newer systems of nosology place MDD and GAD in a shared group that is commonly called the "Distress Disorders" (Watson, 2005). In addition, transdiagnostic approaches (e.g., Mennin et al., 2013; Mennin and Fresco, 2014; Barlow et al., 2017) have sought to identify common underlying disorder processes that cut across classification systems predicated primarily on symptom presentation (e.g., Nolen-Hoeksema et al., 2008; Watkins, 2008).

One candidate transdiagnostic feature common to distress disorders, especially MDD and GAD, is negative self-referentiality (e.g., worry, depressive rumination) which often takes the form of repetitive or perseverative reactive cognitive processes (Mennin and Fresco, 2013; Olatunji et al., 2013; Ottaviani et al., 2016). Negative self-referentiality characterizes the mental activity of individuals when they experience a discrepancy between their current emotional/motivational state and a representation of the future (i.e., planning), the past (i.e., failures/losses), or an idealized self (i.e., self-criticism). This self-conscious ability is normative and crucial for managing a world in which there is ambiguity and uncertainty (e.g., Mennin and Fresco, 2014). However, the tendency to engage in self-referential mental activity can become negatively reinforced *via* a perceived reduction in aversive emotions (Borkovec et al., 2004; Nolen-Hoeksema et al., 2008) especially during highly contrasting emotional states (i.e., positive emotions followed by negative emotions; Newman and Llera, 2011). Further, the propensity to engage in negative self-referentiality can result in considerable deficits in behavioral learning (Lissek, 2012; Whitmer and Gotlib, 2013).

Increasingly, findings from basic and affective science are converging on the neurobehavioral underpinnings of normative and disordered self-referentiality and its association with disorders such as MDD and GAD. For instance, considerable evidence identifies aberrant or excessive neural activity particularly in the default mode network (DMN; Hamilton et al., 2012, 2013; Whitfield-Gabrieli and Ford, 2012; Chen and Etkin, 2013; Andreescu et al., 2014). Similarly, task-based studies examining trait levels of worry or depressive rumination (Paulus and Stein, 2010; Hamilton et al., 2011) or instructions to worry or ruminate (Cooney et al., 2010; Paulus and Stein, 2010; Ottaviani et al., 2016) demonstrate focal activations in nodes of the DMN.

Another important transdiagnostic feature that marks distress disorders is known variously as neuroticism (e.g., Barlow et al., 2014), negative affectivity (e.g., Watson et al., 1988) or dispositional negativity (e.g., Shackman et al., 2016). This construct reflects a tendency to experience frequent and intense negative emotions including anxiety, fear, irritability, anger, or sadness, in response to various sources of stress (Barlow et al., 2014). Shackman et al. (2016) proposed that dispositional negativity is a definable construct reflected at many neurobehavioral levels of analysis (e.g., neural, peripheral, etc.) and is found broadly in nature (e.g., humans, non-human primates, rodents, etc.). This negative emotionality is characterized by under- and over-activation of reward and safety/threat systems respectively, as well as their co-occurrence (i.e., motivational conflict; Higgins, 1997; Klenk et al., 2011; Scult et al., 2016). However, unlike healthy individuals, individuals with distress disorders may be relatively less effective in resolving these motivation states and conflicts. One possible reason is that salience in one or both of these motivational systems may increase levels of subjective intensity and corresponding distress (Shackman et al., 2016). Self-report indices of neuroticism clearly predict a more severe and protracted course for mood and anxiety disorders (e.g., Brown, 2007; Brown and Rosellini, 2011; Barlow et al., 2014). Further, whereas diagnostic comorbidity has long been viewed as a predictor of an inferior treatment response (e.g., Mineka et al., 1998), high levels of neuroticism may contribute to the underperformance of otherwise efficacious treatments (e.g., Brown, 2007; Olatunji et al., 2010; Brown and Rosellini, 2011).

The salience network (SN; e.g., Craig, 2009; Menon, 2015) is involved in orienting attention to external and internal stimuli (Menon and Uddin, 2010), and facilitates the integration of sensory, emotional, and cognitive information in service of optimal communication, social behavior, and self-awareness (Menon, 2015). The insula is a central node which helps evaluate the impact of stimuli on the body (Paulus and Stein, 2006), including generation and regulation of affective responses and detection of emotionally salient stimuli (Paulus and Stein, 2010). Most research findings implicate the right anterior insula (e.g., Critchley et al., 2004) but increasingly, evidence also indicates a relevant role for the posterior insula in emotional processing as well (Kuehn et al., 2016). Negative self-referentiality including worry, may in fact exaggerate arousal (positive or negative; Pollatos et al., 2009; Paulus and Stein, 2010). Paulus and Stein (2010) posit that individuals with anxiety and depression exhibit a propensity to negatively interpret interoceptive afferents, resulting in increased sympathetic arousal, and in turn, increased escape or avoidance behaviors.

When examined *via* functional neuroimaging, patients with GAD and MDD frequently exhibit SN abnormalities (Etkin et al., 2009; Dutta et al., 2014; Kaiser et al., 2015). For instance, compared to healthy individuals, depressed patients show reduced connectivity between anterior insula and other nodes of the SN (Manoliu et al., 2014; Yuen et al., 2014). In task-based studies, MDD and GAD patients consistently show hyperactivity of the anterior insula often accompanied by increased connectivity with nodes of DN including the posterior cingulate cortex (PCC; e.g., Paulus and Stein, 2010; Hamilton et al., 2013; Yuen et al., 2014). Similarly, a recent

study by Kaiser et al. (2015) found that in comparison to healthy control participants, patients with MDD evidenced increased connectivity of the MPFC to the insula and the strength of this connectivity was predictive of depression severity.

The frontoparietal control network (FPCN), with nodes in the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) is involved in "top-down control," monitoring attention, and regulating sensory, and internal networks according to current task goals (Cole et al., 2014). MDD patients often demonstrate within-network hypoconnectivity in FPCN, and hypoconnectivity between the FPCN and the DMN (Mulders et al., 2015). Similarly, in MDD, hypoconnectivity between the FPCN and the dorsal attention network [DAN; underlying volitional deployment of attention toward stimuli and externally-directed cognitions (Corbetta et al., 2008)] may increase depressive rumination and decrease ability to attend to present-moment external stimuli, and thus loss of potential for corrective information for positive reappraisal or access to reward (Schooler et al., 2011). Dysregulation of FPCN may also underlie inefficiency in adaptive switching between task-relevant and irrelevant cognitions and behaviors, as well as deficits in top-down regulation of SN, which is hyperactive and hyper-connected in PTSD and GAD (Rabinak et al., 2011; Sripada et al., 2012; Sylvester et al., 2012; Wang et al., 2016; Akiki et al., 2017). In summary, the distress disorders, especially GAD and MDD, are prevalent and often comorbid conditions at both a diagnostic and symptom level of analysis. When looking beyond surface characteristics, distress disorders exhibit excessive negative self-referentiality along with dispositional negative emotionality. These psychological characteristics are consistent with general hyperconnectivity within the DMN network, hypoconnectivity within the SN network and FPCN, and hypoconnectivity between the FPCN and DMN and DAN (Schooler et al., 2011; Mulders et al., 2015; Williams, 2016). Efforts focused on correcting these circuit-level abnormalities through targeted psychological and pharmacological interventions may result in a more efficacious treatment response.

Using this formulation of distress disorders as a conceptual model, Mennin and Fresco developed emotion regulation therapy (ERT), a theoretically-derived, mechanism focused treatment that integrates findings from affect science with principles from cognitive behavioral therapy (i.e., CBT; see Mennin et al., 2013) to target and normalize these neurobehavioral deficits (Fresco et al., 2013; Mennin and Fresco, 2015; Mennin et al., 2018; Renna et al., 2018b). ERT targets three hypothesized mechanisms: (1) motivational mechanisms, the functional purpose and inclinations of emotional response tendencies; (2) regulatory mechanisms, the ability to alter emotional responses both at less elaborative/attentional levels and more verbally elaborative and effortful levels including the ability to decenter (i.e., the meta-cognitive ability to observe items that arise in the mind with distance and perspective; present sample; Fresco et al., 2007; Bernstein et al., 2015) and reappraise (i.e., reinterpreting the meaning to change emotional trajectory; Ochsner and Gross, 2005); and (3) contextual learning, the use of flexible and adaptive behavioral repertoires, Using a motivational framework (i.e., identifying reward- and risk-based impulses), ERT instructs patients to engage in mindful emotion regulation skills to counteract negative self-referential processing (e.g., worry, rumination, and self-criticism) in service of pursuing intrinsically rewarding and goal-directed actions in their lives.

Three recently published trials of ERT attest to its efficacy in treating GAD and MDD (Mennin et al., 2015, 2018; Renna et al., 2018a). Following promising results from an initial open trial (Mennin et al., 2015), Mennin et al. (2018) found that GAD patients (with and without MDD) treated with 20 sessions of ERT vs. an attentional control intervention) evidenced statistically and clinically meaningful improvement on clinical indicators of GAD and MDD, worry, rumination, comorbid disorder severity, functional impairment, quality of life, as well as hypothesized mechanisms reflecting mindful attentional, metacognitive, and overall emotion regulation. The gains were maintained in post-treatment assessments 3- and 9-months following the end of treatment. In a secondary analysis of these trial data, Renna et al. (2018b) examined ERT-linked changes in behavioral tasks of flexible and sustained attention. Findings indicated that improvements in a specific form of attentional flexibility, conflict adaptation, predicted increases in mindful observing abilities whereas gains in sustained attention were related to mindful non-reactivity, clinical improvement, and decreased functional impairment.

Building on these encouraging efficacy findings, Renna et al. (2018a) utilized a 16-session format of ERT in an open trial design with an ethnically diverse sample of young adults. This trial, which is the parent study for the current study, reported impressive and durable efficacy in reducing worry, rumination, self-reported and clinician rated GAD and MDD severity, and social disability, while increasing quality of life, attentional flexibility, decentering/distancing, reappraisal, and trait mindfulness. In an initial secondary analysis of these trial data, we reported that baseline patterns of resting state functional connectivity (rsFC) within the DMN and SN predicted clinical response to ERT (Fresco et al., 2017). Specifically, higher baseline insula connectivity with parietal cortex, and aMPFC connectivity with precuneus and occipital cortex were associated with decreases in worry. Higher baseline PCC connectivity with the rostral ACC, and insula connectivity with lateral occipital cortex, central opercular cortex and dMPFC was associated with increases in decentering, while aMPFC connectivity with occipital pole was associated with decreases in decentering. Findings from this study implicated disruptions in the default and SNs as promising targets of treatment for GAD with and without co-occurring MDD but did not test how these networks might change as a result of treatment with ERT.

Beyond ERT, recent trials utilizing forms of mindfulness meditation have examined patterns of treatment linked rsFC change in their respective samples. In particular, Creswell et al. (2016) randomized subjectively-stressed unemployed adults to a 3-day intensive program of either mindfulness meditation,

modeled after the mindfulness-based stress reduction curriculum (Kabat-Zinn, 2009), or a well equated relaxation curriculum. Participants completed a resting state scan before and after the intensive intervention. Seed-based change in functional connectivity using a seed in the PCC revealed that the mindfulness intervention, but not the relaxation intervention, was associated with increased connectivity between the PCC and left DLPFC. Comparable findings were reported by King et al. (2016) who randomized combat veterans with post-traumatic stress disorder to either 16 weeks of mindfulness-based exposure therapy (MBET), which was derived from mindfulness based cognitive therapy (Teasdale et al., 2000) and prolonged exposure therapy (Foa et al., 2007) or to a present-centered group therapy (PCGT; (Schnurr et al., 2003), a well equated comparator frequently used in PTSD trials. Consistent with Creswell et al. (2016), the PCC seed revealed that MBET but not PCGT was associated with the strength of functional connectivity between the left DLPFC, the right DLPFC, and the dorsal anterior cingulate cortex (dACC). Further, the strength of activation in the PCC-left DLPFC at post treatment was correlated with post-treatment PTSD avoidance symptoms (r = 0.623) and hyperarousal symptoms (r = 0.675) in patients receiving MBET but not PCGT. These findings combined with results from meta-analysis showing that individuals with depression tend to have decreased connectivity between PCC and DLPFC nodes compared to healthy controls (Mulders et al., 2015) raises the possibility that interventions for depression that include mindfulness meditation exercises, such as ERT, may lead to clinical improvement in part by increasing PCC-DLPFC connectivity.

The present study is drawn from a larger intervention trial (Renna et al., 2018a) and the baseline rsFC prediction study from the subset of the sample (Fresco et al., 2017). Findings from aforementioned trials with mindfulness interventions demonstrated changes in intrinsic functional connectivity in the DMN. Given these findings and our own baseline prediction findings, we sought to examine whether ERT would demonstrate similar patterns of rsFC changes in DMN and SN. Using seed-based connectivity analysis with seeds in the PCC, right anterior insula, and right posterior insula, we sought to identify patterns of ERT-linked rsFC changes of nodes within these networks across the brain and whether these changes would be associated with clinical improvement and ERT model related mechanism variables (e.g., attention control, decentering, and cognitive reappraisal) as well as reductions in MDD and GAD severity. Specifically, we hypothesized that ERT would be associated with decreased connectivity of nodes within the DMN, and that these changes would in turn be associated with decreased rumination. Increased connectivity of nodes within the SN would be expected to be associated with decreased depression and anxiety severity. Increased connectivity between nodes of the DMN and nodes of the FPCN would be expected to be associated with decreased depression and anxiety severity and improvements in attentional and metacognitive regulation (Mulders et al., 2015; Williams, 2016).

MATERIALS AND METHODS

Participants

Participants were 25 treatment-seeking young adults, a subsample of the 31 patients treated in Renna et al. (2018a) who were drawn from an undergraduate and graduate student population in a large urban commuter-based university. Participants completed 16 weeks of ERT (Mennin and Fresco, 2014) and completed fMRI scans before and after treatment, with an average length of time between treatment and scan of less than 2 weeks. Participants were recruited through direct referrals from an on-campus counseling center, fliers posted throughout campus, e-mail announcements sent to the entire student body, and through research staff handing out business cards to students on campus. Four patients were excluded for technical issues that arose during MRI acquisition that resulted in unusable MRI data. The final sample had a mean age of 21.8 years old (SD = 2.6, range 18–27). Sixteen participants were female (76.2%). Seven participants identified as Hispanic and 14 as non-Hispanic. Additionally, participants identified primarily as White (8), followed by Asian (5), Other/mixed race (7), and Black (1).

Inclusion/Exclusion Criteria

The main eligibility criterion was the presence of a primary or secondary GAD diagnosis. In the current study, 16 patients had a primary diagnosis of GAD (primacy based on symptom severity). Sixteen patients also met criteria for MDD; 14 patients met criteria for at least one additional anxiety disorder diagnosis. Other diagnoses included social anxiety disorder (n = 10), panic disorder (n = 6), specific phobia (n = 4), obsessive compulsive disorder (n = 3), post-traumatic stress disorder (n = 1). Participants were required to be stabilized on any psychotropic medications for a period of at least 3 months prior to the start of treatment (n = 1 receiving antidepressant medication) and could not be enrolled in any other form of psychological treatment during the acute phase of ERT (16 weeks). Participants were not taking any other medications at the time. Finally, participants had to be free of active suicidal ideation/intent, psychosis, bipolar I disorder, primary anorexia or bulimia nervosa, somatoform disorders, or substance and alcohol dependence. Given the use of fMRI assessment, other exclusionary criteria included standard MRI contraindications (e.g., ferromagnetic implants; head trauma with loss of consciousness; tattoos above the elbow; pregnancy).

Diagnostic Assessment

Current and lifetime psychiatric disorders were assessed with the Structured Clinical Interview for DSM-IV (SCID; First et al., 2002). Graduate students and senior research assistants, extensively trained on the diagnostic assessment protocol administered this assessment. A principal investigator and an independent assessor, both of whom were blind to the participant's diagnoses assigned at the intake interview, then confirmed participants' diagnoses. Reliability was high, with kappa ratings ranging from 0.708 to 1.000, demonstrating

good to excellent reliability. Reliability for diagnoses of GAD was 100%, whereas MDD was 87.10%. Independent assessors, who remained blind to treatment status of patients, assessed clinical improvement at mid-treatment, post-acute treatment, as well as 3-, and 9-months following the end of treatment.

Treatment

ERT consists of 16-session individual weekly sessions completed within a 20-week span. The first half of the treatment (Phase I) emphasizes psychoeducation and cultivating mindful emotion regulation skills. Participants receive instruction in attention regulation (i.e., orienting, allowing) and meta-cognitive regulation (i.e., decentering, and cognitive reappraisal) skills. In particular, clients are instructed on how to better attend to emotional and motivational cues that arise in daily life so that these cues are noticed with greater acuity and closer to when they first arise. This cue detection is supported by a variety of meditation practices that improve attention and metacognitive capacities that patients are asked to practice daily. Briefer versions of these meditation practices are also introduced so that they can be utilized in both predicted and impromptu stressful situations as an alternative to negative self-referentiality and behavioral responses associated with escape or avoidance. The second half of treatment (Phase II) focuses on context engagement, which involves developing a proactive approach towards life with the goal of living more consistently with one's values through the use of imaginal exposures and internal dialog tasks. Here, therapists direct patients in conducting in-session exposure exercises where patients envision a situation, goal, or outcome that they desire but is presently missing from their lives. This imaginal exposure serves to elucidate the motivational inclinations for reward and approaching a goal as well as the motivations associated with protecting one's self from the threat associated with taking the action and/or costs associated with not succeeding. By giving voice to these motivational inclinations, patients learn to decenter from the intensity of these pulls and derive a behavioral response that reflects an optimal balance of risk and reward. More information regarding the structure and specific components of ERT are described elsewhere (see Fresco et al., 2013; Mennin and Fresco, 2014; Renna et al., 2017).

Clinicians consisted of seven doctoral students in clinical psychology who were trained to administer ERT and received 2 h of weekly supervision. The modal number of cases treated by each clinician was three ($M = 2.75$; range = 1–4). To establish adherence to the treatment protocol, all treatment sessions were audio recorded, and a team of research assistants, not involved in the administration of ERT or assessment of treatment effects, coded 40% of all cases, with 25% of these cases reviewed by a second coder to establish reliability. Reliability rates between the coders were 100%. Coders rated the accuracy of the frequency and skillfulness of actions taken by the study therapists. Overall, skillfulness ratings of the therapists coded were 98.4% (range = 95%–100%), while frequency of actions consistent with the treatment protocol was 91.2% (range = 71%–100%). The adherence ratings for this trial indicate that therapists uniformly delivered ERT with a high degree of adherence and fidelity. Examination of treatment effects associated with particular clinicians revealed equivalence for self-report and clinician-assessed clinical outcomes (p's > 0.70) across the seven trial therapists.

