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Neuroscience of Enduring Change and Psychotherapy

Summary, Conclusions, and Future Directions

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Introduction

This book and the paper that inspired it (Lane, Ryan, Nadel, Greenberg, 2015) were based on the premise that the field of psychotherapy practice could be advanced by incorporating brain science into a foundational understanding of how enduring change occurs. At present, there are hundreds of types of psychotherapy, and the field is searching for ways to bring coherence and order to the situation for the benefit of clients (Kazdin, 2014). The overarching goal is to develop an objective way to make the best use of the techniques available to provide optimal care for any given client—to offer assistance based on the nature of the clinical problem, the goals of the treatment, and the resources of the client.

One time honored approach to the plethora of treatments available has been to define the common factors that characterize clinical success, whatever the modality (Weinberger 1995). For example, a good therapeutic alliance appears to be necessary for any successful psychotherapy (Horvath & Luborsky, 1993); emotional arousal of moderate intensity also appears highly important (Auszra, Greenberg, & Herrmann, 2013; Carryer & Greenberg, 2010). Our approach, however, has been to focus on *how* psychotherapy works—the mechanisms by which change occurs—with a focus on enduring change, given that beneficial changes that are enduring are typically preferred to those that are short-lived. With this approach, it is possible to consider *why* certain common factors such as therapeutic alliance and emotional arousal of moderate intensity are considered to be so important in successful psychotherapy. From the perspective of mechanisms, it is also possible to consider how therapy might be adapted to best fit the needs of a particular client at a given time.

We have chosen to consider psychotherapy practice from the standpoint of its neurobiological underpinnings, based on the foundational assumption that can be

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traced back at least to Sherrington (1909) and Hebb (1949) that all mental events are instantiated in the brain. As noted in the introduction to this book, when the field of psychotherapy was founded over 100 years ago, its creator assumed that mental events were brain-based and that an understanding of neurobiology would inform and constrain the conceptualization and practice of psychotherapy (Freud 1895, 1920). True to that tradition, the field of neuropsychoanalysis has sought to define the brain basis of mind and the theoretical and clinical practice of psychoanalysis from a brain-based perspective (Nerssian & Solms, 1999). Similar efforts have been undertaken with a focus on social, interpersonal, and attachment-related processes (Cozolino, 2017; Schore, 2012). While we applaud these efforts and the pioneering and ongoing work involved, our approach is somewhat broader in scope. We are seeking to provide a framework that would include not only psychoanalysis and related methods but all of the other major psychotherapy modalities as well. This is not an easy task, as therapies differ substantially in their basic theoretical assumptions and the clinical problems that they address. However, it is our view that neurobiology is sufficiently fundamental that it can provide a foundation for all of these perspectives and provide guidance in differentiating between them in the service of clinical care.

Our touchstone for this book has been the integrated memory model (IMM) and the associated Lane–Ryan–Nadel–Greenberg (LRNG) model of change presented in the *Behavioral and Brain Sciences* (BBS) paper (Lane et al., 2015). The book's chapters constitute an in-depth look at both the basic science and clinical applications of the IMM and LRNG models. Although the BBS paper was grounded in brain science, the IMM and LRNG models were largely presented in that paper from a psychological perspective. We believe that the neuroscientific details, many highlighted in the preceding chapters, allow us to outline a rudimentary neural systems model of the IMM and LRNG model of change. The perspective offered herein is grounded in empirical observations—presenting a model such as this highlights what we know and don't know and sets us up to discuss the most urgent basic science and translational clinical science issues to be addressed in the foreseeable future.

A Model

In the BBS paper (Lane et al., 2015), the IMM and the LRNG model of enduring change in psychotherapy were largely described at a psychological level of description. This included the functions of "episodic memory," "semantic memory," and "emotional responses" and the process of reconsolidation of episodic/sematic memories such that associated emotional (and accompanying behavioral) responses became more adaptive. Throughout the book, we and others have attempted to both extend this initial formulation and provide greater specificity with respect to its neural basis. Figure 16.1 provides a sketch of what an

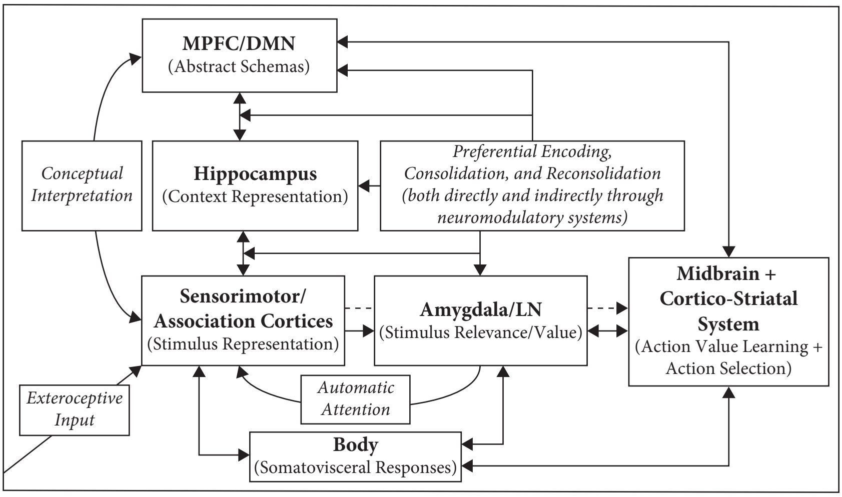

Figure 16.1 A model of the cognitive, emotional, and neural basis of the memory processes proposed to play a role in successful psychotherapeutic change. Exteroceptive input and somatovisceral input are represented at lower and higher levels of abstraction within sensorimotor and association cortices, respectively. Episodic memories are formed via synaptic changes linking these cortical representations to each other and to hippocampal representations of context. Sensorimotor representations are also linked to semantic representations (i.e., conceptualized under schemas/scripts) to infer their meaning in a given situation. This conceptualization process involves interactions between sensorimotor cortices and the default mode network (DMN), where the medial prefrontal cortex (MPFC) hub of this network appears especially important in the context of memories with emotional content. Abstracting across consistent patterns within episodic memories may be one primary means of learning/updating semantic schemas. The amygdala and related limbic network (LN) structures appear to generate affective responses to stimuli, promoting changes in bodily arousal and preferential encoding, consolidation, and reconsolidation of information represented at the time of those affective responses. Interactions between the aforementioned cortical/subcortical regions and the corticostriatal system activate and assess the stored values of different possible actions in a given context, promoting the selection of actions with high values (i.e., actions repeatedly observed to promote positive emotions and reduce negative emotions in previous experience). In this model, updating schemas (via reconsolidation) will promote more adaptive conceptualization processes and more adaptive affective responses, and updating action values will promote more adaptive automatic action tendencies and stable behavior patterns.

extended neural model might look like. Note that there is no part of the brain identified as corresponding to any of the three broad categories referred to in the IMM. Instead, these broad categories here correspond to emergent classes of dynamic interactions between the brain regions/systems depicted. In the following, we articulate the envisioned interlevel mapping between psychological categories and neural processes.