Each diagnosis reaching clinical or subclinical thresholds was assigned a clinical severity rating (CSR) score from 0 to 8, based on criteria outlined in and adapted from the *Anxiety Disorders Interview Schedule for DSM-IV* (ADIS; Brown et al., 1994). Diagnostic criteria at the subclinical threshold for a given disorder are reflected by a CSR less than four. A CSR of four or above indicates that all criteria for a diagnosis were endorsed at the clinical threshold, with higher scores indicating greater severity. Interviewers were trained to assign these scores as per ADIS guidelines based on number and frequency of symptoms endorsed, while also taking into account related levels of distress and impairment attributed to the disorder symptomatology.

Clinical Outcomes

Clinician assessed severity for GAD and MDD were determined by an independent assessor using the ADIS CSR rating for GAD and MDD. Details on assessment and training of these independent assessors and the deriving of these ratings are available in Renna et al. (2018a).

The Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990) is a 16-item self-report measure of pathological worry with scores ranging from 16 to 80. Cronbach's alpha in the current sample was good ($\alpha = 0.80$).

The *Brooding subscale of Response Styles Questionnaire* (RS; Treynor et al., 2003; Armey et al., 2009) is a five-item measure of self-reported rumination free of depression symptom content. Internal consistency for the RS in the current study was moderate at 0.63.

The *Attentional Control Scale* (ACS; Derryberry and Reed, 2002) is a 20-item measure with two subscales that assess the degree to which an individual is able to shift and sustain/focus their attention. Higher scores indicate greater ability to control one's attention. Internal consistency in the current study at pre-treatment was strong ($\alpha = 0.85$ for entire scale, $\alpha = 0.80$ for Focusing Attention, $\alpha = 0.73$ for Shifting Attention).

The Experiences Questionnaire-Decentering Subscale (Decentering; Fresco et al., 2007) is an 11-item measure assessing the meta-cognitive strategy of decentering often defined as viewing oneself as separate from their emotional experience. Cronbach's alpha in the current sample was good ($\alpha = 0.80$).

The Emotion Regulation Questionnaire—Reappraisal subscale (ERQ-R; Gross and John, 2003) is a six-item measure of cognitive reappraisal that demonstrated strong internal consistency in the current study at pre-treatment ($\alpha = 0.86$).

The Mood and Anxiety Symptom Questionnaire-Short Form (MASQ-SF; Clark and Watson, 1991) is a 62 item measure assessing anxiety and depression symptoms. The four factors derived from the MASQ represent: General Distress Anxiety (MASQ–GDA), Anxious Arousal (MASQ–AA), General Distress Depression (MASQ–GDD), and, Anhedonic Depression

(MASQ–AD). Cronbach's alpha for the MASQ subscales in the current study ranged from moderate to strong at pre-treatment (α's = 0.61–0.91).

Procedure

The Institutional Review Board of the college approved all aspects of the study. Participants provided written informed consent for all procedures at the outset of study. At the initial intake visit participants were assessed for current and lifetime psychiatric history *via* the SCID interview and also completed a battery of self-report questionnaires delivered in paper-and-pencil format. Prior to the start of treatment, participants completed an independent assessment with a different interviewer who re-assessed the diagnoses that were of clinical threshold at the initial intake. Finally, participants completed the fMRI scan. Following the first eight sessions (i.e., mid-treatment) and after 16 sessions (i.e., post-treatment), participants returned to the lab to complete another independent assessment and self-report questionnaire packet. They also completed another fMRI session post-treatment. Participants were compensated for all research related study visits.

Analytic Plan

MRI Data Acquisition Imaging data were collected on a 3.0T Siemens Allegra head-dedicated MRI scanner with a standard quadrature head coil at the NYU Center for Brain Imaging in New York, NY, USA. Scan sessions lasted 90 min during which participants completed a resting state fMRI scan, and an anatomical scan, and three task-based scans (not examined in the current study). The resting state scan was always acquired prior to the task-based scans. During the 6-min resting-state sequence, participants were asked to keep their eyes open while a white crosshair was displayed on a black screen. The resting-state scan comprised 180 contiguous whole-brain functional volumes, acquired using a multi-echo echo planar imaging (EPI) sequence (repetition time = 2,000 ms; echo time = 30 ms; flip angle = 90°; 33 slices; matrix = 64 × 64; voxel size = 3 × 3 × 4 mm). High-resolution T1-weighted MPRAGE structural images (TR = 2,500 ms; TE = 3.93 ms, flip = 8°, 1 × 1 × 1 mm voxels) were acquired to facilitate localization and coregistration of functional data.

MRI Data Preprocessing

MRI preprocessing was undertaken in AFNI (Cox, 1996) following the steps detailed in Power et al. (2017). To correct for subject movement, FD and DVARS were calculated before any other preprocessing steps were performed. Despiking was performed using AFNI's 3dDespike for the entire volume. Slice time correction was performed using 3dTShift, shifting all signals to the time when the volume began to be collected, specifying interleaved acquisitions with an odd number of slices, and using the heptic Lagrange polynomial interpolation. The scanner was already steady-state at initial acquisition, so no volumes were skipped at the beginning of the scan. Realignment was conducted with 3dvolreg, using the first volume of a scan as the reference.

Registration of fMRI data to atlas space was conducted next. AFNIs @auto_tlrc command was used to register the first volume of the fMRI scan to each subject's MP-RAGE, and all fMRI scans were registered to the first volume of the fMRI scan in the motion correction step. Registrations were then concatenated to a single transform, which was transformed into AFNIs TT_N27 atlas space and resampled to 3 mm isotropic voxels. All T1-weighted images underwent automated segmentation using FreeSurfer version 6.0, implemented with the recon-all command.

Time-series images for each participant were further processed to limit the influence of motion and other artifacts. Motion regressors were created using each subject's six motion correction parameters (three rotation and three translation) and their first derivatives (Jo et al., 2013; Satterthwaite et al., 2013) yielding 12 motion regressors. White matter and cerebrospinal fluid nuisance regressors were created using CompCorr (Behzadi et al., 2007). Images were bandpass filtered to retain frequencies between 0.008 and 0.1 Hz, and volumes exceeding 0.25 mm frame-wise displacement or 1.55 standardized DVARS (Power et al., 2014; Nichols, 2017) were censored. Nuisance regression, bandpass filtering and censoring for each time series was performed in a single processing step using AFNI's 3dTproject. One patient was excluded from subsequent analyses due to not passing QA procedures. Additionally, one subject's baseline scan and another subject's follow-up scan were excluded for not passing QA procedures, but each of their corresponding scans were included in the group-level rsFC analyses.

Resting State Functional Connectivity (rsFC): Seed-Based Analyses

To investigate changes in connectivity of nodes within the DMN and SN, particular seeds within the DMN (PCC) and SN (Insula) were chosen. Specifically, ROIs were defined based on Fresco et al. (2017). For the PCC, a 2 mm sphere was created around the coordinates (−8, −56, 26). The right anterior insula and right posterior insula seeds (K = 2 clusters per hemisphere) were created by Kelly et al. (2012) and downloaded for the present study from the 1,000 Functional Connectomes Project[1]. For each seed, mean timeseries were extracted and used to create whole brain Z-transformed correlation maps for each participant. Group level analyses were conducted using AFNIs 3dLME (Chen et al., 2013) testing pre- to post-treatment change in rsFC. 3dLME was chosen to be able to account for missing data in repeated measures designs.

Correction for multiple comparisons was conducted using AFNI's 3dClustSim (version 17.3.06) for cluster-size thresholding based on Monte Carlo simulation. An initial, uncorrected, statistical threshold of $p < 0.01$ with option NN1 (faces must touch) was chosen (Cox et al., 2017). Based on this threshold, the number of comparisons in our imaging volume and the smoothness of our imaging data, as measured by 3dFWHMx -acf, a minimum cluster size of nine voxels was required to have a corrected $p \leq 0.05$ with 2-sided thresholding.

Significant clusters were saved as a mask and mean parameter estimates from the clusters were extracted from pre- and post-test scans using 3dROIstats to be entered into statistical models in IBM SPSS Statistics 24 (Chicago, IL, USA).

[1] http://fcon_1000.projects.nitrc.org

Associations Between Change in Resting State Functional Connectivity With Clinical Variables

Time 2 rsFC and clinical variables were regressed onto their Time 1 counterparts and the unstandardized residual was saved as a new variable. We examined the zero order correlations among rsFC change indices with clinical change indices. Given the small sample size of the study, we elected to interpret correlations of at least a medium effect size ($r > 0.30$; Cohen, 1992) and made note of when these correlations also reached conventional probability values ($p < 0.05$).

RESULTS

ERT Linked Clinical Improvement

Mean levels of clinical variables pre- and post-therapy are shown in **Table 1**. The results for the subsample of participants included in the current article are comparable to those found in the parent study (Renna et al., 2018a). Participants demonstrated a significant decrease in clinician assessed severity of GAD and MDD symptoms as well as in rumination and worry. Participants also demonstrated a significant increase in emotion regulation skills of attentional control (both shifting and focusing), decentering, and reappraisal. All clinical indicators exceeded conventions for large effect sizes (Hedges $g > 0.80$).

ERT Linked Change in rsFC

The posterior cingulate seed demonstrated increased connectivity from pre- to post-treatment with five cortical regions consisting of the middle occipital gyrus [Right Brodmann Area (BA) 19], precuneus (Right BA 7), cuneus (Right BA 17), precentral gyrus/motor cortex (Left BA 6) and premotor areas/DLPFC (Right BA 8/9). The anterior insula seed evidenced increased connectivity with precuneus (Left BA 18), while the posterior insula seed showed increased connectivity with anteromedial PFC/dACC (Left BA 32/10) and decreased connectivity with midbrain (**Table 2** and **Figure 1**).

Association of rsFC Change to Clinical Improvement

Table 3 displays zero order correlations between residual change in functional connectivity and clinical outcomes attributable to ERT. Few statistically significant associations were found between the residual change in extracted cluster values and residual change in clinical improvement or measures of emotion regulation. However, findings did reveal a pattern of correlations between rsFC change and clinical outcomes above the threshold for a medium effect size and/or probability values less than 0.05, that may achieve traditional statistical significance with a large sample. For instance, three of the clusters associated with the PCC seed evidenced moderately larger correlation coefficients. In particular, increases in functional connectivity between the PCC-Middle Occipital Gyrus cluster was positively

TABLE 1 | Means and standard deviations of emotion regulation therapy (ERT) linked clinical outcomes.

	Pre-treatment	Post-treatment	*t*(df)	*p*	Hedge's *g*
GAD CSR	5.8 (0.7)	3.4 (0.9)	10.0 (20)	<0.001	2.73
MDD CSR	4.4 (1.0)	2.3 (1.6)	5.1 (16)	<0.001	1.48
Rumination	14.8 (2.8)	10.2 (4.2)	4.5 (20)	<0.001	1.26
Worry	70.4 (6.4)	48.9 (12.6)	8.4 (20)	<0.001	2.08
MASQ-GDA	31.0 (5.8)	19.8 (5.1)	7.2 (20)	<0.001	1.97
MASQ-GDD	41.6 (8.2)	23.1 (9.7)	6.1 (20)	<0.001	1.98
Attentional control	44.5 (8.8)	51.6 (7.9)	4.0 (20)	0.001	0.82
Reappraisal	20.3 (7.6)	29.3 (8.0)	3.8 (20)	0.001	1.11
Decentering	24.9 (6.8)	38.2 (9.3)	5.4 (20)	<0.001	1.57

Note: GAD, Generalized Anxiety Disorder; CSR, Clinician Severity Rating; MDD, Major Depressive Disorder; MASQ-GDA, Mood and Anxiety Symptom Questionnaire, General Distress Anxiety; MASQ-GDD, Mood and Anxiety Symptom Questionnaire, General Distress Depression.

TABLE 2 | Change in connectivity associated with each seed, listed by cluster size and MNI coordinates of peak voxel.

Seed	With region	BA	Cluster size	*x*	*y*	*z*	Max Z
Post > Pre							
PCC	Middle Occipital Gyrus	19	52	43	−74	17	4.66
PCC	Precuneus	7	35	13	−68	47	3.77
PCC	Cuneus	17	22	16	−65	11	3.56
PCC	Precentral Gyrus	6	22	−41	−5	53	4.08
PCC	Pre-motor areas/DLPFC	8/9	20	40	4	35	3.65
raInsula	Cuneus	18	9	−5	−71	29	3.93
rpInsula	Anteromedial PFC/dACC	10/32	10	−5	46	17	4.13
Pre > Post							
rpInsula	Midbrain	n/a	9	13	−29	−25	−4.24

The top five significant clusters are presented for each seed. Note: BA, Brodmann Area; PCC, Posterior Cingulate Cortex; raInsula, Right Anterior Insula; rpInsula, Right Posterior Insula; DLPFC, Dorsolateral Prefrontal Cortex; dACC, Dorsal Anterior Cingulate Cortex.

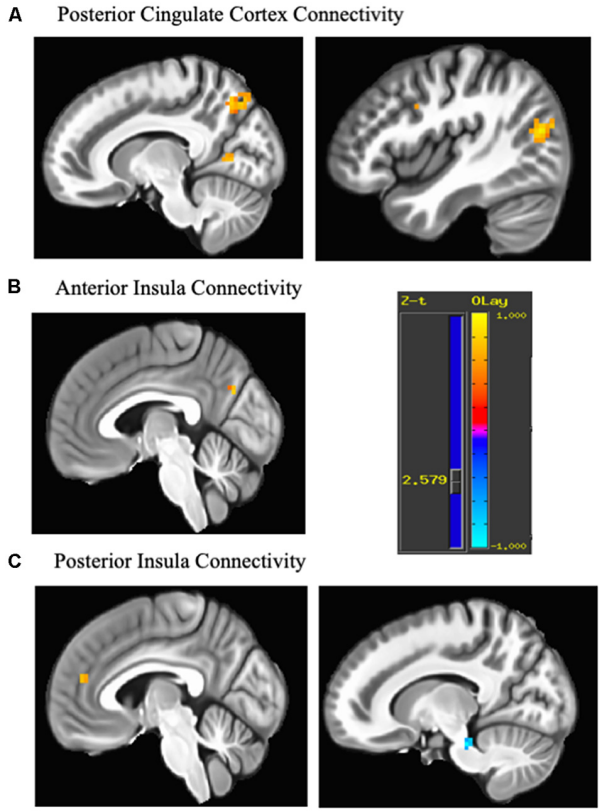

FIGURE 1 | Change in connectivity associated with each seed. Regions demonstrating pre-post emotion regulation therapy (ERT) change in resting state functional connectivity (rsFC). **(A)** The posterior cingulate seed showed increased connectivity with middle occipital gyrus (43, −74, 17), precuneus (13, −68, 47), cuneus (16, −65, 11), precentral gyrus (−41, −5, 53; not shown) and premotor areas/dorsolateral prefrontal cortex (DLPFC; 40, 4, 35). **(B)** The anterior insula seed showed increased connectivity with the cuneus (−5, −71, 29). **(C)** The posterior insula seed increased connectivity with anteromedial PFC/dorsal anterior cingulate cortex (dACC; −5, 46, 17) and decreased connectivity with midbrain (13, −29, −25). Cluster are significant after cluster-based correction for multiple comparisons (>9 contiguous voxels). Yellow scale indicates positive z-scores, and blue scale indicates negative z-scores.

correlated with ERT linked gains in attentional control, decentering, and cognitive reappraisal. Similarly, increases in functional connectivity between the PCC and Precentral Gyrus (Motor Strip) were negatively correlated with ERT linked reductions in GAD severity, anxiety and depression distress, and rumination, as well as gains in decentering and cognitive reappraisal. Increases in functional connectivity between the PCC and premotor areas/DLPFC were negatively correlated with reductions in MDD severity and positively correlated with gains attention control, decentering, and cognitive reappraisal. Finally, functional connectivity of the PCC with the cuneus was associated with ERT-linked gains in attentional control, whereas, PCC connectivity with the precuneus was associated with ERT-linked gains in reappraisal. On balance, rsFC clusters emerging from right anterior insula and right posterior insula seeds were not meaningfully correlated with ERT linked changes on clinical indicators.

DISCUSSION

This study represents the first investigation of changes in rsFC following treatment with ERT, a theoretically-derived, mechanism focused treatment for distress disorders that was developed to target and normalize negative motivational salience and subsequent self-referential processes as reflected in hypothesized neurobehavioral deficits in the DMN and SN (i.e., hyperconnectivity within the DMN network, hypoconnectivity within the SN network and FPCN, and hypoconnectivity between the FPCN and DMN). In this study drawn from a larger intervention trial (Renna et al., 2018a), we utilized a seed-based connectivity analysis with seeds in the PCC, right anterior insula, and right posterior insula. Findings revealed changes in connectivity of nodes in the DMN and SN networks with other nodes in these networks and with other cortical regions post-therapy compared to pre-therapy. Five clusters derived from the PCC seed and three clusters derived from insula seeds were retained and examined in relation to ERT linked improvements in clinical indicators of GAD and MDD severity, worry, rumination, as well as mechanistic emotion regulation variables (e.g., focusing and shifting attention, decentering, cognitive reappraisal). Meaningful and theoretically consistent correlations emerged between PCC seeded clusters and clinical variables of moderately large effect size, but because of the relatively small sample size of the study, only a few achieved conventional thresholds of statistical significance.

Following treatment with ERT, the PCC seeds revealed increased connectivity with a region that includes pre-motor cortex and posterior DLPFC, findings consistent with two recent trials that utilized mindfulness-based interventions (Creswell et al., 2016; King et al., 2016). In these studies, increased connectivity between the PCC and DLPFC was associated with post-treatment PTSD symptoms (King et al., 2016) and reduced serum inflammatory markers (Creswell et al., 2016). Similarly, increased DLPFC function has also been associated with reappraisal (Ochsner et al., 2002; Scult et al., 2017b), and with decreased anxiety (Scult et al., 2017a). The present results also found a trend for this increase in PCC-pre-motor/DLPFC connectivity to parallel decreases in MDD severity and depression distress, and increases in attentional control and emotion regulation. These results fit with previous work showing a unique functional coupling of DLPFC and PCC in instances of cognitive control (Smith et al., 2016), suggesting that the ERT intervention may have enhanced cognitive control of emotional processing through increasing PCC-DLPFC coupling at rest. Increasing connectivity of other brain regions such as the medial PFC (Etkin et al., 2011) with the posterior insula may reflect the appraisal of emotional responses *via* more metacognitive processes that create an empathic distance from the emotion itself (similar to the empathy experienced for the distress of others; Lamm et al., 2011), and indeed this increased connectivity showed a trend for increasing decentering in the present results.

The increases in connectivity of the PCC with other regions of the DMN (e.g., precuneus) were contrary to hypothesis, given

TABLE 3 | Association of ERT linked rsFC change to clinical improvement and model related mechanisms.

Resting state functional connectivity		Clinical indicators						Emotion regulation mechanisms			
		Δ GAD severity	ΔMDD severity	Δ Anxiety distress	Δ Depression distress	Δ Worry	Δ Rumination	Δ Focus	Δ Shifting attention	Δ Decentering	Δ Reappraisal
PCC seed with											
Middle Occipital Gyrus	*r*	−0.063	0.164	0.004	0.264	−0.218	−0.155	0.287	**0.512***	**0.373**	**0.358**
	p	0.798	0.530	0.986	0.274	0.370	0.528	0.233	0.025	0.116	0.132
Precuneus	*r*	−0.215	−0.045	0.066	0.138	**0.336**	0.284	−0.092	0.025	0.116	**0.307**
	p	0.376	0.863	0.789	0.572	0.160	0.239	0.709	0.920	0.636	0.202
Cuneus	*r*	0.123	0.221	0.234	**0.353**	−0.110	−0.005	**0.339**	**0.507***	0.163	0.213
	p	0.615	0.395	0.335	0.139	0.654	0.983	0.156	0.027	0.506	0.381
Precentral Gyrus (Motor)	*r*	**−0.419**	−0.148	**−0.569***	**−0.395**	−0.226	**−0.318**	0.209	0.191	**0.355**	**0.380**
	p	0.074	0.570	0.011	0.094	0.352	0.184	0.391	0.433	0.136	0.108
Pre-Motor areas/DLPFC	*r*	0.101	**−0.417**	−0.194	**−0.367**	−0.049	−0.083	**0.369**	**0.336**	**0.320**	**0.403**
	p	0.681	0.096	0.427	0.122	0.842	0.736	0.120	0.160	0.182	0.087
rpInsula seed with											
amPFC/dACC	*r*	−0.144	0.246	−0.025	−0.152	−0.272	−0.027	−0.084	−0.231	0.060	−0.088
	p	0.557	0.341	0.920	0.533	0.260	0.911	0.733	0.341	0.808	0.720
Midbrain	*r*	−0.087	**−0.346**	0.070	0.018	−0.103	0.209	−0.046	0.120	−0.046	0.017
	p	0.724	0.173	0.777	0.943	0.676	0.391	0.851	0.624	0.850	0.945
raInsula seed with											
Precuneus	*r*	0.202	0.170	−0.030	0.138	−0.104	−0.052	−0.1290.50	−0.129275	−0.239	−0.260
	p	0.936	0.514	0.903	0.573	0.673	0.831	0.600829	0.600228	0.324	0.282

*Note: PCC, Posterior Cingulate Cortex; raInsula, Right Anterior Insula; rpInsula, Right Posterior Insula; DLPFC, Dorsolateral Prefrontal Cortex; dACC, Dorsal Anterior Cingulate Cortex; Correlations in bold exceed conventions for a medium effect size (r > 0.30), *p < 0.05.*

the well-documented patterns of hyperconnectivity within the DMN in depression (Kaiser et al., 2015) which are sometimes normalized with antidepressant medication (Posner et al., 2013). However, recent research suggests that a focus on overall DMN connectivity may be overly simplistic, and that instead, connectivity between anterior portions of the DMN may be positively correlated with anxiety and depression symptoms while connectivity between posterior nodes of the DMN may be negatively correlated with depression and anxiety symptoms (Coutinho et al., 2016). Our results of increasing connectivity of the PCC with other posterior regions both within and beyond the DMN (precuneus, cuneus, middle occipital gyrus) after ERT treatment, paralleling decreases in mood and anxiety symptoms, fit within this framework as further described below.

In particular, the present study found changes in connectivity of brain regions involved in shifting attention towards important situational cues. The PCC has been implicated in self-generated thought irrespective of whether attention is focused internally or externally, while middle occipital gyrus activity has been associated with externally directed attention (Benedek et al., 2016). Areas of the medial PFC overlapping with activations found in the present study showing increased connectivity with posterior insula, have been associated with positively valenced self-related processing (Johnson et al., 2009). Meanwhile, the precentral gyrus is involved in intentional motor activity (Kana et al., 2015). One potential interpretation of these patterns of activation is that these regions are implicated in agentic thoughts and actions, which stands in contrast to the experience of individuals with elevated anxiety and depression, who often overlook overt cues for reward and have difficulty accurately assessing environmental cues signaling danger (Renna et al., 2017). In healthy individuals, DMN and SN activity is linked with processing of internal and external cues that are related to situational awareness. For example, the middle occipital gyrus has been implicated in mentalizing or inferring the emotions of others (Atique et al., 2011; Schurz et al., 2014), while PCC activation has been associated with agentic control (Brewer and Garrison, 2014). One possible explanation, therefore, is that ERT may act by increasing the ability of individuals to accurately shift attention to cues in the environment *via* enhanced connectivity of regions related to perceptual processing and mentalizing (Ganis et al., 2004; Schurz et al., 2014), which in turn, leads to the alleviation of anxious and depressive symptoms.

An important guiding principle of ERT is the contention that refractory conditions such as distress disorders require intervention components that target attention and metacognitive capacities to produce a meaningful and durable treatment response (Fresco and Mennin, 2019). Several reported findings herein are potentially consistent with that premise. For instance, we conducted some *post hoc*, unplanned tests of dependent correlations (Steiger, 1980) comparing the strength of correlation with self-report measures of attention and metacognition to the extract clusters associated with ERT-linked neural change. Findings revealed that rsFC change in the cuneus, an area generally implicated in spatial attention (Simpson et al., 2011) especially when cues may convey threat or anger (Heesink et al., 2017), was more strongly associated with ERT-linked changes in shifting attention as compared with indicators of metacognitive change-decentering (t = 2.59, p = 0.02, Cohen's d = 1.22) and reappraisal (t = 1.82, p = 0.08, Cohen's d = 0.86). Conversely, rsFC change in the precuneus, a node of the DMN implicated in self-consciousness and self-related mental representations (e.g., Cavanna and Trimble, 2006) was more strongly correlated with ERT-linked gains in reappraisal as compared to gains in focused attention (t = 2.02, p = 0.04, Cohen's d = 1.04) and shifting attention (t = 1.61, p = 0.12, Cohen's d = 0.76). Finally, rsFC changes in the middle occipital gyrus, implicated with both attention (Benedek et al., 2016) and metacognition (Atique et al., 2011; Schurz et al., 2014) were similarly correlated with ERT-linked gains in attention, decentering, and reappraisal. Future research may wish to examine these areas for future seed-based analyses, ideally with a larger treatment sample.

There are several limitations of the present study. In particular, this study was preliminary and lacked a control group or treatment comparison, which raises caution in interpreting the findings. Future research, utilizing a randomized controlled trial design is the logical next step to determine what changes are uniquely related to ERT. Similarly, the study was conducted with a modest sample size and given the interest in investigating multiple nodes within the default mode and SN with several clinical variables of interest, larger samples will be needed in the future to robustly test the associations between these variables, as well as to assess moderating factors such as sex.

Future studies will help to test the reliability of the present results and further elucidate a mechanistic understanding of the impact of ERT therapy on psychological and neurobiological variables. Despite the aforementioned limitations, the present findings add a level of nuance to the growing literature on rsFC disruptions in GAD and MDD and highlight the potential impact of treatment on connectivity in these disorders.

DATA AVAILABILITY

Datasets are available on request: the raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

This study was approved by the Ethics Commitee of Hunter College Human Research Protection Program (HRPP). All participants in studies referenced gave full study consent prior to any research procedures.

AUTHOR CONTRIBUTIONS

MS, DF, FG, CL, SS, EG, and DM: substantial contributions to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for

all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REVIEW
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Treating PTSD: A Review of Evidence-Based Psychotherapy Interventions

Laura E. Watkins, Kelsey R. Sprang and Barbara O. Rothbaum*

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, United States

Posttraumatic stress disorder (PTSD) is a chronic, often debilitating mental health disorder that may develop after a traumatic life event. Fortunately, effective psychological treatments for PTSD exist. In 2017, the Veterans Health Administration and Department of Defense (VA/DoD) and the American Psychological Association (APA) each published treatment guidelines for PTSD, which are a set of recommendations for providers who treat individuals with PTSD. The purpose of the current review article is to briefly review the methodology used in each set of 2017 guidelines and then discuss the psychological treatments of PTSD for adults that were strongly recommended by both sets of guidelines. Both guidelines strongly recommended use of Prolonged Exposure (PE), Cognitive Processing Therapy (CPT) and trauma-focused Cognitive Behavioral Therapy (CBT). Each of these treatments has a large evidence base and is trauma-focused, which means they directly address memories of the traumatic event or thoughts and feelings related to the traumatic event. Finally, we will discuss implications and future directions.

Keywords: posttraumatic stress disorder, psychotherapy, treatment, evidence-based medicine, prolonged exposure, cognitive processing therapy, cognitive behavioral therapy

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****Correspondence:***
Laura E. Watkins
laura.e.watkins@emory.edu

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is a chronic, often debilitating mental health disorder that may develop after a traumatic life event, such as military combat, natural disaster, sexual assault, or unexpected loss of a loved one. Most of the U.S. population is exposed to a traumatic event during their lifetime (Sledjeski et al., 2008) and shortly after exposure, many people experience some symptoms of PTSD. Although among most individuals these symptoms resolve within several weeks, approximately 10%–20% of individuals exposed to trauma experience PTSD symptoms that persist and are associated with impairment (Norris and Sloane, 2007). Lifetime and past year prevalence rates of PTSD in community samples are 8.3% and 4.7%, respectively (Kilpatrick et al., 2013), with similar rates (8.0% and 4.8%) observed in military populations (Wisco et al., 2014). PTSD is associated with a wide range of problems including difficulties at work, social dysfunction and physical health problems (Alonso et al., 2004; Galovski and Lyons, 2004; Smith et al., 2005). Fortunately, effective psychological treatments for PTSD exist.

Diagnostic Criteria

The diagnosis of PTSD has undergone a number of changes since it was initially included in the Diagnostic and Statistical Manual of Mental Disorders Third Edition (DSM-III; American Psychiatric Association, 1980), including a revision in the most recent edition released in 2013

(DSM-5; American Psychiatric Association, 2013). Because the majority of PTSD treatment research currently published used criteria from the DSM-Fourth Edition-Text Revision (DSM-IV-TR; American Psychiatric Association, 2000) or from an earlier version of the DSM, it is important to note how the DSM-5 differs from these earlier versions. The DSM-5 reclassified PTSD as a Trauma- and Stressor-Related Disorder instead of an Anxiety Disorder. In the initial formulation of PTSD, a traumatic stressor was defined as an event outside the range of usual human experience. However, with recognition that traumatic events are relatively frequent, this criterion was revised. DSM-IV and DSM-IV-TR required that intense fear, helplessness, or horror were present in the individual's response to the traumatic event, although it became evident that this was not universal, especially in military populations. The DSM-5 increased specification as to what qualifies as a traumatic event (Criterion A) and conceptualized traumatic events as exposure to actual or threatened death, serious injury, or sexual violation, as directly experiencing traumatic events, learning of the traumatic events experienced by a close family member or close friend, or repeated exposure to aversive details of the traumatic events. DSM-5 removed the requirement that intense fear, helplessness, or horror were present in the individual's response to the traumatic event.

The symptom clusters of PTSD also have been revised in DSM-5. DSM-III and DSM-IV included three symptom clusters (re-experiencing, avoidance/numbing and arousal). DSM-5 transitioned from the original three symptom clusters to four symptom clusters including intrusion (five symptoms, one or more required for diagnosis), avoidance (two symptoms, one or more required for diagnosis), negative alteration in cognition and mood associated with the traumatic event (seven symptoms, two or more required for diagnosis) and marked alterations in arousal and reactivity associated with traumatic events (six symptoms, two or more required for diagnosis). The increase to four symptom clusters was a result of splitting avoidance/numbing into distinct clusters (avoidance and negative alteration in mood and cognition). In addition, negative alteration in mood and cognition contains symptoms previously considered numbing symptoms as well as persistent negative emotional states. Marked alterations in arousal and reactivity maintains symptoms previously considered arousal symptoms, in addition to irritable or aggressive behavior and reckless or self-destructive behavior. Consistent with previous editions of the DSM, these symptoms must be present for more than 1 month, cause clinically significant distress or impairment, and not be attributable to substance use or another medical condition. Familiarity with the DSM symptoms of PTSD is important for two primary reasons: diagnosing PTSD and understanding what traumatic event will be the focus of therapy. "Rape victim" or "combat veteran" is not a diagnosis. Before commencing psychological treatment for PTSD, the provider must be assured that PTSD is primary. When the patient presents with multiple traumatic events, current re-experiencing symptoms will often point towards what we refer to as the "index trauma," which will be the focus of psychological therapy.

PTSD Treatment Guidelines

A number of psychological treatments for PTSD exist, including trauma-focused interventions and non-trauma-focused interventions. Trauma-focused treatments directly address memories of the traumatic event or thoughts and feeling related to the traumatic event. For example, both Prolonged Exposure (PE) and Cognitive Processing Therapy (CPT) are trauma-focused treatments. Non-trauma-focused treatments aim to reduce PTSD symptoms, but not by directly targeting thoughts, memories and feelings related to the traumatic event. Examples of non-trauma-focused treatments include relaxation, stress inoculation training (SIT) and interpersonal therapy. Over the last two decades, numerous organizations (e.g., American Psychiatric Association, 2004; National Institute for Health and Clinical Excellence, 2005; Institute of Medicine, 2007; ISTSS [Foa et al., 2009]) have produced guidelines for treatment of PTSD, including guidelines by American Psychological Association (APA) and the Veterans Health Administration and Department of Defense (VA/DoD) that were both published in 2017. Guidelines are lengthy and contain a great amount of information. Thus, the purpose of the current review is to briefly review the methodology used in each set of 2017 guidelines and then discuss the psychotherapeutic treatments of PTSD for adults that were strongly recommended by both sets of guidelines. The guidelines recommended several medications for treatment of PTSD, such as Sertraline, Paroxetine, Fluoxetine, Venlafaxine (see American Psychological Association, 2017; VA/DoD Clinical Practice Guideline Working Group, 2017) however, for the purposes of this review we will focus solely on psychotherapy. The combination of psychotherapy and medication is not recommended by either these guidelines.

In 2017, the VA/DoD and APA each published a treatment guideline for PTSD. Guidelines for PTSD treatment are a set of recommendations for providers who treat individuals with PTSD. Guidelines are not standards, which are requirements or mandatory. Each of these guidelines was based on systematic reviews of the literature examining treatments for PTSD to recommend treatments with the largest and strongest evidence base. The APA guideline is specifically for treatment of PTSD among adults, while the VA/DoD guideline focuses on recommendations for general clinical management, diagnosis and assessment and treatment for providers working within the VA or DoD.

The APA guidelines (American Psychological Association, 2017) are based on a systematic review conducted by the Research Triangle Institute—University of North Carolina Evidence-Based Practice Center (RTI-UNC EPC; Jonas et al., 2013) and fully follow the Institute of Medicine (IOM; now the National Academy of Medicine) standards for developing high quality, independent and reliable practice guidelines (Institute of Medicine, 2011a,b). The review conducted by RTI-UNC included trials published prior to May 2012. The APA panel consisted of individuals from a number of backgrounds, including consumers, psychologists, social workers, psychiatrists and general medicine practitioners. The APA panel considered four factors in their recommendations: (1) overall strength of

the evidence for the treatment; (2) the balance of benefits vs. harms or burdens; (3) patient values and preferences for treatment; and (4) the applicability of evidence to various populations.

The VA/DoD guideline (VA/DoD Clinical Practice Guideline Working Group, 2017) is an update to the 2010 PTSD clinical practice guidelines published by the VA/DoD. This update follows the Guideline for Guidelines, which is an internal document of the VA/DoD Evidence-Based Practice Working Group (2013). Work group members had specialties and clinical areas of interest in ambulatory care, behavioral health, clinical pharmacy, clinical neuropsychology, family medicine, nursing, pharmacology, pharmacy, psychiatry and psychology. A focus group of patients was held prior to finalizing the key questions for the evidence review. The Lewin Team, including The Lewin Group, Duty First Consulting, ECRI Institute and Sigma Health Consulting, LLC, was contracted by the VA and DoD to support development of the guidelines and to conduct an evidence review. The literature review focused on interventional studies published between March 2009 and March 2016. The VA/DoD guideline used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the evidence base and assign a grade for the strength of each recommendation. This system uses four domains to assess strength of each recommendation: (1) balance of desirable and undesirable outcomes; (2) confidence in the quality of the evidence; (3) patient or provider values and preferences; and (4) other implications as appropriate (e.g., resource use, equity, acceptability, feasibility, subgroup considerations).

The recommendations of these two sets of guidelines were mostly consistent. See **Table 1** for an overview of the "strongly recommended" and "recommended" treatments for adults with PTSD. Both guidelines strongly recommended use of PE, CPT and trauma-focused Cognitive Behavioral Therapy (CBT). The APA strongly recommended cognitive therapy (CT). The VA/DoD recommended eye movement desensitization therapy (EMDR; APA "suggests"), brief eclectic psychotherapy (BET; APA suggests), narrative exposure therapy (NET; APA suggests) and written narrative exposure. In our discussion of PTSD treatments, we will focus on treatments that were strongly recommended by both guidelines, which includes PE, CPT and CBT. First, we will describe each treatment and evidence for its use and then we will discuss dropout, side effects and adverse effects of these treatments together.

STRONGLY RECOMMENDED TREATMENTS

Prolonged Exposure

PE is strongly recommended by both the APA and VA/DoD guidelines for treatment of PTSD. PE is based on emotional processing theory (Foa and Kozak, 1985, 1986), which suggests that traumatic events are not processed emotionally at the time of the event. Emotional processing theory suggests that fear is represented in memory as a cognitive structure that includes representations of the feared stimuli, the fear responses, and the meaning associated with the stimuli and responses to the stimuli. Fear structures can represent realistic threats, which is normal. However, fear structures can become dysfunctional. According to Foa and Kozak (1986), fear structures may become problematic when the association between stimulus elements do not accurately reflect the real world, physiological and escape or avoidance responses are induced by innocuous stimuli, responses that are excessive and easily triggered interfere with adaptive behavior, and safe stimulus and response elements are incorrectly associated with threat or danger. PE focuses on altering fear structures so that they are no longer problematic. Two conditions are necessary for fear structures to be altered and for exposure to work. First, the fear structure must be activated and second, new information that is incompatible with erroneous information in the fear structure must be incorporated into the structure.