The core components of *episodic memory* within the IMM correspond to the interactions between the hippocampus and both sensorimotor and association cortices depicted in Figure 16.1. As detailed in Chapter 2 of this volume, when a new episodic memory is formed, the co-activated pattern of cortical representations corresponding to the to-be-remembered experience (e.g., representations of sensory and motor qualities at various levels of abstraction) is linked to a sparsely encoded representation in the hippocampus (a hippocampal "trace") that encodes high-level contextual information (Danker & Anderson, 2010; Nadel, Samsonovich, Ryan, & Moscovitch, 2000; Schacter & Addis, 2007). For example, walking into a childhood home in adulthood would activate a representation of that context, which would in turn activate a range of perceptual and conceptual representations linked to that context (e.g., representations of specific interactions with one's parents and siblings, the sound of a TV in the background, the smell of dinner cooking in the oven, etc.). Retrieving a specific episodic memory corresponds to a reactivation of its hippocampal trace, which in turn promotes the reactivation of the widespread cortical representations corresponding to the details of the previous experience. Relatedly, when an experience in daily life corresponds to an important element of an episodic memory from the past, activation of that one element can reactivate the entire memory in the hippocampal–cortical complex through a process of pattern completion (as well as additional memories to follow' e.g., Proust's [1968] oft-quoted experience of tasting a madeleine dipped in tea). Thus, episodic memory retrieval corresponds to a type of brain-wide internal simulation of past experience. According to the LRNG model, if/when a clinically relevant episodic memory is retrieved or reactivated in this manner within psychotherapy, it becomes labile and is open to revision in light of the therapeutic experience.

The core components of *semantic memory* within the IMM correspond to the interactions depicted in Figure 16.1 between sensorimotor/association cortices, hippocampus, and default mode network (DMN) regions (such as medial prefrontal cortex [MPFC]) that appear to play a role in representing abstract multimodal expectations (schemas) that can span sensory modalities as well as large spatial/temporal scales (Barrett & Satpute, 2013; Binder, Desai, Graves, & Conant, 2009). For example, a person's schema for relationships in certain situations could provide (either implicit or explicit) expectations (or predictions) about how selfish or caring other people tend to be. These high-level expectations are likely derived in part by abstracting from common patterns in episodic memory (i.e., via interactions with hippocampus and the rest of cortex). They are also likely driven in part by implicit statistical learning processes applied to patterns in past experiences, independent of spatial context and hence separate from episodic memory (Reber, 2013). Once in place, descending, schema-driven expectation/prediction signals from DMN regions such as MPFC then have a significant influence on the way new sensory inputs (or retrieved memories) are represented/construed. For example, given schema-derived expectations of low self-worth, ambiguous social signals may be perceived as signs of rejection, and memories of past social interactions could be similarly construed. Whereas given schema-derived expectations of high self-worth, the associated expectations could lead otherwise identical inputs from the senses and from memory to be construed as signs of acceptance.

Emotional responses in the IMM correspond to highly emergent phenomena, as seen in Figure 16.1. First, limbic network (LN) regions such as the amygdala (but also the orbitofrontal cortex, hypothalamus, periaqueductal gray, and neuromodulatory nuclei such as the noradrenergic locus coeruleus) interact to initiate concerted responses to stimuli that are construed as having affective significance/value (Adolphs et al., 2005; Barrett & Satpute, 2013; Gupta, Koscik, Bechara, & Tranel, 2011; Mitchell, 2011; Mitchell & Greening, 2011; Peck & Salzman, 2014; R. Smith, Killgore, & Lane, 2017; R. Smith, Thayer, Khalsa, & Lane, 2017; Yeo et al., 2011). These affective responses include (a) increases in pleasant or unpleasant autonomic arousal (via interactions with the peripheral nervous system), (b) the automatic redirection of attention (via interactions with sensory cortices and paralimbic regions such as the anterior and mid-cingulate cortices), (c) the initiation of particular action tendencies (via interactions with the cortico-striatal system), and (d) the preferential encoding, consolidation, retrieval, and reconsolidation of salient aspects of experience (via influences on hippocampal–cortical interactions). LN regions can initiate such responses based on simple unconditioned stimuli (US) and conditioned stimuli (CS; e.g., increased arousal in response to a snake [US] or to a sound that has been associated with a snake [CS]). However, these responses can also be flexible and context-dependent (Cunningham, Van Bavel, & Johnsen, 2008). Specifically, they can also be initiated in reaction to higher-level phenomena via interaction with regions such as MPFC and hippocampus, which encode context-specific prior expectations. For example, perceiving a knife may lead to the initiation of an unpleasant affective response in the context of a robbery but typically not in the context of a family dinner. In cases such as these, the amygdala and related LN structures can be understood as assigning context-specific positive or negative (or neutral) value to perceived or remembered events and then modulating attention, memory, autonomic arousal, and action tendencies according to that value assignment. This organized, value-/construal-driven modulation of attention, memory, autonomic arousal, and action tendencies corresponds to what was referred to as an "emotional response" in the IMM.

Subcortical LN nuclei such as the amygdala appear sensitive to (i.e., implicitly represent) broad affective dimensions of situations (and the stimuli within them), such as their significance, concern relevance, and value (e.g., the amygdala increases in activation to salient events that are either pleasant or unpleasant; Brosch & Sander, 2013). However, such subcortical structures can participate in generating a broad range of emotional experiences through their many downstream effects. For example, they can initiate body state changes, which in turn lead to cortically represented changes in bodily feelings (R. Smith & Lane, 2015). They can also have a broad modulatory influence on cortical information processing and can thereby alter the best estimates the cortex arrives at for the rest of its internal perceptual/conceptual description (predictive model) of the internal and external world (via precision-modulation, tagging for consolidation, etc.). By modulating the interactions between cortical elements in this way (i.e., which in turn depends on the way situations are affectively construed), these subcortical structures can therefore play an important (indirect) role in producing a potentially enormous variety of emotional experiences represented cortically. Similar cortical–subcortical interactions may be at work when experiencing the emotional content that is an intrinsic feature of a particular event memory.

In psychotherapy, certain stimuli, situations, and episodic memories may initially be represented/construed in a manner that promotes unpleasant affective responses (i.e., they are assigned strong negative value). This would typically be the case for situations/memories related to the clinical problem for which assistance is being sought. However, after learning a new set of prior expectations during the course of therapy (a very complex process in itself involving activation, updating and reconsolidation of memories), those same stimuli, situations, and memories may be interpreted differently and promote a pleasant or neutral response instead (i.e., they now have positive or neutral value). For example, when schemas regarding self-worth are revised through therapeutic interactions, the associated change in expectations could lead to different interpretations of future social interactions and the activation of different autonomic/behavioral responses in such situations. The process of learning these new expectations can result from what we previously referred to as "corrective emotional experiences" (CEEs). Such experiences involve the activation of previous (unpleasant affective response promoting) memories/expectations combined with therapeutic interactions that are inconsistent with those expectations—ultimately leading those expectations to be revised. This can be thought of (at least in part) as involving interactions between sensorimotor/association cortices (representing new exteroceptive and interoceptive experiences in therapy), amygdala and other LN structures (corresponding to affective responses generated in therapy), and DMN/hippocampal regions (encoding expectations based on past experience), resulting in prediction errors (PEs) that initiate an update to those expectations. With revised prior expectations, LN structures such as the amygdala will no longer assign negative value to the previously problematic stimuli, situations, and episodic memories—and therefore will no longer trigger unpleasant affective responses (i.e., and the resulting cortically represented emotional experiences would become more adaptive).

Note also that, due to the previously described influence that an affective response can have on memory processes (e.g., via interactions between the amygdala, the body, and hippocampal–cortical interactions), one would expect that moderate unpleasant arousal in therapy would create a state promoting reconsolidation and the updating of prior expectations more generally. As previously described, this would likely involve LN-mediated (e.g., amygdala-mediated) modulation of hippocampal–cortical interactions that amplify the influence of therapeutically induced PEs (i.e., increasing the rate at which schemas and associated prior expectations are revised). Thus, the role of emotional arousal and the role of updating/reconsolidation in promoting more adaptive emotional responding, which were both discussed in the BBS paper, can be captured via the previously described brain processes, even though no single brain region corresponds to the psychological categories initially used to describe the IMM.

There are also other ways in which emotion can facilitate enduring change. For example, when perceived events/memories initiate an affective response, it is thought that the neurons/synapses encoding those events/memories may be molecularly "tagged" for preferential consolidation/reconsolidation (Payne & Kensinger, 2018). This may occur in part through interactions between the amygdala, the locus coeruleus, and the hippocampus, such that phasic bursts of norepinephrine are initiated at encoding and initiate gene expression changes in relevant neurons/synapses. Then, during sleep, this tagging process leads to preferential hippocampal replay of the relevant memories, ultimately maintaining/strengthening the hippocampal–cortical connections underlying the memory. As a result, when new experiences in therapy include affective responses, the resulting learning may be more likely to be consolidated/reconsolidated and endure.

According to this extended neural model, a major role of emotional responses in therapy is to facilitate the learning process. Initiating an affective response draws attention to deviations from expectations in therapy, it increases the rate at which expectations are revised in response to therapeutic interactions, and it promotes preferential consolidation/reconsolidation of new learning during sleep. Thus, while emotion is not strictly necessary for enduring change (i.e., expectations/memories can be revised/reconsolidated without emotion), this learning process would be much less efficient in the absence of emotion. It is also important to consider that, given the contents of the maladaptive expectations and memories that are typically addressed in therapy, affective responses may also be inevitable when such expectations/memories are activated. In addition, emotional responses will also be generated because of the personal significance of the new learning that has occurred. Ultimately, through reconsolidation of memories (and resulting changes in schemas/expectations), the character of these affective responses (and of affective responses to similar future situations) can become more adaptive.

Aside from the original types of memory discussed in the BBS paper, one theme that has emerged in this book is the need to incorporate another type of memory associated with automatic action tendencies (e.g., habits, automatic urges to act in particular ways, repetitive behavior patterns). This type of memory—which has been called "action value memory" elsewhere in this book—is linked primarily to interactions between frontal cortex, striatum, and the dopaminergic midbrain (Berns & Sejnowski, 1996; Cisek, 2007; Dolan & Dayan, 2013; Frank, 2011; Redgrave, Prescott, & Gurney, 1999). In the cortico-striatal system, each action one considers in a given situation appears to have a stored value, which corresponds to particular synaptic strengths in the striatum that determine the level of inhibition allocated to each cortically represented action option. Action representations with higher stored values receive less inhibition and are therefore selected more easily/automatically. In this system, temporary (phasic) changes in midbrain dopaminergic output appear to alter action values based on a reward PE signal that indicates whether a chosen action led to better or worse outcomes than expected (Reynolds & Wickens, 2002). If the outcome of an action is better than expected, there is a temporary increase in dopaminergic influence, which alters striatal synapses so as to reduce the future inhibition on that action (i.e., the stored value of that action is increased). If the outcome is worse than expected, there is a temporary decrease in dopaminergic influence, which alters striatal synapses so as to increase the future inhibition on that action (i.e., the stored value of that action is decreased). This value learning process is slow, such that many experiences of observing the outcomes of an action are required to make it highly automatic (i.e., very high value) or strongly avoided (i.e., very low value). This was described as model-free learning in Chapters 3, 14, and 15 of this volume.

This type of slow learning by repeatedly observing the outcomes of different actions represents a likely basis for the development of more adaptive automatic behavior patterns as a result of therapy. For example, a client may have initially learned to avoid particular behaviors because they repeatedly led to bad outcomes in their past social environment, even if they are in fact highly adaptive behaviors in their current social environment. Part of the therapeutic process can be seen as providing a client encouragement to repeatedly engage in previously avoided behaviors so that the client can have new emotional experiences while engaging in those behaviors and the client's brain can update the value of those actions and eventually make them automatic (i.e., where the action values start very low and then become higher and higher with repeatedly "better than expected" outcomes).

The willingness of the client to accept the therapist's encouragement to engage in the work of therapy is not a simple matter either. Although we previously discussed the essential role of the therapeutic relationship and the therapeutic alliance in making enduring change possible, we did not discuss the therapeutic alliance itself from a neuroscientific perspective. If one considers a client entering therapy who has experienced interpersonal abuse or neglect earlier in life, those experiences will likely determine the expectations the client brings to the interaction in therapy. Anticipating mistreatment or disregard, as in other previous relationships, the experience of a therapist as kind, caring, and compassionate will be experienced as counter to expectation and generate PE. The discomfort that this engenders may be softened by the emotional tone established by the therapist and, over time (if all goes well), will lead to an updating of expectations. As such, the establishment of the therapeutic alliance may itself constitute a series of CEEs that may or may not reach the level of conscious awareness of the client.

The importance of the emotional tone and emotional dynamics of the therapy relationship highlight that another possible influence of emotion on the therapy process could involve mood-congruent memory and mood-dependent memory effects (i.e., in which one's current mood state facilitates the retrieval of some memories over others; Kiefer, Schuch, Schenck, & Fiedler, 2007; Lewis, Critchley, Smith, & Dolan, 2005). For example, a change in one's emotional state due to the support of the therapist, as well as the direct suggestions of the therapist, could promote the retrieval of clinically relevant memories (some of which may have been less accessible due to suppression/avoidance) and change the way those memories are construed—thus paving the way for new CEEs. This could then alter the way in which similar future situations are automatically construed.

According to this extended IMM/LRNG model, once the therapeutic alliance is established, a sufficiently trusting relationship is created and the goals of therapy are agreed upon, the next steps in therapy may be primarily about altering prior expectations (again, a very complex process involving the activation and updating/reconsolidation of memories), such that situations are construed differently and therefore lead to more adaptive affective responses in the future. The alteration of prior expectations may come about from experiences within the therapy relationship itself, experiences outside the therapy, or both. The change to more adaptive affective responses can in turn increase the initial tolerability of taking avoided actions and entering avoided situations. The later steps in therapy may be more about updating action values. In this case, the client's explicit expectations about (and model of) the world have become more adaptive, but their tendencies to habitually engage in maladaptive behaviors may still be strongly engrained. Thus, it is helpful for them to be encouraged to repeatedly engage in the new adaptive behaviors and experience the emotional consequences of such new behaviors, so as to slowly alter their action value memories and make the more adaptive behavior patterns automatic.

It is important to highlight that, while this summary describes these psychological and neural processes in a somewhat linear and sequential manner, such processes are better understood as operating in a more parallel and distributed fashion. For example, at each moment the hippocampus and MPFC (as well as the DMN more broadly) can be thought of as representing the brain's "best guess" about how to construe a situation, continuously issuing top–down predictions/expectations based on this evolving construal. These top–down predictions/expectations simultaneously govern interpretation of new sensory input at each moment (which then generates PEs that update expectations); they also continuously modulate the value that the amygdala (and other LN structures) assigns to stimuli/events. The aforementioned moment-to-moment situational construal also interacts with the cortico-striatal system to determine moment-to-moment estimates of which actions have high and low values under that construal.