The evidence-based manual describing PE indicates that this therapy is typically completed in 8–15 sessions (Foa et al., 2007). PE includes psychoeducation about PTSD and common reactions to trauma, breathing retraining, and two types of exposure: *in vivo* exposure and imaginal exposure. During psychoeducation, patients learn about PTSD, common reactions to trauma and exposure. Breathing retraining is a skill taught to assist patients in stressful situations but not to be used during exposure. The two main components of treatment are *in vivo* exposure and imaginal exposure. *In vivo* exposure assists patients in approaching situations, places and people they have been avoiding because of a fear response due to the traumatic event repeatedly until distress decreases. Imaginal exposure consists of patients approaching memories, thoughts and emotions surrounding the traumatic event they

TABLE 1 | Clinical practice guidelines for treatment of posttraumatic stress disorder (PTSD).

Clinical practice guideline	Methodology	Strongly recommended therapies	Recommended therapies
American Psychological Association (2017)	Independent systematic review; RCTs published from 5/25/12-6/1/16; Expert Review	CBT, CPT, PE, CT	BEP, EMDR, NET
VA/DoD Clinical Practice Guideline Working Group (2017) (revision of 2010 guidelines)	Independent systematic Review; RCTs published 1/1/09-March 2016; Expert Review	PE, CPT, EMDR, specific CBT for PTSD, BEP, NET and written narrative exposure	SIT, PCT, IPT

Note. CBT, Cognitive Behavioral Therapy; CPT, Cognitive Processing Therapy; PE, Prolonged Exposure; CT, Cognitive Therapy; EMDR, Eye Movement Desensitization Therapy; BET, Brief Eclectic Psychotherapy; NET, Narrative Exposure Therapy; SIT, Stress Inoculation Training; PCT, Present-Centered Therapy; IPT, Interpersonal Psychotherapy.

have been avoiding. Patients recount the narrative of the traumatic event in the present tense repeatedly and tape record this recounting to practice imaginal exposure for homework. The patient and therapist then process emotional content that emerged during the imaginal exposure. Through these two types of exposures, patients activate their fear structure and incorporate new information. PE is a particular program of exposure therapy that has been adopted for dissemination through the VA and DOD. The treatment manual has been translated into about nine different languages. A revised PE manual is due to be published in 2019. It has been shown to be helpful across survivors, in different cultures and countries, regardless of the length of time since traumatization or the number of previous traumatic events (Powers et al., 2010).

As suggested by its strong recommendation by both set of guidelines, there is a large body of research evidence that indicates the effectiveness of exposure therapy and particularly PE. Individuals randomly assigned to exposure therapy have significantly greater pre- to posttreatment reductions in PTSD symptoms compared to supportive counseling (Bryant et al., 2003; Schnurr et al., 2007), relaxation training (Marks et al., 1998; Taylor et al., 2003) and treatment as usual including pharmacotherapy (Asukai et al., 2010). In addition to the RCTs used to determine recommended treatment in the guidelines, several meta-analyses have found that exposure therapy is more effective that non-trauma focused therapies (Bradley et al., 2005; Powers et al., 2010; Watts et al., 2013; Cusack et al., 2016). A meta-analysis on the effectiveness of PTSD found the average PE-treated patient fared better than 86% of patients in control conditions on PTSD symptoms at the end of treatment (Powers et al., 2010). The effect sizes for PE were not moderated by time since trauma, publication year, dose, study quality, or type of trauma. A second meta-analysis, which examined psychological treatments for PTSD, found a high strength of evidence for the efficacy of PE (Cusack et al., 2016). Regarding loss of diagnosis, rates vary across studies. Among PE participants, 41% to 95% lost their PTSD diagnosis at the end of treatment (Jonas et al., 2013). In addition, 66% more participants treated with exposure therapy achieved loss of PTSD diagnosis than in waitlist control groups (Jonas et al., 2013).

Cognitive Processing Therapy

In addition to PE, CPT is strongly recommended by both the APA and VA/DoD guidelines for treatment of PTSD. CPT is a trauma focused therapy drawing on social cognitive theory and informed emotional processing theory as discussed above Resick and Schnicke (1992). CPT assumes that following a traumatic event, survivors attempt to make sense of what happened, often time leading to distorted cognitions regarding themselves, the world, and others. In an attempt to integrate the traumatic event with prior schemas, people often assimilate, accommodate, or over-accommodate. Assimilation is when incoming information is altered in order to confirm prior beliefs, which may result in self-blame for a traumatic event. An example of assimilation is "because I didn't fight harder, it is my fault I was assaulted." Accommodation is a result of altering beliefs enough in order to accommodate new learning (e.g., "I couldn't have prevented them from assaulting someone"). Over-accommodation is changing ones beliefs to prevent trauma from occurring in the future, which may result in beliefs about the world being dangerous or people being untrustworthy (e.g., "because this happened, I cannot trust anyone"). CPT allows for cognitive activation of the memory, while identifying maladaptive cognitions (assimilated and over-accommodated beliefs) that have derived from the traumatic event. The main aim of CPT is to shift beliefs towards accommodation (Resick and Schnicke, 1992).

Resick et al. (2017) have developed an updated treatment manual for CPT. CPT consists of 12 weekly sessions that can be delivered in either individual or group formats. Generally, CPT is composed of CT and exposure components (Resick and Schnicke, 1992; Chard et al., 2012). Clients work to identify assimilated and over-accommodated beliefs and learn skills to challenge these cognitions through daily practice (Resick et al., 2002). Initial sessions are focused on psychoeducation about the cognitive model and exploration of the patient's conceptualization of the traumatic event. The individual considers: (1) why the traumatic event occurred; and (2) how it has changed their beliefs about themselves, the world and others regarding safety, intimacy, trust, power/control and esteem. The original version of CPT included a written trauma account where the patient described thoughts, feelings and sensory information experienced during the traumatic event. However, following evidence from recent dismantling studies, the most recent version of the protocol does not include the written trauma narrative (Resick et al., 2008, 2017; Chard et al., 2012). CT skills are introduced through establishing the connection between thoughts, feelings, and emotions related to the individual's stuck points (maladaptive cognitions about the event) and learning ways to challenge cognitions that are ineffective (Chard et al., 2012). These skills are used to examine and challenge their maladaptive beliefs. CPT concludes with an exploration on the shifts in how the individual conceptualizes why the traumatic event occurred, focusing on the shift to accommodation rather than assimilation and over-accommodation.

CPT has been widely supported as an effective treatment for PTSD. While CPT was developed to treat survivors of rape (Resick and Schnicke, 1992), it has been researched and implemented successfully across trauma types and populations (Chard et al., 2012). Research findings suggest CPT effectively treats PTSD in sexual assault survivors (Chard, 2005), veterans who served in Vietnam, Iraq and Afghanistan (Chard et al., 2010), and adult males with comorbid TBI and PTSD (Chard et al., 2011). CPT has been found to exhibit clinically meaningful reduction in PTSD, depression and anxiety in sexual assault and Veteran samples, with results maintained at 5 and 10 year post treatment follow-up (Resick et al., 2012). Meta-analyses suggest that CPT is effective in significantly reducing PTSD symptoms (Watts et al., 2013; Cusack et al., 2016). Similar to findings for PE, the number of individuals who no longer meet criteria for PTSD after CPT varies across studies. Rates of participants who

no longer met PTSD diagnosis criteria ranged from 30% to 97% and 51% more participants treated with CPT achieved loss of PTSD diagnosis, compared to waitlist, self-help booklet and usual care control groups (Jonas et al., 2013).

Cognitive Behavioral Therapy for PTSD

Another strongly recommended therapy by APA and the VA/DoD is CBT for PTSD. The VA/DoD includes only trauma-focused CBT. APA included both trauma-focused and non-trauma-focused CBT in its recommendations including CBT-mixed, which included studies using cognitive behavioral techniques that did not fit in well with other categories, and CT, which included CT studies that were not specifically CPT. Brief trauma-focused CBT categorized by the VA/DoD included studies examining trauma-focused cognitive and/or behavioral techniques that were not specifically PE or CPT. Thus in this section, we will discuss brief therapies using trauma-focused behavioral and/or cognitive techniques as these are included in both sets of guidelines as strongly recommended.

Trauma-focused CBT is based on cognitive and behavioral models that tend to draw from other CBT theories, such as PE and CPT. For example, Ehlers and Clark (2000) proposed that individuals with PTSD hold excessively negative appraisals of the trauma and that their autobiographical memory of the trauma is characterized by poor contextualization, strong associative memory and strong perceptual priming, which leads to involuntary reexperiencing of the trauma. Ehlers and Clark suggest that individuals with PTSD engage in problematic behavioral and cognitive strategies that prevent them from changing negative appraisals and trauma memories. Thus, goals of this treatment include modifying negative appraisals, correcting the autobiographical memory, and removing the problematic behavioral and cognitive strategies. Kubany et al. (2004) suggest that guilt-associated appraisals may evoke negative affect and may be paired with images or thoughts of the trauma. These guilt appraisals may repeatedly recondition memories of the trauma with distress and may lead to tendencies to suppress or avoid trauma-related stimuli.

Trauma-focused CBT typically includes both behavioral techniques, such as exposure, and cognitive techniques, such as cognitive restructuring. CBT that includes exposure to the traumatic memory uses imaginal exposure, writing the traumatic narrative, or reading the traumatic memory out loud (Marks et al., 1998; Kubany et al., 2004; Ehlers et al., 2005). CBT that includes exposure to trauma-related stimuli typically uses *in vivo* exposure (Kubany et al., 2004) or teaching patients to identify triggers of re-experiencing and practice discrimination of "then vs. now" (Ehlers et al., 2005). Cognitive restructuring focuses on teaching patients to identify dysfunctional thoughts and thinking errors, elicit rational alternative thoughts, and reappraise beliefs about themselves, the trauma, and the world (Marks et al., 1998; Kubany et al., 2004; Ehlers et al., 2005). A CT targeting PTSD among battered women focused specifically on CT for trauma-related guilt in three phases: guilt issue assessment, guilt incident debriefings and CT (Kubany et al., 2004).

Consistent with the recommendations of the guidelines, research supports the effectiveness of trauma-focused CBT for PTSD. CBT has been shown to be more effective than a waitlist (Power et al., 2002), supportive therapy (Blanchard et al., 2003) and a self-help booklet (Ehlers et al., 2003). Researchers have compared different components of CBT (i.e., imaginal exposure, *in vivo* exposure, cognitive restructuring) with some mixed results. Marks et al. (1998) compared exposure therapy (that included five sessions of imaginal exposure and five sessions of *in vivo* exposure), cognitive restructuring, combined exposure therapy and cognitive restructuring, and relaxation in an RCT. Exposure and cognitive restructuring were each effective in reducing PTSD symptoms and were superior to relaxation. Exposure and cognitive restructuring were not mutually enhancing when combined. Bryant et al. (2008) compared imaginal exposure alone, *in vivo* exposure alone, imaginal and *in vivo* exposure, and imaginal, *in vivo*, and cognitive restructuring. In contrast to Marks et al. (1998), Bryant et al. (2008) found the treatment condition with both exposure components and cognitive restructuring had the largest effect size and resulted in fewer patients with PTSD at a 6-month follow-up. Regarding loss of diagnosis, 61% to 82.4% of participants treated with CBT lost their PTSD diagnosis and 26% more CBT participants than waitlist or supportive counseling achieved loss of PTSD diagnosis (Jonas et al., 2013).

Dropout, Side Effect and Adverse Effects

One common concern with trauma-focused treatment is dropout and rates of dropout appear to be similar across PE, CPT and trauma-focused CBT (Hembree et al., 2003). A substantial minority of individuals drop out of PTSD treatment (e.g., Imel et al., 2013). Imel et al. (2013) conducted a meta-analysis of treatment dropout in PTSD treatment. The aggregate proportion of dropout across all active treatments was 18.28%, however, there was a large amount of variability across studies. The dropout rate varied between active interventions for PTSD across studies, but the differences were primarily driven by differences between studies. In addition, an increase in trauma focus did not predict an increase in the dropout rate. Imel et al. (2013) did find evidence across three relatively large trials that dropout is lower in present centered therapy (PCT; 22%) compared to trauma specific treatments (36%).

Unfortunately, few studies explicitly report on side effects and adverse effects of PTSD psychotherapy (Cusack et al., 2016). The American Psychological Association (2017) guidelines recommends that research be conducted on side effects. When examining the results of large controlled trials there is no evidence that trauma-focused treatments are associated with a relative increase in adverse side effects (American Psychological Association, 2017; VA/DoD Clinical Practice Guideline Working Group, 2017). Clearly more research should examine and report on side effects and adverse effects of PTSD treatment.

IMPLICATIONS AND FUTURE DIRECTIONS

PE, CPT and trauma-focused CBT have been strongly recommended as treatments for PTSD in treatment guidelines

by the APA and the VA/DoD. Each of these treatments have a large evidence base supporting their effectiveness in treating PTSD. Although exposure-based therapies have the largest and strongest research evidence base (Cusack et al., 2016), research and meta-analyses comparing PE, CPT and trauma-focused CBT do not find that one treatment outperforms the other (Resick et al., 2002, 2008; Powers et al., 2010; Cusack et al., 2016).

The guidelines and strong research evidence suggest that PE, CPT and trauma-focused CBT should be the first line of treatment for PTSD whenever possible, considering patient preferences and values and clinician expertise. Research examining patient preferences suggests that individuals prefer PE, CPT and trauma-focused CBT to other treatments. Analog studies have demonstrated that participants have preferences for CT and exposure therapy over psychodynamic psychotherapy, EMDR, and therapies using novel technologies (e.g., virtual reality, computer-based therapy; Tarrier et al., 2006; Becker et al., 2007). In addition, results from studies examining clinical samples show that patient prefer psychotherapy, such as PE and CBT, to medication (Angelo et al., 2008; Feeny et al., 2009; Zoellner et al., 2009). Findings are similar among veteran and military samples, with soldiers showing greater preference for PE and virtual reality exposure (VRE) to paroxetine or sertraline (Reger et al., 2013) and veterans in a PTSD specialty clinic showing greater preference for CPT to other psychotherapies, PE to nightmare resolution therapy and PCT, and both PE and cognitive-behavioral conjoint therapy were preferred to VRE (Schumm et al., 2015).

The recommendations to use these treatments by the guidelines has not been without controversy in the provider community, as evidenced by online petitions against the APA guidelines (there is also a petition supporting the guidelines). Those who petition these guidelines may be concerned that trauma-focused treatments could pose a risk to some patients because of distress elicited by focusing on the trauma memory, may limit providers' ability to get reimbursed for other types of treatment, or they may believe that RCTs lead to false conclusions (for a rebuttal, see McKay, 2017; Shedler, 2017). However, as stated above, there is no evidence that trauma-focused treatments are associated with a relative increase in adverse side effects (American Psychological Association, 2017; VA/DoD Clinical Practice Guideline Working Group, 2017). In addition, although RCTs cannot answer all questions in clinical psychology science, they do eliminate more sources of error (e.g., placebo effect, confirmation bias) than other research designs, such as naturalistic or observational studies. Thus, dissemination of information about effective treatments, benefits and harms related to treatment, and effective research methodology to treatment providers who work with individuals with PTSD is imperative. There is also concern that these trauma-focused treatments may not be as effective among military samples (Steenkamp et al., 2015; Steenkamp, 2016). According to a review of trauma-focused treatment among military samples, approximately 60% to 72% of military patients retained PTSD diagnosis after treatment (Steenkamp et al., 2015). However, this rate was lower than comparison groups including waitlist and PCT (range 74%–97%), within-group posttreatment effect sizes for CPT and PE were large, and 49%–70% of patients receiving CPT or PE attained clinically meaningful symptom improvement (defined as a 10–12 point decrease in interviewer or self-report symptoms (Steenkamp et al., 2015). Findings from this review support the recommendation of the guidelines that PE, CPT and trauma-focused CBT should be the first line of treatment for PTSD and also suggest that outcomes from these treatments can be improved.

Future directions in PTSD treatment research include identifying ways to enhance effective treatments including among particular populations (e.g., military), further examination of treatments that are "recommended" rather than "strongly recommended", keeping individuals engaged in treatment (i.e., reducing dropout), and determining individual factors predicting response/nonresponse. Avoidance symptoms are a core feature of PTSD and maintain PTSD over time. Thus, it is not surprising that the dropout rate for PTSD treatment is high across treatment modalities. In addition, a portion of individuals do not respond adequately to PTSD treatment. One potential future direction is medication-enhanced psychotherapy for PTSD. Medication could potentially strengthen learning and memory, inhibit fear, and facilitate therapeutic engagement (Dunlop et al., 2012). Research is beginning to examine pharmacological agents to enhance response to trauma-focused therapies such as MDMA, D-cycloserine and the neuropeptide oxytocin (e.g., Mithoefer et al., 2011; de Kleine et al., 2012; Koch et al., 2014; Rothbaum et al., 2014). Non-pharmacological enhancement of therapy is also being explored such as rTMS (Kozel et al., 2018), exercise (Rosenbaum et al., 2015), and other cognitive training (Fonzo et al., 2017). Another potential avenue to increase engagement and reduce dropout is through use of intensive treatment programs, in which patients attend massed multiple sessions within a short period of time (e.g., one or 2 weeks) instead of weekly sessions spaced over several months. These types of programs are beginning to be evaluated with promising results (e.g., Harvey et al., 2017; Foa et al., 2018; Hendriks et al., 2018) and report excellent retention rates (90%–100%).

Further research on particular PTSD treatments is needed. As research continues to transition to the utilization of DSM-5 criteria, it will be essential to update the guidelines informed by the new criteria as this new conceptualization could impact the measurement and efficacy of these treatments. Examining biomarkers of PTSD, treatment response, and precision medicine, i.e., matching treatment to the individual, are the wave of the future. We need to compare interventions and determine if any treatment approaches are more or less effective for particular groups of people. Finally, further research is needed to develop new treatment approaches that are effective and acceptable to PTSD sufferers, as recommended in the 2014 IOM report (Institute of Medicine, 2014).

CONCLUSION

The guidelines put forth by the VA/DoD and the APA in 2017 are recommendations for providers who treat individuals with PTSD and both strongly recommend PE, CPT and trauma-

focused CBT. Each of these treatments has a large evidence base showing their effectiveness. These treatments are all trauma-focused, which means they directly address memories of the traumatic event or thoughts and feelings related to the traumatic event. Treatments with the strongest evidence should be the first line of treatment for PTSD whenever possible, with consideration of patient preferences and values and clinician expertise.