To summarize, in this type of neural model (and related computational models discussed in other chapters) prior expectations (or schemas) have a strong influence over operations throughout the rest of the brain. As a consequence of this, changing prior expectations can lead to a cascade of transformative effects. For example, by updating schemas through reconsolidation (altering prior expectations) one can alter situational construals, which will in turn alter which action options are considered in a situation (i.e., those actions with high values under that construal will be given primary consideration). The construal of the situation will also launch predictions about the metabolic requirements that any behavioral responses to the situation will require and thus alter affective bodily responses (and the emotional experiences that often result). Corrective experiences in therapy constitute a specific kind of therapeutic exploitation of these mechanisms to bring about reconsolidation and updating of memories—leading to more adaptive expectations. As a result, the nature of future construals, emotional responses and action dispositions may be altered in a way that is better adapted to the person's current environment. The old behavioral responses may still be automatically elicited, but can be held in check by virtue of revised expectations regarding the consequences of those old behaviors. As the person then repeats this new way of construing and responding emotionally in previously problematic situations and practices responding behaviorally in a different way, the action values gradually change and allow more adaptive behavioral patterns to become less effortful and more automatic. To the extent that this pattern of changes is applied to a variety of circumstances and variations on those circumstances, one may say that the individual's internal working model of the social world has been adaptively updated.

The dynamics of this extended model can successfully capture many important aspects of the change process. For example, it can account for why emotional responses are an important component of the change process; it illustrates how revised schemas/expectations can promote more adaptive perceptions, beliefs, construals, and emotions; and it can account for the importance of repeated practice of new behaviors to avoid falling back into maladaptive behavior patterns. However, aspects of this model remain underspecified, which leads us to consider the future research agenda both in terms of basic science and translational clinical science.

Basic Science of Memory and Memory Updating/Reconsolidation

Across most of the chapters there is agreement that PE is necessary (if not sufficient) for memory updating. As was noted earlier, this is a truism—without some mismatch between a reactivated memory and the current situation (the source of PE) there would be nothing to update. What seems to matter more is how much PE there is, because this affects what happens next—strengthening or altering the memory, or leaving the memory completely alone when the system decides there is no linkage between the reactivated memory (the "prediction") and the current situation. In computational terms, this latter possibility would be described as determining that the latent causal structure of the current situation is sufficiently different from the reactivated memory and updating is not appropriate (Gershman, Monfils, Norman, & Niv, 2017. This results in a separate memory being formed, as would be the case in extinction training, for example. The challenge for future research is to determine how the extent of PE affects decisions about latent causal structure that then determine whether the system integrates or segregates the networks of brain activity linked to the retrieved memory and the present moment in which the memory is being reactivated.

Also important will be research on the various boundary conditions that control whether or not memory destabilization and updating will be observed. Strength of learning, age of the memory, frequency with which that memory is retrieved—all of these and more might affect the likelihood of these outcomes and hence must be understood at a level of precision that currently eludes the field (see Chapter 2 of this volume). One tantalizing possibility is that better understanding of the metaplastic mechanisms controlling stabilization and destabilization of memories at the synaptic level could lead to pharmacological manipulations capable of opening up even strongly imprinted memory circuits to change (Gerlicher, Tüscher, & Kalisch, 2018; Haaker et al., 2013). A great deal of basic science needs to be done before we get to that stage, in particular informing our understanding of exactly what happens at the cellular and network levels when a memory is reactivated and what consequences this has for what happens next when reactivated memory meets current reality. The payoff for this kind of basic science is clear: insight into the best way to approach and update problematic memories.

As pointed out earlier, there are multiple memory systems (cf. Schacter & Tulving, 1994), and enduring change in psychotherapy is likely to necessitate change in many or all of them. The questions raised about boundary conditions on memory destabilization and updating must be addressed for each kind of memory. Most important, the existence of multiple systems means we need also to understand interactions between the different kinds of memory—between episodes and schemas in particular.

We have argued that episodic memory reconsolidation (MR)—triggered by a CEE—is central to the change process. But, this is just the start of a process leading to behavior change. We need to understand how the reconsolidation of an updated reactivated episodic memory leads to semantic transformation, to the revision of schemas, scripts and habits, and the expectations they generate. Schemas/expectations can be revised through new experiences in the absence of the capacity for episodic memory (e.g., in individuals with certain forms of amnesia; Kan, Alexander, & Verfaellie, 2009), showing that semantic updating can proceed on its own. However, such updating occurs much more slowly in those with damage to the episodic memory system, suggesting that episodic learning processes contribute significantly to schema revision and the efficiency with which this is accomplished. As noted earlier (see Chapter 2 of this volume), schema incongruent inputs activate the episodic system, providing a mechanism for this effect, but exactly how and how deeply implicit and explicit schema-driven expectations can be altered is a question that future research should target.

Another consequence of shifting control between episodic and semantic systems could be a change in the perspective from which one experiences a memory. One can either experience a memory from a bird's-eye (allocentric) perspective, standing outside of it, or one can experience a memory from the inside, standing in specific relation to the things and actions taking place (an egocentric perspective; see Waller & Nadel, 2013; Ekstrom, Spiers, Bohbot, & Rosenbaum, 2018 for background). It may make a difference which of these perspectives is in control as one is trying to alter memories. Advocates for experiential approaches to therapy clearly believe that re-experiencing past events from an egocentric perspective is more effective at producing enduring change. Although the hippocampus creates allocentric maps, accessing these maps typically involves taking an egocentric perspective. Recall that schema-incongruency drives hippocampal activation under conditions of sufficient PE the system may shift into first-person perspective, with positive consequences for therapeutic outcome. Clearly, we need to better understand how one's personal point of view is represented in the hippocampus and elsewhere. Is it easier to change memories when an egocentric perspective is taken? Or, conversely, would it be easier to change memories when a more "distanced" allocentric perspective is taken? And how can we use brain activation data, or any form of data, to inform us about what state the brain is in at any given moment?

Basic Science of Emotion-Memory Interactions

Another major area where additional basic research is needed involves the specific mechanisms by which emotion alters memory. In the IMM model we held that whenever episodic memory, semantic memory and emotion are activated, the other two are as well. According to this perspective, emotion is always present. We might qualify this and say that at times the role of emotion is negligible or even nonexistent if no significant physiological arousal has occurred (i.e., emotion activation can, at times, equal zero). But that still leaves the question of how emotion alters memory when it is activated. In the LRNG model we stated that CEE is necessary for change in the context of psychotherapy. The foregoing chapters have highlighted that many, if not most, psychotherapy modalities recognize the important role of emotion in the change process, although we note that Bruce Ecker (see Chapter 11 of this volume) takes a different position. He argues that what is critical for the change process is MR and that although changes in emotion are observed clinically as change occurs, these changes are incidental and independent of the MR process.

This leads to the basic question of how emotional arousal alters memory. What is well established is that emotional arousal tags memories such that they are more likely to be remembered and easier to retrieve (Bradley, Greenwald, Petry, & Lang, 1992; Cahill & McGaugh, 1998; LaBar & Phelps, 1998; Mather, Clewett, Sakaki, & Harley, 2016). There is good evidence to suggest that if emotional arousal is too high, the ability to encode the context of the memory is reduced by virtue of hippocampal inhibition (Diamond, Campbell, Park, Halonen, & Zoladz, 2007). One may ask how one determines at what point encoding/retrieval ability declines as emotional arousal level increases. A related important consideration involves individual differences in the threshold at which this occurs. For example, do people vary in the arousal level at which memory encoding and retrieval declines? Might individuals with early childhood adversity be more likely to have a lower threshold for this effect (Corrigan, Fisher, & Nutt, 2011)? Put another way, the relation between arousal level and memory encoding and retrieval may be described by a quadratic or inverted parabolic (inverted U) function (Diamond et al., 2007), but the location and height of that curve may vary across individuals. A related question is how best to measure arousal in this context. Is reportable experience a reliable indicator, or are implicit measures such as heart rate or cortisol level better measures in this context?

Translating these issues into neural systems terms, the amygdala is well established as a key structure involved in coding memories for emotional salience in a classical conditioning context (Phillips & LeDoux, 1992). The following facts about the amygdala are also well established: (a) the amygdala is known to have direct connections to the hippocampus as well as indirect connections to it through the parahippocampal gyrus, locus coeruleus, and other subcortical structures (Amaral, 1992; Höistad & Barbas, 2008); (b) the amygdala is known to participate in a circuit with the ventromedial prefrontal cortex (vmPFC) and hippocampus involved in the evaluation of the emotional significance of current circumstances (Roy, Shohamy, & Wager, 2012); and (c) the amygdala has rich and widespread connections to the cerebral cortex (Amaral, 1992; Aggleton & Saunders, 2000). Thus, to the extent that episodic memories involve ensembles of hippocampal–cortical interactions, the amygdala may interact with these ensembles both at their origin in the hippocampus and at their targets in the cortex.

One key question, therefore, is whether the amygdala primarily represents concern relevance/value as described in our previously described model (e.g., addressing questions such as, "Is this important?"; "How much should I attend to and learn from this?"; and "Does this call for a change in autonomic arousal?") or whether, by virtue of its interactions with vmPFC and hippocampus, as well as its projections to the cortical targets of hippocampal–cortical complexes, it can represent more nuanced aspects of emotional meaning. A related question is whether the modulation of a memory by the amygdala (and other subcortical structures), as instantiated in a hippocampal–cortical complex, consists of amplifying and/or diminishing various elements of the complex, thus rendering the hippocampal–cortical complex altered in an enduring manner once reconsolidation has occurred. If so, this would constitute a tangible means by which emotion might alter memory in an enduring manner. It would support Bruce Ecker's claim that the core process of change in psychotherapy is a change in memory through reconsolidation, but it would also suggest that emotion, as exemplified by amygdala-mediated modulation, is playing a substantive role in altering those memories if emotional arousal at the appropriate level of intensity has occurred when old memories are exposed to contradictory information (generating a PE).

This would correspond to the notion, previously described in the section of this chapter on our proposed model (and elsewhere in this book), that unpleasant arousal may amplify the degree to which PE updates memories/expectations (in computational terms, via altering precision-based modulation; Clark, Watson, & Friston, 2018; Joffily & Coricelli, 2013).

A second major question is how the phenomenon of mood-congruent memory encoding and retrieval come about (Bower, 1981; Eich, 1995; Erk et al., 2003; Kiefer et al., 2007; Lewis et al., 2005). How do memories get sorted or stored so that they become accessible by virtue of the emotional meaning or pattern of emotion activation at a given moment? An important hypothesis to test is that the consolidation/reconsolidation process associated with sleep plays a major role in creating and maintaining an index within the hippocampus that renders memories retrievable by virtue of their content, including their emotional content (see Chapter 7 of this volume). A related question is how retrieval of emotion-laden memories occurs. Might it be the case that if a certain pattern of amygdala-vmPFC–hippocampal–cortical activity is activated in real time, it automatically facilitates access to mood- or emotion-relevant memories? If so, what is the precise nature of this process? Might it correspond to traditional models of spreading semantic activation (Collins & Loftus, 1975) and/or context-facilitated retrieval (Erk et al., 2003; Godden & Baddeley, 1975; S. Smith & Vela, 2001)? Or does emotion-cued retrieval operate in a different manner?

A related question is how construal of the social context at a given moment influences the memories that are retrieved to guide action. It may be relevant to note here that the indirect connection from the amygdala to the hippocampus via the parahippocampal gyrus is quantitatively greater than the direct connection from the amygdala to the hippocampus (Pitkänen, Pikkarainen, Nurminen, & Ylinen, 2000). The parahippocampal gyrus is a hub in the brain networks representing places (Mormann et al., 2017), and it seems likely that the amygdala input allows the system to attach affective significance to places. This raises questions about how emotion and spatial context influence which memories in the hippocampus are accessed to facilitate interpretation of and guide reaction to current circumstances.

There is also a need to develop a nomenclature or classification system for types of memory with emotional content and to define and differentiate the neural basis of each. These include, but are not limited to, (a) classical conditioning—associative learning that involves a CS and US; (b) associative learning in which content that is emotionally neutral is remembered better because of coincident and unrelated emotional arousal; (c) reinforcement learning in which the affective consequences of an action change its value and likelihood of recurrence (Gershman, 2017)—one important example being negative reinforcement, in which avoidance behaviors are reinforced by the associated reduction of distress that they cause (e.g., procedures or actions that serve an emotion-regulatory function through avoidance, such as avoiding eating or speaking in public places); (d) episodic memories with strong emotional content versus those without; (e) schemas with inherent emotional content such as the implicit affective learning described by Bruce Ecker; and (f) A combination of schemata that constitute an internal working model of the social world that captures expectancies regarding interpersonal interactions and emotional responding in prototypical situations.

These questions are important because they constitute a mechanistic reification of the change processes described originally at the level of clinical observation. They raise the possibility that each type of memory–emotion interaction could provide the basis for a different type of CEE. For example, CEEs that alter schematic expectations about relationships most plausibly involve updates within semantic processing networks (e.g., vmPFC/DMN; Binder et al., 2009), whereas CEEs that alter maladaptive repetitive behavior patterns most plausibly involve updates within action control networks (e.g., cortico-striatal loops; Cisek, 2007; Dolan & Dayan, 2013; Frank, 2011; Redgrave et al., 1999). They also have the potential to be translated into questions that can be addressed using objective methods such as functional magnetic resonance imaging (fMRI) and autonomic and neuroendocrine measures of arousal, as well as other methods. Elucidation of mechanisms in this way paves the way for interventions that could improve clinical care.

Memory Reconsolidation Research in the Context of Psychotherapy

The phenomenon referred to as MR has a relatively brief history and its application to clinical disorders is even newer. There exists some confusion about the term and what it refers to. Put most simply, MR refers to the fact that when a memory is reactivated, it appears to be put into a labile state, and a cellular process (reconsolidation) is needed to return the memory to a stable state. What is interesting about this process is that during the labile phase reactivated memories apparently can be changed—weakened perhaps, even erased, strengthened perhaps, or updated with new information. While there remains some debate about whether such malleability has been established in humans, our project relies on the assumption/conviction that the phenomenon is real across many species, including humans (see Chapter 2 of this volume). With that as a foundation, the question becomes how to make the best use of the phenomenon to improve the human condition.

It is with that goal in mind that we have undertaken this book project focused on enduring change in psychotherapy. Within the community of scholars, researchers, and clinicians interested in adapting the phenomenon of MR for clinical purposes, there is debate about how best to move this field forward. Some argue that it has been very difficult to demonstrate that a change in psychotherapy is due to MR (Elsey, Van Ast, & Kindt, 2018). Until this has been demonstrated with appropriate scientific rigor, particularly in human contexts that parallel the well-established phenomenon in animal models, they feel that it is dangerous to apply such concepts to other clinical contexts. At the other end of the spectrum, others claim that the phenomenon is well established and has already been successfully implemented in a variety of human clinical contexts (see Chapter 11 of this volume). Our position is somewhere in between. For several reasons, which we enumerate in the following discussion, we believe that there is much to be gained now by considering the full range of application of the phenomenon of MR to psychotherapy.