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LW, KS and BR discussed and conceived the topic and content of the review. LW and KS drafted the manuscript. BR wrote portions that appear throughout the manuscript. All authors provided critical revisions and approved the final manuscript.

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Neuroscience Informed Prolonged Exposure Practice: Increasing Efficiency and Efficacy Through Mechanisms

Monika M. Stojek[1,2], *Lauren B. McSweeney*[1,2] *and Sheila A. M. Rauch*[1,2,3]*

[1]Department of Psychiatry, Emory University School of Medicine, Atlanta, GA, United States, [2]Emory Healthcare Veterans Program, Atlanta, GA, United States, [3]Atlanta VA Medical Center, Atlanta, GA, United States

Prolonged exposure (PE) is an empirically supported efficacious treatment for posttraumatic stress disorder (PTSD). In this focused review, we briefly review the neurobiological networks in PTSD relevant to PE, discuss the theoretical basis of PE, review the neurobiological mechanisms underlying the effectiveness of PE and identify the enhancements that can be applied to increase treatment response and retention. Based on the reviewed studies, it is clear that PTSD results in disrupted network of interconnected regions, and PE has been shown to increase the connectivity within and between these regions. Successful extinction recall in PE is related to increased functional coherence between the ventromedial prefrontal cortex (vmPFC), amygdala and the hippocampus. Increased connectivity within the dorsolateral PFC (dlPFC) following PE is associated with more effective downregulation of emotional responses in stressful situations. Pre-existing neural connectivity also in some cases predicts response to exposure treatment. We consider various enhancements that have been used with PE, including serotonin reuptake inhibitors (SSRIs), D-cycloserine (DCS), allopregnanolone (ALLO) and propranolol, repetitive transcranial magnetic stimulation (rTMS), oxytocin and MDMA. Given that neural connectivity appears to be crucial in mechanisms of action of PE, rTMS is a logical target for further research as an enhancement of PE. Additionally, exploring the effectiveness and mechanisms of action of oxytocin and MDMA in conjunction with PE may lead to improvement in treatment engagement and retention.

Keywords: PTSD, prolonged exposure, psychotherapy, exposure therapy, neuroscience, extinction learning

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***Correspondence:**
Sheila A. M. Rauch
sheila.a.m.rauch@emory.edu

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Posttraumatic stress disorder (PTSD) has been increasingly recognized as a public health concern, with increased visibility as military service members return from combat deployments. Due to the psychological burden associated with its symptoms, PTSD is associated with significant physical, psychosocial and economic hardships (Ramchand et al., 2015). The hallmark symptoms of PTSD include: (1) re-experiencing the memory of the traumatic event through thoughts, images or nightmares; (2) avoidance of the reminders of trauma; (3) negative self-image and/or deterioration in mood; and (4) physiological hyperarousal (American Psychiatric Association, 2013). Trauma focused therapies, such as exposure-based

and cognitive therapies, particularly prolonged exposure (PE) and cognitive processing therapy (CPT), are efficacious for the treatment of PTSD (Watts et al., 2013) and are recommended in professional treatment guidelines (American Psychological Association, 2017; Department of Veterans Affairs & Department of Defense (VA & DoD), 2017) and the Institute of Medicine Report (Institute of Medicine, 2014). PE has been studied extensively and has consistently demonstrated causal reduction of symptoms of PTSD, anxiety and depression (Watts et al., 2013). In the era of precision medicine (Shukla et al., 2015) and objective (e.g., neurobiological and psychophysiological) measures of treatment outcome, it is crucial to move beyond establishing efficacy of treatment approaches and to investigation of the mechanisms of action of such efficacious treatments. A focus on mechanisms of action will contribute to increasing efficacy (remission and response), efficiency (time to response) and access (moving the active ingredients to new models of application).

In this review article, we will bridge two bodies of knowledge: the clinical mechanisms of action of an empirically-supported treatment for PTSD and the neurobiological underpinnings of such intervention. As such, we are bridging the bench and the bedside by writing for clinicians who provide these interventions and for the researchers designing future studies. We will begin by briefly reviewing neural circuits implicated in PTSD that are relevant in PE, followed by a description of PE and its theoretical underpinnings. We will examine the state of current knowledge on how PE impacts the neural circuits related to PTSD. We will provide a synthesis of findings to date and discuss neurobiological enhancements that have been or may be used in conjunction with PE to enhance its effectiveness. Finally, we will offer some neurobiologically-informed directions for future research and practice.

NEUROBIOLOGY OF PTSD

In recent years, several reviews have summarized the state of knowledge regarding neural circuits implicated in PTSD (Duval et al., 2015; Liberzon and Abelson, 2016; Sheynin and Liberzon, 2017). In the current article, we briefly review the circuits most relevant to understanding therapeutic mechanisms of action in PE.

The neural circuit underlying fear-related learning is most commonly implicated in models of PTSD (Rauch et al., 2006; Shin and Handwerger, 2009; Jovanovic and Ressler, 2010; Shvil et al., 2013). The fear neurocircuitry consists of several brain structures including the amygdala, anterior cingulate cortex (ACC) and the ventromedial prefrontal cortex (vmPFC; Shin and Liberzon, 2010). The fear network is implicated in evaluating whether a stimulus should be approached or avoided, and activity in this network is correlated with anxiety (Shin and Liberzon, 2010). The evidence from fMRI studies indicates that the amygdala, which receives sensory input and orchestrates the response to threatening signals, is overactive in PTSD, likely contributing to the exaggerated fear response and re-experiencing symptoms (Rauch et al., 2006; Shin et al., 2006; Milad et al., 2009). The vmPFC downregulates the amygdala and appears to play a critical role in extinction recall (Quirk et al., 2000). In PTSD, vmPFC is hypoactive, thus projecting less inhibitory input and contributing to the hyperactivation of the amygdala (Rauch et al., 2006; Shin et al., 2006; Liberzon and Abelson, 2016). ACC which, along with the amygdala, processes aversive stimuli and projects to the peripheral nervous system to trigger a response, has been shown to be hyperactive during extinction recall in individuals with PTSD (Hayes et al., 2012; Koch et al., 2016). This dysregulation in the fear neurocircuitry is purported to underlie the failure to extinguish the fear response over time (Rauch et al., 2006; Jovanovic and Ressler, 2010; Liberzon and Abelson, 2016) and possibly the overgeneralization of fear to non-threatening cues (Stevens et al., 2013; Lopresto et al., 2016).

The neurocircuitry implicated in context processing has also received attention in relation to PTSD etiology and maintenance (Liberzon and Abelson, 2016). Within the fear neurocircuitry, hippocampus is involved in the process of contextualization, or accurately discriminating threat in the environment (Maren and Fanselow, 1995). Hippocampal inputs provide contextual information to the amygdala and to the vmPFC, thus downregulating the amygdala and facilitating extinction learning as the network normally functions (LeDoux, 2000). In the overgeneralized conditioned fear response present in PTSD, hippocampus and vmPFC are hypoactive in environments that are safe thus projecting dampened inputs to the amygdala and failing to downregulate amygdala's functioning in those contexts (Garfinkel et al., 2014). Hypoactivity of the vmPFC and the hippocampus may contribute to the re-experiencing symptoms via difficulties in extinction learning, a process further reinforced by avoidance (Pitman et al., 2012). Individuals with PTSD have demonstrated difficulty in maintaining learned fear extinction, or extinction recall (Milad et al., 2008, 2009). In fMRI studies, patients with PTSD have reduced hippocampal and vmPFC activation, and increased ACC activation during extinction recall (Milad et al., 2009; Hayes et al., 2012; Shvil et al., 2014; Koch et al., 2016) and the contextual processing period of extinction recall (Rougemont-Bücking et al., 2011). Previous studies have found that smaller hippocampal volume is associated with PTSD (Gilbertson et al., 2002). Hippocampus volume does not appear to change longitudinally over the course of PTSD in adults (Lindgren et al., 2016) but there is some evidence for impaired hippocampus development during childhood maltreatment (Dannlowski et al., 2012; Keding and Herringa, 2015). This suggests that hippocampal volume is vulnerability factor for PTSD that is likely epigenetically shaped.

Finally, emotion regulation deficits, or difficulties in awareness and modulation of intense negative emotional states, may be a transdiagnostic factor for the development and maintenance of many psychological disorders, including PTSD (Bradley et al., 2011; Sheynin and Liberzon, 2017). Based on neuroimaging findings, two broad types of emotion regulation include explicit and implicit emotion regulation (Gyurak et al., 2011). Explicit emotion regulation is effortful and requires some level of insight and awareness (Etkin et al., 2015). The most known example is reappraisal, or an alteration of the

meaning of an emotion-inducing stimulus. The brain regions implicated in reappraisal include dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC) and parietal cortex (Buhle et al., 2014; Kohn et al., 2014). Implicit emotion regulation is automatic in response to a stimulus and can occur without insight or awareness (Gyurak et al., 2011). The vmPFC is the brain region primarily implicated in implicit emotion regulation (Gyurak et al., 2011). Therefore, a neurobiological emotion regulation model posits that the PFC regions are responsible for cognitive control via stimulus interpretation (either explicit or implicit), thus downregulating the amygdala activation in response to emotionally salient stimuli (Ochsner et al., 2012; Buhle et al., 2014). Only a handful of studies examined neuropsychological and neurobiological correlates of emotion regulation in PTSD (New et al., 2009; Aupperle et al., 2012; Rabinak et al., 2014; Shepherd and Wild, 2014). The results point to the pattern of suppressing emotions, using less cognitive reappraisal (Shepherd and Wild, 2014), deficits in inhibitory control (Aupperle et al., 2012), and diminished downregulation of emotional response including hypoactivation of dlPFC (New et al., 2009; Rabinak et al., 2014). While these three broad neural circuits are not an exhaustive representation of neurobiological underpinnings of PTSD, they comprehensively represent the regions of interest when considering the effects of PE on neural activity.

PROLONGED EXPOSURE AND ITS THEORETICAL UNDERPINNINGS

PE (Foa et al., 1991) is an exposure-based psychological intervention designed to treat PTSD following trauma. The main goal of PE is to promote emotional processing through deliberate systematic confrontation with trauma-related stimuli (Foa, 2011). The key components of PE are: (1) repeated imaginal exposure (IE), which requires the individual to revisit their trauma memory in a therapeutic context; (2) *in vivo* exposure (IVE) to places and situations that are avoided because they evoke stress and anxiety; and (3) emotional processing that focuses on reviewing the experience of exposure and its impact on thoughts related to the trauma. A significant body of evidence has demonstrated the efficacy and effectiveness of PE in the treatment of PTSD and related depression, general anxiety, guilt, anger, and physical health concerns (e.g., Foa and Rauch, 2004; Rauch et al., 2009). In relation to PTSD, PE has reliably established clinically significant reduction in symptoms, with large effect sizes among various treatment samples with a variety of trauma histories (Powers et al., 2010). Based on intent to treat analyses, on average, 53% of those who initiate PE no longer meet diagnostic criteria for the disorder, and the rate of diagnostic change increases to 68% among individuals who complete treatment (Bradley et al., 2005).

Development of PE was based on Emotional Processing Theory (Foa and Kozak, 1986). The fundamental tenet of EPT is that there are fear structures (expanded later to include other emotions as well as fear; Rauch and Foa, 2006; expanded later to include other emotions as well as fear; Rauch and Foa, 2006) that include stimulus, response, and meaning elements, and that these structures are there to assist in response to situations of danger or threat. Activation of the adaptive fear structure is viewed as a normal and rational response to a stimulus (e.g., a car racing towards me), meaning (dangerous) that elicits a fear response (increased heart rate), followed by an action (moving out of the way) to remain safe (Foa and Kozak, 1986). Following trauma, additional unhelpful fear (or other emotion) structures develop that represent the stimulus, response, and meaning elements from the time of the trauma but that may not represent actual threat or danger outside of the specific trauma context. Rauch and Foa (2006) state that an optimal level of activation including all elements of the trauma structure is necessary for successful treatment. When the full memory, including all the emotional and cognitive responses, is activated, updated information that is incompatible with the trauma memory can be incorporated (reconsolidated) into the memory structure. Extinction[1] occurs in the context of repeated exposure to the feared stimulus and is marked by a reduction in physiological and emotional intensity of response to that stimulus (Sripada and Rauch, 2015). They argue that the trauma structure of individuals with PTSD contains maladaptive cognitions that underlie the maintenance of PTSD (Foa et al., 1991).

Theoretically, the learning principles of classical conditioning explain the acquisition of the fear response (Rothbaum and Davis, 2003; Blechert et al., 2007). Specifically, the traumatic event represents the unconditional stimulus (UCS), which produces the unconditioned response (UCR; e.g., fear, helplessness or horror). Neutral stimuli that were present during traumatic event become conditioned stimuli (CS) that can elicit a conditioned response (CR) similar to the reaction during the initial traumatic event. In an effort to reduce the experience of fear (or other negative emotions), individuals will avoid stimuli which evoke the emotional response. Consistent with the operant conditioning model (Mowrer, 1960), this avoidance serves as a negative reinforcement strategy, reducing the experience of negative emotions associated with the CS. In patients with PTSD, the overgeneralization of conditioned fear maintains and exacerbates PTSD symptoms (Lissek and Grillon, 2012).

While EPT and the learning theory are two separate theories of PTSD, there is considerable overlap in the concepts from both theories, and the mechanisms of PE have been conceptualized using both theories (Rauch and Liberzon, 2016). The EPT concept of extinction in PE can be better described in terms of extinction and relearning including contextualization of learning and memory (Rauch and Liberzon, 2016). Extinction occurs when new inhibitory associations are formed on top of the fear associations, and is marked by a reduction in subjective fear response to the feared memory and its reminders. This relearning is facilitated through the process of contextualization, or learning to discriminate between safety and threat cues, depending in the context in which they occur (Maren et al., 2013). The cognitive and emotional processing changes that

[1]We have chosen to use extinction rather than the term habituation used by Foa and Kozak (1986) based on more recent theorists and neuroscience research that aligns more with extinction processes (see Rauch and Liberzon, 2016 for review).

occur in tandem with extinction and relearning are marked by increased sense of competence, reduced sense that the world as dangerous, and reduction in social and emotional withdrawal (Rothbaum et al., 2005; Rauch and Liberzon, 2016). Although change in self-efficacy and trauma-related beliefs is not central to learning models, this learning of increased competence to cope with negative affect and reduced sense of a dangerous world can be viewed as a form of inhibitory learning (Rauch and Liberzon, 2016), which has been speculated to be a one of the key mechanisms of action in exposure-based treatment for PTSD (Craske et al., 2008).

NEUROBIOLOGY OF PE

Development of PE was not rooted in a neurocircuitry-based framework but its purported mechanisms of action and effectiveness may be examined using that framework. The fear and contextualization neurocircuitry is implicated in extinction learning and recall, one of the putative active components of PE (Jovanovic and Ressler, 2010; Liberzon and Abelson, 2016; Lopresto et al., 2016). A few early studies which used exposure-based therapy (but not PE specifically) have found increased activation in the prefrontal regions in individuals with PTSD following a course of psychotherapy (Felmingham et al., 2007; Peres et al., 2007). Following therapy, increased activation in the left PFC was correlated with decreased activation of the amygdala and increased activation in the hippocampus during retrieval of the traumatic memory by individuals with PTSD (Peres et al., 2007). During processing of threatening stimuli, individuals with PTSD demonstrated increased vmPFC (particularly rostral ACC) activation and decreased amygdala activation from pre- to post-treatment (Felmingham et al., 2007). Recent studies examined the effect of PE on extinction in laboratory settings. During fear extinction recall paradigm, individuals who underwent PE demonstrated a decrease in rostral ACC activation from pre- to post-treatment (Helpman et al., 2016a). Structurally, those who remitted from PTSD following a course of PE demonstrated volume reduction and thinning in the left rostral ACC, compared to those who did not remit and to controls (Helpman et al., 2016b). No between-group differences in ACC volume and thickness were observed prior to treatment (Helpman et al., 2016b).

One putative explanation of these functional and structural brain changes following PE is the extinction of maladaptive cognitive-emotional connections resulting from extinction learning (Helpman et al., 2016b). In PTSD, fear neurocircuitry may reinforce existing connections and contribute to the formation of new ones (Johansen et al., 2011). These results suggest that effective extinction that occurs during PE contributes not only to a more balanced feedback loop between the vmPFC and the amygdala (Felmingham et al., 2007; Peres et al., 2007) but also to the thinning of the ACC via decreased activation and pruning of the connectivity (Helpman et al., 2016b). This reciprocal relationship between neural connectivity and treatment response may also work the other way. There is some evidence that individual's capacity to benefit from PE may be modulated by the degree of spontaneous PFC downregulation of the amygdala when processing threat cues prior to treatment (Fonzo et al., 2017). Specifically, patients who before receiving a course of PE had greater activation of the dlPFC as well as less amygdala activation during an emotional reactivity task (detection and processing of threatening cues), showed the biggest gains from PE (Fonzo et al., 2017). This finding potentially suggests that extinction learning and recall may be more difficult for some individuals to achieve based on the extent to which their vmPFC is able to downregulate the amygdala during exposure. Hippocampus is another structure integral to the fear neurocircuitry. Structural differences in the contextualization neurocircuitry, particularly the hippocampus, have been shown to be associated with vulnerability to PTSD (Gilbertson et al., 2002; Lindgren et al., 2016). PE responders and controls had greater baseline hippocampal volume compared to treatment non-responders (Rubin et al., 2016), indicating that hippocampal volume may not only confer risk for PTSD development (Gilbertson et al., 2002; Lindgren et al., 2016) but also be related to better outcome in PE. PE does not affect hippocampal volume (Rubin et al., 2016). Recent research linked deficits in accurately discriminating context between threating and safe situations to a smaller hippocampus (Negash et al., 2015), thus extinction recall in PE may be affected by it. While a few studies using other exposure-based treatments for PTSD have demonstrated increased hippocampal activation in patients with PTSD following psychotherapy (Felmingham et al., 2007; Peres et al., 2007), no study to date has demonstrated increased activation with PE (Lindauer et al., 2005; van Rooij et al., 2015; Rubin et al., 2016). Overall, the fear and contextualization neurocircuitries (amygdala, vmPFC, ACC and the hippocampus) appear to be heavily involved in the processes of extinction learning and recall in PE. As expected, PE restores the balance in the vmPFC-amygdala loop and decreases the activation in the ACC during extinction recall. Interestingly, the functioning and volume of some of these structures may also be a prognostic indicator for PE's efficiency and a target for enhancement interventions.