One reason is that there are different memory systems in the brain (Schacter & Tulving, 1994), and the mechanisms of reconsolidation may operate differently in these different systems. To the extent that different forms of psychotherapy exploit different memory systems, understanding change in each of these systems becomes paramount. The fundamental facts of reconsolidation involve (a) retrieval of memories, which renders them labile and open to change, and (b) system-specific alterations of these labile memories as a function of current conditions. There remains much to be learned about reconsolidation within each memory system—indeed, in some systems, we have barely scratched the surface of possibilities.

Explicit memory—the ability to consciously recall facts and events—is mediated by a network of brain structures, with a likely hub in the hippocampus and associated medial temporal lobe structures. Implicit memory—things we know (i.e. that affect our behavior) but can't describe in words, including skills and habits, and classical conditioning—is mediated by networks including the striatum, amygdala, and neocortex, respectively (Gazzaniga, Ivry, & Mangun, 2018).

The original observation about MR in rodents involved fear conditioning (classical conditioning) that was disrupted by injection of protein synthesis inhibitors in the amygdala (Nader, Schafe, & Le Doux, 2000). The phenomenon of fear extinction from exposure therapy involves an inhibition of fear conditioning mediated by the ventromedial prefrontal cortex (Milad & Quirk, 2002). The science of psychotherapy of anxiety disorders has been significantly influenced by this model and its behavioral predecessors (Craske, Hermans, & Verliet, 2018). As noted by Jonathan Huppert in this volume (and others), the treatment of anxiety disorders may also involve a cognitive component (cognitive-behavior therapy) that can include emotion processing (as a supplement to inhibition due to extinction). By talking about and coming to an understanding of the experiences in exposure therapy, the effects of treatment may be generalized to other settings and become more enduring. This can be understood as the creation of new episodic and semantic memories that compete with and replace old problematic memories. As such, exposure therapy plus cognitive processing of that new learning can be considered change due to a combination of new memories (extinction and semantic memories). Within that context, it is challenging indeed to demonstrate the form of MR that involves a revision of the original memories (Elsey, Van Ast, & Kindt, 2018).

Consider, however, the role that schemas play in current theories of more experiential and exploratory forms of psychotherapy. Such schemas are a form of semantic memory. When we discuss the updating or reconsolidation of semantic memories, this necessarily involves the influence of episodes. Semantic memories are best understood as the distillation of the central features of a variety of episodic experiences and the memories formed from these (Barsalou, 1988). Our literature review showed that relatively little is known about the updating and reconsolidation of schemas or semantic memories (Gilboa & Marlatte, 2017). It's clear to us that this is an important area of future basic science research that could have significant translational impact.

A second reason for exploring reconsolidation as it applies to psychotherapy relates to the distinction between memory erasure and memory updating. Classical conditioning can be inhibited by extinction but the generally accepted view is that the original memory trace remains unchanged (Pavlov, 1927). If the original memory is to be altered, the association between the conditioned and unconditioned stimulus must be disrupted. This latter is equivalent to erasure. To the extent that a given memory is the cause of clinical symptoms, erasure of the memory could plausibly provide complete relief of symptoms—a highly desirable goal of clinical intervention. In our current state of knowledge, however, updating in this context (modifying but not erasing the linkage between the conditioned and unconditioned stimulus) is not an option. Thus, if erasure is not achieved the original memory remains intact and symptoms may recur.

Contrast this with clinical conditions that are based on problematic semantic memories. In our view, semantic memories can be updated (reconsolidated) by the same mechanisms that created the semantic memories in the first place—by incorporating salient episodic memories. Thus, we believe that considerable clinical benefit can be obtained from memory updating, as it may lead to different construals, emotional experiences, and behavioral responses which over time can have enduring effects. Altering problematic ways of responding to recurrent situations is a worthy clinical outcome that may be related to but not identical with symptom relief.

A third reason involves the role of emotion in the change process. As we previously noted, for reconsolidation of semantic memories emotion may play a particularly important role in tagging particular episodic memories as important and relevant for the purpose of updating the original memories (or the current version of them; Bradley et al., 1992; Cahill & McGaugh, 1998; LaBar & Phelps, 1998; Mather et al., 2016). In this context the amygdala (and other emotion-generating structures) modulates hippocampal–cortical complexes (Inman et al., 2008). In other words, the activation of emotion in psychotherapy may be important and highly facilitative of the clinical change process depending upon which modality is being practiced. Contrast this with classical conditioning, in which the memory trace linking the conditioned and unconditioned stimulus seems to depend on the amygdala (Phillips & LeDoux, 1992). In this context, the aim is to attenuate excessive emotional arousal that is causing clinical symptoms. Moreover, given the nature of the memory in classical conditioning, activating new emotional experiences will not alter the original memory trace, whereas emotional arousal for the purpose of creating new episodic memories that will update semantic memories could potentially be quite effective in therapies that aim to modify problematic schemas.

A fourth reason pertains to the influence such exploration may have on how psychotherapy is practiced. The potential aims of this project span the gamut from radically altering how psychotherapy is performed based on strict application of MR principles to simply using MR principles to explain what is already being done without any effort to affect how clinicians practice psychotherapy (Elsey & Kindt, 2017; Elsey, Van Ast, & Kindt, 2018). We believe that a middle ground is warranted—we assume that clinicians who are trained in therapies for which efficacy has been demonstrated can benefit from considering the phenomenon of MR to optimize how they do therapy. In particular, attention to the three basic principles outlined in the LRNG model would lead therapists to enhance certain elements and deemphasize others within their own technique for the purpose of improving efficiency and effectiveness. This will be particularly true in the context in which clinical decision-making is needed at any particular juncture and in cases where therapy is not progressing as it should.

For all of these reasons, we believe that the preceding chapters have raised important considerations for future research. We endorse the recommendations that have been made in those chapters and highlight ones that we consider particularly important.

Clinical Research Agenda

In light of the previous discussion, we now briefly describe 12 topics for which investigation seems particularly timely.

Need to Define and Set Standards for "Enduring Change"

The sine qua non of evidence-based practice is demonstrating change from the beginning of treatment to the end of treatment and perhaps at follow up for periods such as 3 or 6 months. This is entirely understandable when it is considered how long research grants are for and how long it takes to recruit a sample and provide treatment under controlled conditions. Our perspective on enduring change emphasizes the need to (a) define what would constitute enduring change and (b) create standards for the field regarding the follow-up time periods needed to ensure that enduring change has occurred. It raises the issue of the need for treatment studies to obtain permission for long-term follow up and for funding agencies to provide funding for longer-term follow up studies.

Defining Outcome Variables Indicative of Enduring Change

The standard approach to assessing outcome in psychotherapy is to assess the symptoms that constitute the mental health disorder being treated before and after treatment and at regular intervals thereafter. This may be perfectly adequate for many clients who seek psychotherapy but does not cover the full range of what is needed.

There is also a need to assess psychotherapy process variables that are indicative of change as the therapy is being conducted, and thereafter. In Chapter 12 of this volume, the Narrative Emotional Process Coding System (NEPCS; Angus et al., 2017) was described and used to support the claim that enduring change had occurred. This approach is fitting if the focus of clinical intervention is broader than symptoms per se, including broader patterns of behavior, thought, action, and feeling, both interpersonal and intrapersonal, that are the source of distress and symptoms. The NEPCS is well-suited for capturing changing narratives indicative of clinical improvement while therapy is ongoing. It would be useful to develop a method of follow-up assessment involving the NEPCS including criteria that would need to be met to demonstrate enduring change.