Emotion regulation neurocircuitry is not a unified neurocircuitry but a set of circuits that share regions with the fear neurocircuitry (Ochsner et al., 2002; Sheynin and Liberzon, 2017) but there is some evidence to suggest that activation in and connectivity between these circuits may underlie treatment outcomes in PE. In one neuroimaging study, patients underwent an implicit (unintentional) emotion regulation task and an explicit (intentional and deliberate) emotion regulation task before receiving a course of PE (Fonzo et al., 2017). Individuals with greater vmPFC activation during the implicit emotion regulation task showed larger PTSD symptom reduction at the end of treatment (Fonzo et al., 2017). This points to the possibility that certain individuals' brains may have diminished capacity to reduce interference from an emotionally-salient cue in the environment, possibly making it more difficult to fully engage in PE. Interestingly, activation during the explicit emotion regulation task at baseline did not predict symptom change (Fonzo et al., 2017). This

is consistent with EPT's emphasis on emotional engagement during exposures to facilitate extinction and inhibitory learning insofar that efforts at attenuating emotional responses during exposure are counterindicated and interfere with learning (Craske et al., 2008; Foa, 2011). Increased competence to cope with negative affect is a type of inhibitory learning speculated to be an active ingredient in PE's effectiveness (Rauch et al., 2001; Foa and Rauch, 2004; Zalta et al., 2014). These emotion regulation skills are acquired both through successful exposures and through processing that occurs following exposures. In a study examining the effect of PE on emotion regulation skills in a sample of individuals with PTSD (Jerud et al., 2016), PE was associated with clinically meaningful improvements in emotion regulation skills, but a course of sertraline had a similar effect (Jerud et al., 2016). Therefore, it is difficult to determine whether the PE effects on emotion regulation are specific to PE or more generalized to any effective PTSD intervention. One neuroimaging study examined connectivity in the "default mode network" (mPFC, parietal cortex) which has been implicated in attentional control (Fox et al., 2015) before and following a mindfulness based exposure therapy (King et al., 2016). Following exposure therapy (but not present-centered therapy), increased connectivity of the default mode network to the dlPFC was observed, and this increased connectivity was associated with decreased avoidance and hyperarousal symptoms of PTSD (King et al., 2016). This pattern of neural activation suggests increased attentional control, one of the components of emotion regulation (Thompson, 2008; Wilcox et al., 2016), following mindfulness based exposure therapy. Correlation with decreased avoidance and hyperarousal also points to greater deployment of emotion regulation skills at the behavioral level. However, no study has examined the effects of PE on the emotion regulation neurocircuitry, therefore, it is impossible to know how much of the effect is due to mindfulness training and how much is to the exposure component. As suggested previously, emotion regulation deficits may be a transdiagnostic factor contributing to the development and maintenance of various types of psychopathology (Bradley et al., 2011; Sheynin and Liberzon, 2017), therefore, increased connectivity in that region may reflect an alleviation in symptoms due to an effective treatment in general, rather than due to a mechanism specific to PE. PTSD results in a disrupted network of interconnected brain regions. The neuroimaging studies to date suggest that changes in some neurocircuitries are more unique to the putative mechanisms of PE (e.g., the fear and contextualization neurocircuitries are affected by the extinction learning and recall component of PE) while changes in others may be more generally related to mechanisms not unique to PE (e.g., inhibitory learning related to increased emotion regulation skills). Successful extinction recall in PE appears to be related to increased functional coherence between vmPFC, amygdala, and the hippocampus (Helpman et al., 2016a). Similarly, increased connectivity between areas implicated in attentional control (default mode network) and areas implicated in explicit emotion regulation (dlPFC) appears to be indicative of more effective coping with negative affect and downregulation of emotional responses in stressful situations (King et al., 2016; Fonzo et al., 2017). Therefore, while the functioning of individual brain structures is important and clearly impacted by the active components of PE, it appears that increased and more efficient communication between various structures that regulate each other, is of greater importance in PTSD remission.

NEUROBIOLOGICAL ENHANCEMENTS OF PE TREATMENT

The purpose of this focused review is to create a bridge between neuroscience and practice of PE therapy by examining the effects of exposure therapy on the neural circuits implicated in PTSD. Further, we aim to use the advances in neuroscientific treatment outcome research in order to propose potential enhancement to the practice of PE based on the neurocircuits that have been shown to be affected by it. The neurobiological findings to date may be applied in two ways: (1) to identify potential PE treatment enhancements in order to facilitate emotional engagement, extinction and emotion regulation/inhibitory learning; and (2) to identify individuals who may be more likely to respond to certain enhancement, in order to provide personalized treatment.

Selective serotonin reuptake inhibitors (SSRIs) are recommended in treatment guidelines as treatment for PTSD, following the evidence-based psychotherapies such as PE (Institute of Medicine, 2014; American Psychological Association, 2017). Preliminary evidence suggests that facilitation of serotonergic transmission produced by SSRIs results in increased activation in the vmPFC regions (Brady et al., 2000; Davidson et al., 2001). A recent study compared the effects of PE alone or sertraline alone on attentional inhibition (as measured by a laboratory task) in individuals with PTSD to examine the effects of each of these therapies on one of the purported main mechanism of change in treatment of PTSD, inhibitory learning (Echiverri-Cohen et al., 2016). The authors found that those who showed more symptom improvement with PE treatment showed greater improvements in inhibitory processes from pre- to post-treatment. In contrast, those who showed greater symptom reductions on sertraline made less improvement in their inhibitory processes (Echiverri-Cohen et al., 2016). This discrepancy may point to different mechanism of action of each of these treatment and support the hypothesis that SSRIs bring about more bottom-up neurochemical changes in the fear circuitry, vs. the top-down changes produced through extinction and inhibitory learning in PE. In addition, another study found emotion dysregulation was improved equally as a result of PE or sertraline in individuals with PTSD from pre- to post-treatment but the mechanisms of action of each treatment were not tested (Jerud et al., 2016). Given that SSRIs may have a suspected different path of action than PE on restoring the balance in the limbic-prefrontical system, many have speculated that combining these interventions may augment each alone or alternatively that different people may respond to each treatment. In two studies using reverse designs (one augmenting PE on SSRI non-responders and the other augmenting SSRI for PE non-responders), results supported

that for partial responders to SSRI augmentation with PE was effective (Rothbaum et al., 2006). However, when SSRI was added for those who only partially or did not respond to PE, there was no added benefit (Simon et al., 2008). Identification of genetic variants associated with more robust response to SSRIs or PE in PTSD could allow for more personalized and effective treatments. Ongoing biomarkers studies of treatment response (e.g., project PROGrESS; Rauch et al., 2018) promise to inform our field in these areas over the next several years.

Glutaminergic and GABAnergic neurotransmission has been implicated in fear conditioning and extinction (Riaza Bermudo-Soriano et al., 2012), and D-cycloserine (DCS), a partial agonist at the *N*-methyl-D-aspartate (NMDA), has been implicated in fear extinction through the modulation of NMDA receptors in the amygdala (Norberg et al., 2008). While preclinical studies showed promising results (Walker et al., 2002; Ledgerwood et al., 2005; Yang and Lu, 2005) when DCS was used to facilitate extinction learning in rodents, human studies using exposure therapy yielded mixed results. Of studies that examined DCS as an augmentation agent in exposure therapy, only one found improved treatment outcomes with DCS (Difede et al., 2014). Two studies found no noticeable added benefit from supplementing exposure therapy with DCS (de Kleine et al., 2012; Rothbaum et al., 2014), while one study found poorer treatment outcomes in the group who received DCS-augmented exposure therapy compared to placebo (Litz et al., 2012). These mixed findings suggest that DCS may be an effective exposure enhancer for a certain subgroup of individuals with PTSD. For example, de Kleine et al. (2012) found that patients with high initial scores and who completed all treatment sessions actually benefited from DCS augmentation. DCS has also been shown to facilitate reconsolidation (or updating) of fear memory in animal studies (Lee et al., 2006). Therefore, it is possible that in the case of an exposure in which extinction is insufficient, fear memory is reconsolidated in a more intense form (Litz et al., 2012), basically making an unsuccessful exposure worse. To date, the majority of studies using DCS and exposure therapy for PTSD have failed to find a clear enhancing value of DCS. Studies with individuals with fear of heights as well as social anxiety found that administering DCS following a successful exposure, did indeed augment those exposures (Smits et al., 2013a,b; Tart et al., 2013). It appears that DCS may be a very specific intervention and has to be carefully tailored to individual's symptom severity and their response to IE, and more studies of moderators and mediators of DCS impact on extinction and learning are needed before recommending it as an augment to PE.

Exogenous administration of the neurosteroids DHEA(S) and pregnenolone that modulate GABA action in the brain has also been studied in PTSD interventions. Dehydroepiandrosterone (DHEA) and its sulfated metabolite (DHEAS) are endogenous neurosteroids with negative modulatory effects (GABA antagonist) on the GABAnergic system (Maninger et al., 2009). DHEA(S) levels have been shown to be inversely related to depression (Barrett-Connor et al., 1999; Wong et al., 2011) and positively related to executive function (Alhaj et al., 2006; Davis et al., 2008). Allopregnanolone (ALLO), an endogenous neurosteroid, is one of the most potent GABA agonists (Lambert et al., 2003) and has been shown to have anxiolytic effects (Paul and Purdy, 1992). In a sample of healthy men, single-dose DHEA administration was associated with decreased activation in the amygdala, and increased connectivity between the amygdala and the hippocampus during emotion regulation laboratory task (Sripada et al., 2013b). Administration of pregnanolone was associated with decreased amygdala activation and with increased connectivity between prefrontal cortical regions and the amygdala during that same task (Sripada et al., 2013c). Therefore, it appears that DHEA(S) and ALLO may be involved in the emotion regulation neurocircuitry and affect communication between the amygdala and the prefrontal regions related to executive functioning. Of note, ALLO has been shown to have positive effects on pain tolerance (Scioli-Salter et al., 2016), symptoms of traumatic brain injury (Marx et al., 2016), and depression and bipolar disorder (Osuji et al., 2010; Brown et al., 2014). The same way emotion dysregulation may be a transdiagnostic indicator of emotional disorders, DHEA(S) and ALLO may have a transdiagnostic therapeutic effect, independent of the mechanisms of action of PE and therefore not specific to PTSD (Rasmusson et al., 2017).

As increased neural connectivity within and between different neurocircuits is emerging as an important mechanism of action in psycho- and pharmacotherapies, repetitive transcranial magnetic stimulation (rTMS) has been of interested as a stand-alone and add-on treatment for PTSD (Karsen et al., 2014; Yan et al., 2017). rTMS uses an electromagnetic field to non-invasively stimulate cortical neurons through repeated changes in the coil's magnetic field (George et al., 2002; George and Post, 2011) and has been approved by the Food and Drug Administration for the treatment of drug-resistant depression. The most common target for these studies has been broadly the dlPFC (Karsen et al., 2014), with its projections to the fear and contextualization circuits (i.e., the amygdala, the hippocampus, and the vmPFC). To date, several reviews and/or meta-analyses have demonstrated the effectiveness of rTMS for treatment of PTSD by targeting the right dlPFC regions (Karsen et al., 2014; Clark et al., 2015; Yan et al., 2017). Fonzo et al. (2017) found that when the right dlPFC was stimulated via rTMS, it downregulated the inhibition of the left amygdala; the magnitude of that effect was a predictor of PE response. A study that used TMS as a stand-alone treatment (no exposure therapy) found that the pre-existing connectivity between the ACC and the default mode network responsible for attentional control as well as connectivity between the amygdala and the vmPFC predicted patient's response in rTMS treatment (Philip et al., 2018). Therefore, assessing patient's brain activation patterns pre-treatment may be used as a predictor of treatment response. More importantly, the rTMS studies to date identify neurostimulation-accessible brain regions that may serve as targets for enhancing exposure therapy either prior to or during the course of PE (Fonzo et al., 2017).

One novel candidate enhancement to PE that is purported to target the actual engagement in treatment and the quality of therapeutic alliance is a neuropeptide oxytocin (Olff et al., 2010). Oxytocin's properties of enhancing prosocial behavior, trust and warmth may be useful in facilitating extinction and inhibitory learning in exposure therapy through successful

therapeutic alliance (McLaughlin et al., 2014) and decreasing dropout rates (Tuerk, 2014). One unpublished small study found that a single administration of oxytocin to individuals with PTSD decreased anxiety scores, irritability, intensity of intrusive symptoms, and increased the desire for social contact (Yatzkar and Klein, 2010). Thus far, only one pilot randomized controlled trial examined the efficacy of administering intranasal oxytocin 45 min prior to each IE in patients with PTSD who were undergoing PE (Flanagan et al., 2018). The group who received oxytocin demonstrated lower PTSD and depression symptoms during PE and had higher therapeutic alliance scores but these differences were not statistically significant, potentially due to low power (Flanagan et al., 2018). Therefore, larger RCTs are warranted to further explore the efficacy of oxytocin as a supplement to PE. Another promising novel augmentation to PE is MDMA (Thal and Lommen, 2018), a substituted amphetamine (i.e., a class of compounds based on the amphetamine structure derived by replacing one or more hydrogen atoms in the amphetamine core structure) with properties similar to mescaline, psilocybin, and other psychedelic compounds. The cognitive effects of MDMA in clinical studies have included enhanced mood, happiness, physical and mental relaxation, increased emotional responsiveness, increased openness and extraversion, and increased prosocial behaviors such as trust and feelings of closeness to other people (Harris et al., 2002; Vollenweider et al., 2002). In addition, MDMA has been demonstrated to facilitate extinction retention in mice (Young et al., 2017). The exact pharmacological mechanisms of MDMA's action are not well-understood. MDMA is known to acutely facilitate the release of serotonin and oxytocin (Dumont et al., 2009; van Wel et al., 2012), potentially contributing to decreased avoidance and greater engagement in exposure-based therapy.

To date, there have been three clinical trials examining the effectiveness of MDMA as an adjunct to psychotherapy for treating PTSD (Mithoefer et al., 2011, 2018; Oehen et al., 2013). In all three of these studies, MDMA was administered shortly before the psychotherapy session and participants demonstrated significant decreases in PTSD symptoms at the end of treatment and at follow up (Mithoefer et al., 2011, 2018; Oehen et al., 2013). Of note, psychotherapy administered in these studies was not one of the empirically supported exposure-based treatments for PTSD and was instead non-directive and focused more on experiencing than on verbal exchanges (Mithoefer, 2011). MDMA remains to be tested as an enhancement to PE. Given the proposed mechanism of action in MDMA (i.e., increases in serotonin and oxytocin, increased trust and openness to new ideas), it is possible that it would be particularly helpful to apply it during the processing portion of the session, when patients' beliefs about themselves, others, and the world are reflected and become less rigid. Alternatively, MDMA may be useful only for those patients who exhibit slow or no extinction during IE. One recent study found that, on a personality trait level, patients who received MDMA during psychotherapy exhibited an increase in the Openness trait post-treatment and at follow-up, while their Neuroticism trait remained unchanged (Wagner et al., 2017). This suggests that indeed the mechanism of effective action in the case of MDMA may be greater openness to new ideas and decreased cognitive rigidity rather than decreased negative emotionality. While promising, the efficacy and effectiveness of supplementing PE with MDMA remains an empirical question.

FUTURE DIRECTIONS AND CONCLUSIONS

The mechanisms of action of PE have been of great interest in the past decade and neuroimaging studies followed suit. Currently, it is clear that various neural circuits are impacted in the course of PE but it also appears that certain patterns of neural activation and connectivity predict patient's response in PE. Generally, exposure therapy appears to have an impact on the fear and contextualization neurocircuitry by facilitating improved communication between the vmPFC, hippocampus, and the amygdala, leading to downregulation of the fear response in the amygdala (Helpman et al., 2016a). PE has been shown to decrease the activity in and the volume of the ACC. This increased coherence between these particular regions may be the mechanisms unique to PE (or exposure therapy in general) given that successful exposures lead to extinction learning and recall, thus extinguishing the overgeneralized fear response. There appears to be a more general process of emotional regulation that is of importance as well. Similarly, increased connectivity between areas implicated in attentional control (default mode network) and areas implicated in explicit emotion regulation (dlPFC) appears to be indicative of more effective coping with negative affect and downregulation of emotional responses in stressful situations (King et al., 2016; Fonzo et al., 2017). This process has been conceptualized as more transdiagnostic and less specific to PTSD or PE. Finally, it appears that neural connectivity *prior* to treatment may have profound impact on treatment response, offering some directions for future use of prognostic indicators as well as enhancements.

One future direction concerns identifying the types of patients who would most benefit from PE (and those who might not). Larger hippocampal volume has been shown to be associated with better outcomes in PE (Rubin et al., 2016). Increased connectivity between the fear and the emotion regulation neurocircuitries during emotionally salient tasks is also a predictor of treatment success is PE (Fonzo et al., 2017). Therefore, neuroimaging or electroencephalography should be used in future studies to not only corroborate these findings but also potentially establish certain cut-off benchmark for the magnitude of connectivity or the relative size of the hippocampus in optimal PE response. Given consistently positive findings regarding the effectiveness of rTMS in PTSD symptom improvement, it is a priority to continue to research this potential PE enhancement. Specifically, future studies should focus on neurobiological and psychological moderators and mediators of rTMS effects on PE response, as well as on identifying those individuals who would most benefit from rTMS. Currently, it appears that rTMS may be of particular importance for those people whose brains do not "let" them engage fully in exposure therapy, i.e., those with pre-existing decreased connectivity between the key neurocircuitries, however, that is an empirical question.

Further examination of the enhancements that promote the sense of connectedness and self-compassion (i.e., oxytocin and MDMA) is also warranted. Currently, it is unclear whether these agents affect neural circuits that are more unique to exposure therapy (such as the fear or the contextualization circuits) or the transdiagnostic emotion regulation circuitry, or another circuitry altogether. They may be promoting decreased behavioral avoidance (Dumont et al., 2009; van Wel et al., 2012) but neuroimaging studies examining these agents' effects on neurocircuitries that are of most importance in PE would clarify that conjecture. Concurrently, studies examining the effects of these agents on PE response would be helpful in clarifying whether these agents offer any added benefit above and beyond regular PE. If so, then identifying patients who would be appropriate candidates for such enhancements would be the logical next steps, especially given the heterogeneity of PTSD symptoms.

In order to tap into the change in the ability to handle and regulate negative emotions and identify individuals most likely to benefit from treatment, future studies should employ various emotion regulation tasks during neuroimaging scans pre- and post-treatment. For instance in the PROGrESS trial (Rauch et al., 2018), participants engage in an emotional faces matching task aimed at isolating the amygdala reactivity to threat (i.e., angry and fearful faces) and non-threat (i.e., happy and neutral faces; Hariri et al., 2002). Additionally, participants engage in the Emotion Regulation Task designed to measure both, the explicit emotion regulation (Gyurak et al., 2011) activation in the prefrontal cortical regions including dlPFC and vmPFC, as well as the implicit emotion regulation manifested by the activation in vmPFC and the amygdala (Costafreda et al., 2008; Buhle et al., 2014). Finally, the implicit emotional regulation processes (Gyurak et al., 2011) are also measured using attentional control with emotional faces task (SEAT; Sripada et al., 2013a). Administration of such tasks while undergoing neuroimaging pre- and post-PE is essential in identifying not only connectivity changes resulting from treatment in the fear, contextualization, and emotion regulation neurocircuitries but also pre-existing connectivity patterns that may be indicative of individuals who might require enhancements in order to fully benefit from PE. It would be useful to develop and utilize neuropsychological measures of hippocampus activity in order to evaluate PE's effect on its function. Additionally, salivary and plasma concentrations of DHEA(S) and ALLO have been shown to be associated with increased communication between prefrontal cortical regions and amygdala (Sripada et al., 2013c). Therefore, establishing benchmarks for the extent of connectivity related to certain concentrations of DHEA(S) and ALLO, and measuring these concentrations pre and during PE may be a potentially less burdensome method of identifying increased communication between the relevant brain structures.

While most of our focus has been on improving response to PE, retention, as previously mentioned, is a key area for improvement across PTSD interventions (Tuerk, 2014). Neurobiological advances can also provide insights that drive better retention through more personalized, more efficient, and more effective care. Dropout rates across populations and treatment setting are approximately 30% or more (Bradley et al., 2005; Eftekhari et al., 2013), which is not surprising given that PTSD is characterized by behavioral avoidance. Therefore, further exploring the effectiveness and the mechanisms of action of oxytocin and MDMA as enhancements to PE is warranted in an effort to improve retention in PE. For instance, for those who have higher potential for dropout, administration of intranasal oxytocin may be particularly effective in retaining them in treatment through increased connectedness with their PE provider. Identifying neurobiological biomarkers of those who are at risk of dropping out would aid in clinical decision-making process regarding patients who are good candidates for such an enhancement.

CONCLUSIONS

In this focused review, we reviewed the neurobiological mechanisms underlying the effectiveness of PE, an empirically-supported efficacious treatment for PTSD, and the enhancements that can be applied to increase treatment response and retention. One of the proposed mechanisms of action in PE is exposure which facilitates extinction of a fear response and new adaptive learning. Neurobiologically, PE and successful extinction recall has been associated with increased neural connectivity between vmPFC, amygdala and the hippocampus. Increased connectivity in regions implicated in emotion regulation has also been shown to result from PE although it appears that this change in activation is more transdiagnostic and not unique to PE. Since neural connectivity and communication seem to be at the heart of symptom alleviation in PTSD, treatment enhancements that promote such connectivity, particularly rTMS, offer the most appropriate targets for future research into effectiveness of PE. Further research into the effects of oxytocin and MDMA on treatment response and retention is also warranted. Finally, establishing neurobiological benchmarks for identifying individuals who are less likely to benefit from treatment would be an exciting development to help guide clinical decision-making as to who should receive enhancements to PE.

AUTHOR CONTRIBUTIONS

MS involved in planning, lead author, primary writer and editor. LM involved in planning, led the literature review, wrote sections and edited. SR senior author involved in planning, review, writing and editing.

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A Theory of Everything: Overlapping Neurobiological Mechanisms of Psychotherapies of Fear and Anxiety Related Disorders

*Arash Javanbakht**

Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI, United States

Similarities within the phenomenology, neurobiology, psychotherapeutic, and pharmacological treatments of distinctly categorized anxiety and fear related disorders suggest the involvement of common neurobiological mechanisms in their formation. This theory of integration is the focus of the Research Domain Criteria (RDoC) approach initiated by the NIH. The current article explores potential facets of overlap among mainstream methods of psychotherapy for anxiety, fear, and trauma related disorders. These overlaps include associative learning of safety, cognitive reappraisal and emotion regulation, therapist as a social safety cue, and contextualization. Temporal contextualization and placing memories in their time and place will be suggested as a potentially important, and less explored aspect of psychotherapy.

Keywords: psychotherapy, neurobiology, neuroscience, psychoanalysis, cognitive therapy, exposure therapy, anxiety, PTSD

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Nuno Sousa,
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Sorbonne Universités, France
Gerald Paul Perman,
George Washington University, United States

***Correspondence:**
Arash Javanbakht
ajavanba@med.wayne.edu

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INTRODUCTION

As our understanding of the neurobiology of mental processes and disorders solidifies, we are beginning to attempt theory integration across phenomenologically and categorically distinct psychiatric disorders. This new approach aims to examine the similarities of these disorders through the lens of specific mental functions. The hallmark of this new direction in neuroscience is Research Domain Criteria (RDoC), which aims to "develop, for research purposes, new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures" (Insel et al., 2010). Discussion of similarities between seemingly distinct mental disorders has been present in psychiatry since the days of Freud. Defense mechanisms, for example, were developed to explain a plethora of mental illnesses including anxiety disorders, depression, and somatoform disorders (Cramer, 2015). Similarly, psychoanalysis, psychodynamic psychotherapy, cognitive therapy, and behavioral therapy, are offered to treat a wide range of anxiety, fear, and trauma related disorders, with only minor adjustments (Butler et al., 2006). When introduced to the armamentarium of psychiatric treatments, psychopharmacology also provided evidence of similar treatment across these diagnoses. After decades, Serotonin Reuptake Inhibitors (SSRIs), and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) are still the mainstream treatments for all of the anxiety disorders, posttraumatic stress disorder (PTSD), Obsessive Compulsive Disorder (OCD), and depressive disorders, with similar efficacy across the board (Finley, 1994).

Our current neurobiological understanding of anxiety and trauma related disorders is still virtually indistinguishable. In the majority of these disorders the main areas of anatomical and functional significance are the medial PFC (mPFC), the dorsolateral prefrontal cortex (dlPFC), the anterior cingulate cortex (ACC), the insula, the hippocampus, and the amygdala (Duval et al., 2015). One could argue that these similarities are the product of the lack of precision our current methods in neuroscience provide. This could explain why the current general treatment for anxiety disorders is not very effective- for example; SSRIs are only moderately more effective than placebo in treatment of anxiety and depressive disorders (Goodnick and Goldstein, 1998). One could also argue (without the intent of being mutually exclusive) that there may be similar mechanisms, both biological and psychological, involved in formation of seemingly different anxiety disorders.

In this article, considering both the immense foundation of contemporary psychology and latest findings in neurobiology of anxiety disorders and trauma, I suggest multiple facets of overlap between the seemingly distinct mainstream psychotherapeutic methods for the treatment of fear, anxiety, and trauma. I will then discuss the use of these mechanisms within each method of psychotherapy, and the clinical implication. The intention of this work is not to fully explain the neurobiology of psychotherapy, but to discuss the commonalities between the mainstream methods.

ASSOCIATIVE LEARNING OF FEAR AND SAFETY, STIMULUS GENERALIZATION, COGNITIVE SCHEMAS, AND TRANSFERENCES

Associative learning is a common method used across species to make sense of the world. The most commonly studied form of associative learning is Pavlovian fear conditioning, during which a neutral cue (e.g., a triangle) is paired with an inherently aversive stimulus (e.g., a shock), repeatedly (Milad and Quirk, 2012). After the training phase, which consists of this repeated pairing, the organism learns that the previously neutral cue is a predictor of the aversive stimulus. As a result, the conditioned stimulus invokes the same fear response as the aversive stimulus. Interestingly, the brain areas involved in associative fear learning (mainly amygdala, insula, ACC, and hippocampus) largely overlap with those involved in psychopathology of anxiety disorders and PTSD (Greco and Liberzon, 2016). Similarly, appetitive conditioning creates an associative learning between a neutral cue and an inherently appetitive stimulus (e.g., food; Martin-Soelch et al., 2007). In humans, associative learning can take place by personal experience, social observation, or verbal information relayed through instruction (Olsson and Phelps, 2007). For instance, one can be afraid of a dog by being personally attacked, by seeing another person attacked, by being told the dog is dangerous, or by reading a sign that says, "beware of dog." Associative learning can occur with simple cues (e.g., a triangle), social cues (e.g., a picture of a face), or a more complex combination of perceptual inputs, namely context (contextual conditioning; Rudy et al., 2004). During contextual conditioning, an aversive stimulus is paired with a physical environment rather than a specific cue. However, it is suggested that context is not only physical environment, but social, temporal, internal, and cognitive input as well (Maren et al., 2013). Cognitive information, acting as a vital element of learning in humans, seems to function similarly to physical context in fear and safety learning (Javanbakht et al., 2017).

Whether one agrees to the broader definition of context or not, it is conceivable that a combination of physical, temporal, and cognitive cues could be paired with an aversive or appetitive response. For instance, both words "red" and "car" could be paired with an aversive experience separately, as could the combination "red car" in creating a fear response to a "red car." Clinically, a person hit by a red car could develop a fear of cars, driving, red cars, or even proximity to roads where cars are seen.

More complex cognitive constructs (cognitive schemas or distortions in cognitive therapy) can similarly be paired with an aversive or appetitive response. According to cognitive theory, cognitive schemas are organized patterns of thoughts (Piaget, 1950), while cognitive distortions (Beck, 1963, 2008) are biased cognitive concepts. Similar to associative learning, schemas can form by personal experience similar to experiential conditioning (red car driven by a young man hit me last year => view of a red car, or a red car driven by a young man trigger the emotion of fear), social observation (red car driven by a young man hit my neighbor last year), or verbal information (I heard that the young man with the red car in the neighborhood is a careless driver). All these seemingly different inputs can evoke a fear response at perception, imagination, or news of the young neighbor driving a red car. Such learning can be then generalized to other similar conditions, leading to the expansion of a cognitive schema.

Associative learning of fear can be generalized to perceptually, conceptually, or cognitively similar cues (Dunsmoor and Paz, 2015). Stimulus generalization is a process through which associative learning extends to new stimuli that are related in some way to the stimulus originally associated with an emotional response. Fear generalization is shown to positively correlate with fear intensity, suggesting anxiety's crucial role in fear generalization (Dunsmoor et al., 2009). Generalization is an adaptive response that helps organisms survive by avoiding relatively similar threats. For example, if one was attacked by a black bear, generalized fear of brown bears is reasonable in respect of avoiding a future attack. In an early work on stimulus generalization, Guttman and Kalish (1956) showed that pigeons can generalize the associative learning response to colors of light with nearly similar wavelengths to the light used in associative learning. Human studies have also shown generalization of fear response to shapes close in size to the conditioned cue (Lissek et al., 2008). This form of learning seems to be involved in development of phobias: one can become afraid of all breeds of dogs after being attacked by a single breed of dog. While stimulus generalization can occur to physical sensory aspects of the stimulus, tone of sound, or even facial structure in humans (Honig and Urcuioli, 1981), recent research

supports possibility of generalization of associative learning to conceptually or semantically similar stimuli (Maltzman, 1977). In an interesting study, Dunsmoor et al. (2011) showed that fear generalization was stronger in a group of participants that had learned association between two conceptually similar words, compared to the groups who learned the same association between unrelated or mismatched words.

At a more complex level, generalization of fear may occur to more abstract cognitive schemas or social constructs, such as the concept of "authority." Such conceptual and symbolic generalization has been a core focus of psychoanalysis and psychodynamic theory. For example, a person frequently mistreated by a parental figure during childhood, may generalize a fear of authority figures, and "*transfer*" the same response onto a similar relational pattern (Javanbakht and Ragan, 2008). *Transference* is a process during which one transfers emotions that were experienced in the past, to a conceptually or socially similar context in the here and now. Transference can be explained as a form of generalized fear or other emotions to a current social cue, similar to those of the past. In other words, an emotional response is linked to a specific social, cognitive, or conceptual pattern.

In summary, associative learning can occur with internal and external stimuli, a variety of simple cues, social cues, social context, cognitive context, and more abstract cognitive concepts such as schemas, cognitive distortions, and transferences by a relatively similar mechanism.

In *Extinction Learning*, it is learned that a previously conditioned stimulus is not associated with an aversive experience anymore. In the laboratory during extinction learning, the conditioned stimulus is repeatedly presented in the absence of the aversive stimulus, leading to extinction of the fear response (Milad and Quirk, 2012). Importantly, extinction learning is not simply erasure of the learned fear, but rather an additional learning that the conditioned stimulus is safe in the new physical/temporal/social context; for that reason, the extinguished fear can return (Milad et al., 2005). Similar to fear, extinction learning can take place *via* personal experience, social observation, and cognitive instruction (Koenig and Henriksen, 2005; Javanbakht et al., 2017). Contemporary laboratory models of exposure therapy, a mainstream treatment of fear related disorders, are based on extinction learning (Abramowitz, 2013). The brain areas that are involved in retention of extinction learning (vmPFC, dlPFC, and hippocampus) commonly show impaired anatomy and function in anxiety and trauma related disorders (Duval et al., 2015; Greco and Liberzon, 2016). The same areas are involved in the cognitive modulation of fear responses, such as in reappraisal. In laboratory, during reappraisal, effortful change of the meaning or narrative of an experience will reduce activation in fear related areas (Hermann et al., 2014). Such reappraisal of negative experiences and memories often takes place in psychotherapy, especially cognitive and psychodynamic methods. Additionally, in logotherapy (a method created by Frankl (1992) based on his observation of people making sense of experience of extreme adversity), positive meaning is created for negative experiences, leading to less negative emotion and behavior.

CONTEXTUAL BRAIN AND SAFETY LEARNING

Context plays a very important role in human behavior. Broadly, context is a set of circumstances that brings additional background information about specific cues and directs behavior. For example, the emotional response caused by exposure to a lion in the African Sahara could differ greatly from exposure to the same animal in a zoo. The physical components of context in exposure modify the natural fear response to the predator in the zoo. Context plays an important role in laboratory models of the learning of fear, and specifically its extinction. Though fear can be linked to a specific context, cue-related fear learning is independent of context (Bouton and King, 1983). This means that a person who is attacked by a dog will be afraid of dogs in any context. On the other hand, extinction learning is context-dependent. In the laboratory setting, extinction learning is best recalled in the same physical context where it took place. Therefore, return to the fear-learning context can lead to renewal of learned fear (Maren et al., 2013). This phenomenon is familiar to clinicians: exposure therapy done in the clinic does not always generalize to the original trauma context or other neutral contexts than the clinic office, which necessitates *in vivo* exposure in as many contexts as possible. Specifically in PTSD, impairment of context processing has been a recent focus of research. In this disorder, learning of fear does not differ greatly from healthy controls, but context dependent recall of extinction learning is a major impairment (Garfinkel et al., 2014).

As it was noted earlier, the broader concept of context involves perception of time, cognition, internal emotions, hormones, and physical aspects (Maren et al., 2013). Our team has previously shown that cognitive context provided in the form of instruction can function similarly to physical context in the recall of extinction learning (Javanbakht et al., 2017).

A less explored aspect of context is the perception of time. The ability to perceive time allows an organism to make sense of a sequence of events, and differentiate those of the past from those of the present. *Spontaneous recovery*, a phenomenon through which, by passage of time, a formerly extinguished fear response resurfaces, is one presentation of temporal context in fear and safety learning (Dunsmoor et al., 2015). A similar phenomenon that is commonly observed in clinic is the resurfacing of formerly treated phobias, OCD, and PTSD. To prevent this phenomenon, patients are encouraged to keep practicing *in vivo* exposure even after treatment goals are achieved. Similar to other elements of context, the processing of time is highly dependent on the hippocampus (Preston and Eichenbaum, 2013; Eichenbaum, 2013), and the anterior insula (Craig, 2009). To reiterate, both of these areas are commonly involved in extinction learning and recall, and show aberrant anatomy and function in anxiety disorders. Interestingly, the subjective experience of time can be modulated by other contextual information such as physical attributes and emotional valence (Fraisse, 1984; Noulhiane et al., 2007; Droit-Volet and Gil, 2009). In clinical practice, patients often react to the recall of a memory as if it is happening in the here and now; as if the psychic apparatus

does not differentiate between "there and then," and "here and now." This phenomenon is often explained as "timelessness" of the unconscious in psychoanalytic theory (Scarfone, 2006). Difficulties in temporal context processing may explain fear reactions to the recall of a memory of an aversive situation, which is harmless in here and now, especially in disorders of context processing such as PTSD. One function of methods like mindfulness or meditation is training the person to bring attention from there and then, to here and now.

PATTERN SEPARATION AND PATTERN COMPLETION

Pattern separation enables a network to differentiate between two partially similar patterns, and prevent error in recall (Guzowski et al., 2004). Impairments in pattern separation are suggested to play a role in the overgeneralization of fear responses observed in fear disorders and PTSD (Kheirbek et al., 2012). In pattern completion, familiar components of a newly input pattern trigger recall of a relevant previously learned pattern to complete missing or unclear components of the new input (Rolls and Kesner, 2016). This allows accurate generalization when facing a noisy or partially known input pattern (Paleja et al., 2014). The dentate gyrus and the CA3 region of the hippocampus, with its auto-associative structure, have been the main focus of animal and human studies of pattern recognition and separation (Kolassa et al., 2010; McClelland and Goddard, 1996). Although the majority of experiments in this field are focused on spatial and visual pattern recognition, due to extensive inputs from distinct cortical areas, pattern recognition can combine perceptual, temporal, and cognitive inputs. For example, spatial inputs from the parietal lobe, and visual information from inferior temporal lobe, can enter a single hippocampal neuron (Kolassa et al., 2010). In this sense a pattern can be composed of visual and auditory components to represent a familiar person speaking, or determining a distinct language. Theoretically, prefrontal inputs to the hippocampus can present patterns of cognitive or social content. This form of pattern recognition integrates complex inputs and recognizes them as a coherent event (Barsalou, 2013). Processing the temporal component allows not only the identification of the spatial location of an object, but also its place in time (Paleja et al., 2014). Both the integration of diverse sensory information and function of pattern separation and completion contribute to contextual processing in the hippocampus. Besides generalization, pattern completion may play a role in the formation of cognitive schemas and transferences (Javanbakht, 2011; Javanbakht and Ragan, 2008). In case of transference, similar characteristics of a relational pattern (intimate, trusting, and important nature of relationship with the therapist) can trigger emotional memories, and relational patterns experienced with significant caregivers of childhood. If that caregiver was perceived as critical and judgmental, those attributes will complete what is not known about the therapist (transference), and the therapist will be perceived as judgmental. A function of the psychoanalyst is then to repeatedly present a new and adaptive pattern of relation, to help the patient encode a new relational pattern and expand the reservoir of memorized relational patterns. The empathic and understanding nature of the therapist may for long be reduced and removed as "noise" before new learning happens, which is observed in clinical practice of psychoanalysis. Furthermore, negative emotions and cognitive expectancy of a negative experience, may narrow attention to negative/threat related input (attention bias), and limit access to all of what is happening in the therapeutic context, especially positive experiences (Bar-Haim, 2010).