There is also a need to extend the range of outcome variables that can be assessed in long-term follow up that evaluate mental health as opposed to the presence or absence of psychopathology. For example, the Shedler–Westen Assessment Procedure (aka SWAP-200) assesses personal and interpersonal characteristics that influence the capacity to enjoy life, the quality of interpersonal functioning, the capacity for emotion self-regulation, etc. (Shedler & Westen, 2007; see Table 16.1). This can be thought of as a method for assessing the degree to which a person's internal model of the social world is working well

Table 16.1 A Definition of Mental Health: Items From the Shedler–Westen Assessment Procedure

- Is able to use his/her talents, abilities and energy effectively and productively
- Enjoys challenges; takes pleasure in accomplishing things
- Is capable of sustaining a meaningful love relationship characterized by genuine intimacy and caring
- Finds meaning in belonging and contributing to a larger community (e.g., organization, church, neighborhood)
- Is able to find meaning and fulfillment in guiding, mentoring or nurturing others
- Is empathic; is sensitive and responsive to other people's needs and feelings
- Is able to assert him/herself effectively and appropriately when necessary
- Appreciates and responds to humor
- Is capable of hearing information that is emotionally threatening (i.e., that challenges cherished beliefs, perceptions, and self-perceptions) and can use and benefit from it
- Appears to have come to terms with painful experiences from the past; has found meaning in and grown from such experiences
- Is articulate; can express self well in words
- Has an active and satisfying sex life
- Appears comfortable and at ease in social situations
- Generally finds contentment and happiness in life's activities
- Tends to express affect appropriate in quality and intensity to the situation at hand
- Has the capacity to recognize alternative viewpoints, even in matters that stir up strong feelings
- Has moral and ethical standards and strives to live up to them
- Is creative; is able to see things or approach problems in novel ways
- Tends to be conscientious and responsible
- Tends to be energetic and outgoing
- Is psychologically insightful; is able to understand self and others in subtle and sophisticated ways
- Is able to find meaning and satisfaction in the pursuit of long-term goals and ambitions
- Is able to form close and lasting friendships characterized by mutual support and sharing of experiences

Source: From Shelder and Westen (2007).

and identifying areas where fine-tuning could be useful. Tools such as this are needed that can chart progress over time and evaluate if changes are enduring.

Optimal Number of Corrective Emotional Experiences

In the BBS article we raised the question of how many CEEs are needed to bring about enduring change. Recall that in the LRNG model we proposed that Step 2 involved a CEE that updated old memories through reconsolidation. One essential feature of a CEE is that it is contrary to expectation and hence generates a PE, rendering the old memory labile and available for revision. A second essential feature is that the quality of the emotional experience in a CEE differs from what is expected, providing specific new content to potentially replace the old prediction. A third essential feature of a CEE is that it is emotionally arousing and thus has the memory-enhancing effects of emotional arousal that facilitate reconsolidation.

From this perspective, CEEs may be more common than previously appreciated. For example, entering into a collaborative, supportive, and empathic relationship with a therapist may feel very different to a client than what they are used to. To what extent does this involve a type of CEE, which does not necessarily reach the threshold of conscious awareness and verbal description, but which may be essential in creating a therapeutic alliance and facilitating the emergence of explicit CEEs that will later be recalled and remembered as critical moments in therapy?

This question illustrates that CEEs often arise spontaneously when therapists do what they are trained to do and, by virtue of the client's past history, which may still be unknown to the therapist, provide clients with experiences that may be quite different from what they have previously experienced. A second question therefore is whether therapists can use historical information and case formulation to plan CEEs that will be experienced by the client as genuine and authentic. If so, how quickly (in terms of number of sessions) can this be accomplished?

Contrary to the typical view in clinical settings that faster is always better, slow progress may be necessary for enduring change to occur. One of the challenges in therapy is providing experiences during sessions that will generalize to the client's social and occupational settings outside of therapy. If the therapy setting is experienced as too different from one's life in the world it may be difficult to achieve this goal of generalization (Gershman et al., 2017). This is one way of understanding why some therapies can go on for many years or even decades. The challenge is to induce an optimal level of PE, which is defined as the level that favors the modification of old memories. What is to be avoided is PE so large that it favors the creation of new memories. Research is needed to determine how best to promote such conditions in therapy as well as how to promote CEEs outside of therapy.

Selecting Treatment Modalities Based on Malleability of Schemas

One of the major conclusions from this project is that schemas, which are a particular kind of semantic memory, are one of two principal categories of memory that requires modification in order for enduring change to occur (i.e., the other being action value memories). Schemas or semantic memories by definition arise from a distillation of numerous personal experiences and are not easy to change. They vary in terms of their age, number of repetitions, and integration with other content, all of which will affect their malleability In the BBS paper, we suggested that one could potentially decide about whether to recommend behavioral therapy, cognitive-behavior or experiential therapies, or psychodynamic psychotherapy based on whether the symptoms were situation specific, state dependent and potentially temporary, or not state- or situation-specific. One could add to this by determining the schemas that contribute to maladaptive behavior and developing ways to assess their malleability. This knowledge would help the therapist decide whether longer-term or more time-limited approaches are indicated.

Exploration of Avoided Pathways

One of the important implications of a computational approach, consistent with many standard therapy techniques, is helping clients to overcome recurrent patterns by exploring pathways (e.g., behaviors and situations that evoked aversive emotion in the past) that have been avoided. As highlighted in Chapter 14 of this volume, avoidance of intolerable emotions may be a core basis for recurrent patterns, and exposing oneself to such experiences within tolerable limits may be key to expanding one's behavioral repertoire. Some forms of therapy explicitly describe such an approach (e.g., exposure therapy) whereas others do the same (psychodynamic, experiential) without emphasizing this in their theory. What steps and procedures are needed to prepare clients to explore the avoided pathways? To what extent can this approach be operationalized and linked to CEEs? Can understanding this from a computational perspective promote more efficient learning and exploration of these avoided pathways?

Recurrent patterns involve behavioral responses to prototypical situations that were adaptive in the past but are maladaptive in adulthood. Recurrent patterns therefore involve situated conceptualizations that link to preferred response scripts and learned action values (i.e., state-action pair values within reinforcement learning models; Sutton & Barto, 1998). The supportive and trusting relationship with the therapist, which may have resulted from CEEs, makes it possible to try out exposure to the avoided behavior/pathway/situation, and the resulting experience of it being better than expected may constitute another type of CEE. The repeated practice of taking this previously avoided but more adaptive path can be understood as slowly updating the action values so that they become increasingly positive over time and thus may be another type of CEE. This may therefore be an important framework for considering how to promote CEEs outside of the therapy context.

Explicit Experiencing of Memories and Emotions

One of the observations from MR research is that memories need not be retrieved into conscious awareness for them to be made labile; all that is needed is a reminder or cue that activates the memory. An important research question is whether change in psychotherapy is better accomplished with explicit vivid recall of past experiences that are problematic as opposed to reminders only. A reminder could, for example, take the form of a current experience that has particular salience for a person because it resonates with past experience (from a predictive processing perspective the interpretation of a current experience begins by applying prior expectations to the current situation). It is recognized that it is difficult if not impossible to know whether an experience in the past was a cause of present difficulty, but a recalled experience from the past could illustrate the current clinical problem. Is it important to explicitly recall the past, not because "insight" is what brings about change or is otherwise helpful, but rather because explicit recall maximizes the number of elements of the old memory that are activated/destabilized and thus potentially modifiable through MR?