MEMORY RECONSOLIDATION RESEARCH

A growing body of research suggests that emotional memories may not be as solid as we once thought they were. Recent animal and human studies have shown that when memories are recalled, they become labile and vulnerable to change. In one of the first animal studies, Nader et al. (2000) showed that when fear memories are reactivated up to 14 days after fear conditioning, infusion of anisomycin in the amygdala led to amnesia of learned fear. While extinction learning involves encoding additional information to the fear memory traces indicating safety of feared cues in the new context, reconsolidation involves erasure or change of the emotional component of the fear memory. It is important to know that reconsolidation does not erase the declarative knowledge of the events, but rather the fear response to the conditioned cues (Treanor et al., 2017).

Memory reconsolidation research has led to a large amount of excitement about new ways of treating fear and anxiety related disorders, especially PTSD. While extinguished fear memories can return (clinically seen in relapse after exposure therapy), reconsolidated memories cannot. Some authors have suggested that memory reconsolidation plays an important role in psychotherapeutic process (Lane et al., 2015), while others have been more cautious (Treanor et al., 2017; Elsey et al., 2018). Evidence within memory reconsolidation research is mostly based on single cue recent fear conditioning studies. But does this apply to extremely aversive, complex traumatic memories (e.g., PTSD) repeatedly reinforced in humans? We still do not know how aversive, how complex, or how distant a memory is vulnerable to reconsolidation (Liberzon and Javanbakht, 2015). In summary, while promising, more evidence is needed to implicate memory reconsolidation research in clinical practice.

Having discussed the above processes, below I will discuss their relevance to the overlap between seemingly distinct mainstream psychotherapeutic approaches to treating fear and anxiety related disorders.

BEHAVIORAL THERAPY

Behavioral therapy, which is based on principles of associative learning of fear and its extinction, is one of the most commonly used treatments for fear related disorders, OCD, and trauma (Newman, 2016). In behavioral therapy, the patient is exposed to a feared cue or situation, in a safe context. After repeated exposure, extinction learning occurs and the cue will no longer

trigger a fear response. This method is used for a diverse array of anxiety disorders, where there is an internal or external cue or situation that is feared. In phobias, the cue is an external perceived object or situation. In PTSD, exposure is to autobiographical memories, and overly generalized fear response to safe cues. In OCD and nightmare disorders, exposure is to autobiographical memories and cognitive constructs. As in extinction learning, contextualization plays an important role in exposure therapy. Commonly in clinical practice it is observed that the safety learned in a clinic setting may not apply to real life conditions. Similarly, return to the context of trauma (e.g., the parking lot where the assault happened), may lead to *renewal* of the fear response. Furthermore, because extinction learning is not an erasure of the learned fear, even after successful therapy, fear responses may return (Milad and Quirk, 2012). For all these reasons, patients are encouraged to continue *in vivo* exposure in as many contexts and with as many cues possible, even after completion of treatment, to prevent such *renewal*, or *spontaneous recovery* of the fear response.

An important element of exposure that is often overlooked in laboratory models is the use of the therapist as a social safety cue and as an anchor in time. The therapist is a continuous reminder to the patient that they are in a different temporal, physical, and social context than the time trauma happened and fear was learned. In the disorders where fear is linked with an autobiographical intrusive memory (OCD, PTSD, nightmare), the therapist's communication with the patient frequently brings them back from "there and then" to the "here and now," which facilitates the process of contextualization of fear memories. In other words, the therapist helps the patient to put those memories back in their time and place. The therapist also provides a sense of safety (social learning of safety), and enforces a sense of control in the patient. This sense of control is pivotal as the person chooses to encounter the feared situation, rather than being surprised by it.

In summary, cue generalization, safe social cue, sense of control, and contextualization seem to be the most important elements of successful exposure therapy.

COGNITIVE THERAPY

Cognitive therapy is commonly used in the treatment of anxiety disorders, especially those with a larger component of anxiety than fear, such as GAD, and is often used in combination with exposure therapy. In such therapy, cognitive constructs that trigger negative emotions are addressed and challenged, and pros and cons of such beliefs are discussed with the patient, and then replaced by more adaptive and realistic patterns. In that sense, reappraisal plays a role in cognitive therapy, as often times the meaning and interpretation of the experiences are what changes during this process.

The process of cognitive therapy may also include some level of associative learning, linking emotions to complicated cognitive constructs rather than simple cues. For example, in the red car example explained earlier, perception of a young person driving a red car, can trigger the combination "young person, driving, red, car = threat" which is linked with a fear response. During cognitive therapy, this cognitive compound is challenged and modified to a more adaptive one. When maladaptive cognitive constructs are recalled, there is an opportunity for a new associative learning of safety to take place. In other words, frequent exposure to the cognitive construct happens in presence of a safe social cue (therapist), who challenges the emotional response, and prevents avoidance, leading to safety learning. In this sense, exposure and cognitive therapy overlap not only in method, but also in mechanism. In the first method the focus is on safety learning for an external object or autobiographical memory, and in the latter, it is a cognitive construct, and related real life experiences.

Similar to exposure therapy, the therapist's role (other than offering new explanations to enrich the schematic patterns of interpretation and make sense of events) is to enforce contextualization, and provide a sense of control and safety. During exposure therapy the patient experiences safety near a feared object with the therapist, while in cognitive therapy the patient experiences safety in exposure to a feared cognitive construct. Temporal contextualization brings the patient to here and now, and away from the possible threat environment of the past where the distorted cognitive constructs formed.

PSYCHOANALYSIS AND PSYCHODYNAMIC THERAPY

Traditional psychoanalysis is mainly composed of transference interpretation and free association. Transferences are emotional patterns formed towards significant persons of the past, and are transferred onto the therapist in the context of treatment. During free association, patients share their automatic flow of thoughts in response to the discussed events, memories, and experiences without the therapist's influence (Tuch, 2017). Then the two will try to make sense of this stream of thoughts. Another important element of psychoanalysis and psychodynamic theory (the less traditional form of therapy rooted in psychoanalysis) are defense mechanisms, introduced by Anna Freud. Defense mechanisms are thought to be automatic unconscious processes developed to avoid anxiety and conflict stirred by internal or external experiences (Freud, 1967). The underlying mechanism of this defense is still to be explained (Northoff et al., 2007).

Although on the surface, psychoanalysis seems to be the most distant method from behavioral therapy, there may be similarities in mechanisms. As was noted earlier, transference formation can be explained as associative learning involving complex cognitive or interpersonal patterns, and overgeneralization of such associative learning. For instance, childhood exposure to a hypercritical parent may link that parent to experience of fear, insecurity, or anger. Alternatively, the fear may become associated with the parent's role as an authority, and be generalized to relationship patterns with other authority, intimate, or important figures. This could apply to any other component of the parent, e.g., their gender (e.g., maternal transferences toward significant female persons). Consequently, the context of the therapeutic relationship can trigger recall of relevant autobiographical memories or implicit cognitive

constructs related to a parental figure, leading to a fear or anger response. In this context, similar to exposure therapy, one mechanism of therapy work is frequent exposure to the feared perceived object of authority/parental figure, or other relationship patterns. When the transferences are repeatedly experienced without an aversive critical response from an empathic therapist, extinction learning occurs and the new relational pattern is added to the memory reservoir. This process in psychoanalysis is referred to as *corrective emotional experience*, "to re-expose the patient, under more favorable circumstances, to emotional situations which he could not handle in the past. The patient, in order to be helped, must undergo a corrective emotional experience suitable to repair the traumatic influence of previous experiences" (Alexander et al., 1946).

In psychoanalysis, implicit associative learning may also include experience of an emotion. For instance, a person who was often punished when having fun during childhood, learns that the experience of joy, or internal context of positive emotions predict threat/pain. Consequently, the experience of joy and pleasure-related contexts would trigger fear or sadness without an explicit awareness of the association. A patient of mine complained about drinking too much in social contexts, and then embarrassing herself. At further exploration, she identified an automatic thought that she is only accepted and perceived as fun when she is drunk. Later on, she remembered that during her childhood, home was a sad place, but she always found a happy respite at the Smith's home (the neighbors). She explained that they were "the only people who paid attention to me." The Smith couple was always drunk when she visited them, and the patient realized later that she associated drinking, and even the smell of alcohol, to experience of being loved and accepted. Although the formulation is a psychodynamic one, the cognitive distortion, and the associative learning are evident in this example. For this patient, the scent of alcohol, social and sensory cues related to alcohol, triggered associated memories of feeling safe and happy, and being loved and accepted.

Becoming aware of the underlying associative memories that trigger automatic emotional responses is an overlapping function of psychoanalysis and cognitive therapy. While in cognitive therapy, awareness is directed toward automatic distorted cognitive constructs that trigger maladaptive emotional response, in psychoanalysis, awareness is of the autobiographical memories, both cognitive and emotional, which are automatically generalized to a range of internal and external contexts and cues. In both methods of therapy, besides bringing implicit functions to awareness, reappraisal and development of a different meaning for the same experience is a key element.

Defense mechanisms are used in clinical practice even by clinicians who do not use other psychodynamic principles such as transference and free association. Defense mechanisms are functions of the "ego" that serve the purpose of avoiding anxiety provoking or conflicting thoughts, memories, or impulses (Freud, 1967). Among the most common defense mechanisms are projection (when one's own thoughts or emotions are attributed to others to avoid acknowledging their presence in oneself), displacement (when thoughts or impulses are displaced to a safer object, e.g., yelling at the dog because it is safer than yelling at the boss), and denial (of anxiety provoking stimulus, thought, or impulse). Although defense mechanisms are commonly used in clinical practice to understand behavior, the underlying mechanism is unclear and they have yet to be explained in the context of modern neuroscience.

A defense mechanism is not always a planned process to avoid conflict or emotional pain. An example of displacement is when a person is angry with their boss, but releases it at home. At the workplace, other contextual (work related social context), cognitive (if I yell at authorities, I will get hurt, or fired), and autobiographical or factual memories (my friend got fired because he talked back to his boss) prevent the person from acting out an anger impulse. When at home, the internal context of anger, and anger related behavioral and relational patterns are still present. Shifted attention towards negative external cues, will enforce perception of what the dog is doing wrong, and yelling at the dog is less costly. In this sense, yelling at the dog is not replacing the boss, but is triggered by it. Reduction in functional connectivity between emotion regulatory, cognitive, and contextual processing prefrontal cortices, and amygdala may explain the defense mechanism of denial/absence of conscious awareness of highly conflicting autobiographical memories or perceptions (Birn et al., 2014; Bijsterbosch et al., 2015). In this case, the emotion is not removed from awareness to protect the ego against anxiety, but rather is not experienced simply because of reduced connectivity. Similarly, projection defense may result from attention bias and pattern completion of external stimuli due to internal emotional and cognitive contexts (Javanbakht and Ragan, 2008).

Similar to cognitive and behavioral therapy, the therapist has a pivotal role as a safe social cue in learning of safety, and in helping the patient in physical, social, and temporal contextualization. The analysand moves back and forth between the context of old autobiographical memories and associated implicit and explicit emotions, to therapist, who is anchored in the here and now physical, interpersonal, and temporal contexts.

It is important to note that psychoanalysis is a complex theory with a variety of facets and implications. For instance, this theory has important contribution to personality and its disorders, which is beyond the scope of this work. Here I only address psychoanalysis and its use in anxiety related disorders and trauma.

PSYCHOTROPIC MEDICATIONS AND PSYCHOTHERAPY

Currently, medications used for the treatment of all fear and anxiety related disorders remain the same: serotonin specific reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and at times benzodiazepines. These medications seem to work by reducing the phasic and tonic level of arousal, anxiety, and the phasic fear response. They can reduce the amygdala's response to negative stimuli, and increase prefrontal emotion regulation (McCabe et al., 2010;

Outhred et al., 2013). Reduced baseline and reactive anxiety can modulate threat-oriented biased attention, and recall of negative memories, signal a safer internal context, and facilitated more realistic pattern recognition and contextualization of the input information.

Based on the context in which they are received, the relevant cognitive schemas and emotions linked to the experience of taking medication, drugs may trigger different emotional and cognitive patterns. For instance, while in one patient taking medication may implicitly trigger associated cognitive and autobiographical components of "mom, Fluoxetine, hospital, angry dad," in another patient the associated memories may include "mom, medication, happy, vacation," and yet in a third person they may be "green pills, girlfriend, conflict, suicide." While in the first patient the cue "anxiety medication" can trigger emotions of fear, despair, or anger, in the second patient it may trigger hopeful feeling of relief, and in the third patient disappointment and guilt. This function of the medication in triggering autobiographical and emotional memories, associative learning, and cognitive schemas, may explain placebo effects, the unpredictable level of effect across patients, and side effect variability despite their similar mechanism of action, and their unexpected quick effects in some. Despite the fact that SSRI medications require several weeks to start benefiting the patient, reports of quick effects even in less than a week are common in clinical practice.

From the psychoanalytic standpoint, medication may work as a *transitional object*, first described by Winnicott (1969). A common example of a transitional object is the teddy bear that represents mother's presence, and allows the child to wander away from mother, while carrying a piece of her. Medication can operate as a transitional object for the treating physician, and taking it can evoke emotional, cognitive, and social patterns of perception of the physician, and those transferred onto the treatment relationship.

Recent research has been done on pharmacological agents as enhancers of extinction learning, or disrupters of reconsolidation of aversive memories. While several agents are used for these purposes in laboratory research of single cue conditioned memories, there is limited clinical evidence for a few of these agents. A few studies have shown small effects for the partial NMDA agonist D-Cyclocerin, SSRI's, and endocannabinoids as enhancer of exposure therapy (For reviews see Fitzgerald et al., 2014; Mataix-Cols et al., 2017). The beta-adrenergic blocker propranolol has been suggested as a disruptor of reconsolidation of traumatic memories (Gardner and Griffiths, 2014; Giustino et al., 2016). In a recent promising study, use of propranolol 90 min before reactivation of traumatic memories in PTSD patients for 6 weeks, led to larger decline in symptoms severity than placebo (Brunet et al., 2018). Authors suggest this effect is through disruption of reconsolidation of recalled and labile memories. Another function of propranolol may be reduction of adrenergic arousal level, leading to a calmer internal context while the memories are recalled. This may help in dissociating the traumatic memory from the extremely aversive emotional tone, and helping in contextualization of the memories in the safe here and now.

CONCLUSION AND CLINICAL IMPLICATIONS

As our understanding of the neurobiological mechanisms of formation and regulation of fear has evolved, we seem to find not only overlapping clinical use, but also neuronal mechanisms for seemingly distinct methods of therapy used for the same psychopathologies. In this work, I proposed some of these common mechanisms including associative learning of safety and extinction learning, its generalization, and contextualization. As our laboratory understanding of the concept of context has evolved, more complicated aspects of cognitive, internal, social, and temporal contexts seem to play a role in contextualization of safety learning in clinical setting. Cognitive reappraisal, and modification of meaning of experiences is another important component of different therapies. Finally, the therapist seems to play a critical role as a social cue in safety learning, an anchor in the here and now, that promotes social, physical, and temporal contextualization of memories of the past.

Maslow (1966) once wrote: "If the only tool you have is a hammer, every problem begins to resemble a nail." The possibility that different methods of therapy have overlapping mechanisms encourages utilizing these methods in combination. It seems reasonable to thoughtfully utilize principles of the seemingly distinct therapies to increase and expedite the outcome, rather than orthodoxy in using only one method. For example, while interpretation of transferences in psychoanalysis helps in development of conscious insight to the common patterns of perceiving self and others, extinction learning may be a mechanism in reducing fear response to perception of these patterns. Consequently, besides the traditional approach of psychoanalysis, it seems reasonable to encourage *in vivo* exposure to those patterns to foster generalization and contextualization of safety learning. In psychodynamic therapy, if the concept of "authority" is disentangled from threat, then this new learning of safety can more easily generalize to other conditions (Bieber, 1980). On the other hand, in exposure-based therapies, a psychodynamic understanding of the broader patterns of fear generalization will help in development of broader approaches to the feared object category, and prevent future emergence of the fear response to similar patterns. This fluid exchange of mechanism and execution could potentially create a far more effective intervention than any one theory alone could provide.

Similarities of mechanism in therapies may also suggest a possibility of more efficient approaches to psychoanalysis and psychodynamic therapy. Traditional psychoanalysis often involves years of intense treatment with several sessions a week, which is not affordable for most patients. However, there is evidence for use of psychodynamic treatment with lesser density and shorter time periods (Kernberg, 2015). If indeed some of the same mechanisms of extinction learning and reappraisal are involved in psychodynamic therapy, then briefer methods may reasonably work in shorter lengths of time. Furthermore, the idea of a therapist as a blank screen introduced by Freud (rather an obsolete concept in modern psychoanalysis) should

perhaps be replaced by a more empathic and involved therapist, which will play a better role as a social safety cue in learning of safety.

An old debate (especially in psychoanalysis) surrounds the efficacy of combining medications and psychotherapy, or therapist and prescriber, some suggesting their separation (Cabaniss, 2001). A combined approach may seem more reasonable, keeping in mind that medications can help in the process of therapy, by reducing the anxiety level within the optimal learning window. Extremely high levels of anxiety may reduce the amygdala's connectivity with brain's emotion regulatory areas, general cognition, and the patient's ability to be involved in therapy. If exploration into the use of memory modulating agents is proven successful by research, then the argument for integration may be furthered (Singewald et al., 2015). On the other hand, overuse of medications may impair learning by reducing the arousal level below the optimal learning window, or by simply impairing learning, in case of benzodiazepines use (Tyng et al., 2017). Finally, since medication plays a broader psychological role beyond the pharmacological agent affecting neurotransmission, it seems reasonable to be discussed in the process of therapy.

The use of technology in psychiatry and psychotherapy has been emerging in recent years. Telepsychiatry has brought providers to patients' homes and is a rapidly growing field with similar efficacy to office treatment, even used by psychoanalysts (Hilty et al., 2015). Telepsychiatry can also provide therapists with the opportunity of an *in vivo* contextualization. Additionally, virtual reality methods have enabled therapists to bring more exposure scenarios to the clinic, and advance cue generalization by providing a diverse number of feared objects (Opriş et al., 2012). The newest technology, augmented reality, offers the ability to overlay virtual objects onto real life physical contexts. This technology, combined with telepsychiatry, can provide us with the unique opportunity of connecting therapist and patient in their real life context, and adding a diverse range of feared objects to the *in vivo* context. This way, the social safety cue, cue generalization, and contextualization may all happen at the same time and place!

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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