Therapies vary in their view of how explicit the experience of old problematic affect needs to be to bring about change. In exposure therapy outcome is better if heart rate is more elevated (Pitman et al., 1996). Does it matter if that visceral change is accompanied by the experience of fear or other affective state that can be described in words? Vivid experience of painful affect associated with past memories is emphasized in experiential and psychodynamic approaches as preparation for CEEs. Are CEEs more effective if they occur in the context of vivid experiences of painful affect from the past? As we discussed in the chapter on computational approaches, it appears that negative affect may be more likely to promote change because it heightens the salience of new sensory inputs and their ability to update prior expectations in a way that positive or neutral affect likely do not.

Conversely, in his chapter Bruce Ecker argues that implicit emotional learnings need to be explicitly articulated and corrected with accurate or updated information (see Chapter 11 of this volume). According to this view, emotional experience is observed but is not necessary for change. Can research be developed to determine if this is so, and in what contexts?

Erasing Memories

Bruce Ecker clearly expressed the view that implicit emotional learnings can be permanently erased through procedures that optimally exploit MR mechanisms. Is this possible (Kindt, Soeter, & Vervliet, 2009)? One way of understanding his approach is that he is promoting alteration of implicit statistical learning through an explicit, verbal intervention. Specifically, his primary target is implicit emotional learnings gleaned from emotionally salient experiences earlier in life, often consisting of repeated experiences with consistent patterns. He helps individuals to become aware of their implicit emotional learnings, and then juxtaposes this new awareness with facts or knowledge of which they were previously aware but that had not been linked to the previously unconscious learning. This lack of connection may be because the implicit learnings cannot be brought into direct contact with conscious knowledge, because they are not stored in the same way in the brain. Only by making someone aware of their implicit learnings can this new awareness be brought into contact with other conscious knowledge. In so doing, this can create insight and the opportunity to be aware of the situation in a new way—to have a cognitive map that was not previously available. Essentially this means that explicit understanding, which involves the hippocampus, may now better compete with implicitly learned behavior, which was not hippocampus-dependent.

A key question is whether the juxtaposition of a new awareness of old implicit learning with contradictory information in conscious awareness is sufficient to undo the previous learning such that the working through process (Step 3 in the LRNG model), consisting of the repeated experience of updating action values and statistical learning in the previously problematic context, is no longer needed. The clinical research proposed by Bruce Ecker in his chapter would address this question (see Chapter 11 of this volume).

Sleep and Napping After Psychotherapy Sessions

One of the benefits of considering the mechanisms of action of psychotherapy from a neurobiological perspective is that it brings into focus variables that might not otherwise be considered from a psychological perspective alone. As discussed in Jessica Payne's chapter (see Chapter 7 of this volume), the fact that rapid eye movement (REM) sleep has been shown to preferentially support the consolidation of emotional aspects of memory (Diekelmann, Wilhelm, & Born, 2009) and that napping has been shown to enhance explicit recall of verbal material both immediately and after a delay (Mednick, Cai, Kanady, & Drummond, 2008) raises plausible possibilities about how sleep and napping may contribute to MR mechanisms in psychotherapy.

To our knowledge, little is known about the relation between sleep quality and quantity and psychotherapy outcome. A particular focus could be on maximizing the effects of CEEs on MR with sleep or napping. It is not unreasonable to consider a 20-minute "power nap" after a session to facilitate reconsolidation. It is not known if REM is necessary or if non-REM would be beneficial or what the optimal timing and duration of a nap would be after a session. It is possible that rehearsal or review at bedtime of a CEE that occurred earlier in the day could increase the likelihood that the experience will be recognized as salient during sleep. In addition, targeted memory reactivation is a technique involving delivery of specific cues during sleep to enhance or modify memory (Schouten et al., 2017) that could be applicable to psychotherapy (Diekelman & Focato, 2015; Simon et al., 2018). All of these questions and others seem wide open for investigation.

Duration, Number, and Spacing of Psychotherapy Sessions

Elsey, Van Ast, and Kindt (2018) mentioned that the potential exists to radically alter how psychotherapy is done based on MR principles. One approach to this is to consider Dunsmoor and Kroes's chapter on emotion-memory interactions (see Chapter 6 of this volume), which highlights the duration of the time window during which retrieved or activated memories are available for reconsolidation. This raises major questions about whether the way psychotherapy is currently practiced optimally capitalizes on the change processes at work. For example, people typically see therapists weekly, biweekly, or less often for a variety of reasons including work schedules, clinician schedules, insurance policy restrictions, etc. Is it possible that such infrequent sessions are working at cross purposes because reconsolidation windows remain open after therapy sessions have ended, and no one gives serious thought to the effects of what happens after sessions that may influence the effectiveness of what happened during the session? To what extent are sessions later in the day less likely to be "polluted" by extraneous experiences before sleep than sessions earlier in the day? Would it be advantageous to "lock in" the effects of a session with a nap shortly thereafter rather than waiting until later in the evening to sleep?

One of the key principles of MR research is that PE must be present to update a memory but must not be so large that a new memory is formed. Is it better to continue current practices and bring about change slowly, so that the original memory is transformed rather than abruptly changing context so much that the brain interprets the therapy context as unrelated to the previous memory? This raises an important question about the time frame needed to define a therapy process as slow; it is possible that slowness in this context refers to how much change occurs on a given day that can then be consolidated after a night of sleep? If so, it would call for a shift to a paradigm involving a retreat from usual activities for a week or two devoted to frequent sessions (daily or more frequently, depending on how the first session went, or whether a nap was taken) identifying problematic memories and reworking them through reconsolidation mechanisms, one bit at a time. A challenge is that if one undertakes a short-term intensive approach such as this, one has the challenge of applying the changes to one's everyday circumstances. According to Step 3 in the LRNG model, the new emotional experiences would need to happen in a variety of contexts, but perhaps that could be built into a short-term intensive program.

Combining Medications and Psychotherapy

As we discussed in the BBS article, the combination of medications and psychotherapy is thought to be the most effective treatment approach for the most common mental disorders (e.g., anxiety and depressive disorders; Cuijpers et al., 2014). However, many medications alter REM sleep (Tribl, Wetter, & Schredl, 2013) and thus interfere with the MR process that may be essential for enduring change resulting from psychotherapy. Research is needed to determine whether responsiveness to combined treatments in which psychotherapy is being used to bring about change is delayed or prevented by medications that reduce REM sleep. If so, the effectiveness of alternative medications or behavioral techniques that promote sleep without altering REM, which could facilitate rather than thwart MR, should be evaluated.

Along these lines, one potentially positive interaction between medication and psychotherapy has recently been studied in the context of extinction learning. Specifically, while return of fear is a common problem after extinction, recent work has illustrated that simultaneous administration of certain medications (e.g., dopaminergic agonists) can prevent return of fear and lead to more enduring change. This highlights the possibility that enduring change could be made more likely after psychotherapy by combining it with targeted pharmacological interventions.

Physiological Monitoring During Psychotherapy

In the BBS paper we emphasized the importance of moderate arousal to optimize the effectiveness of CEEs. This raises the question of whether physiological monitoring devices, which are now readily available at reasonable cost, can be incorporated into psychotherapy practice. For example, heart rate variability (HRV) measures of cardiac vagal control can be measured and displayed in real time (Chen et al., 2015). This could potentially help with timing of interventions to ensure that clients are functioning in the moderate range of arousal, which would be the optimal zone of the inverted-U Yerkes–Dodson curve that describes the association between arousal and performance of complex cognitive functions (Yerkes & Dodson, 1908). One can imagine defining the typical range of HRV responses for a given person through ambulatory recordings and using HRV in the moment to determine whether someone needs assistance with upregulating versus downregulating arousal. It would also potentially be useful to compare the therapist's and client's ratings of the client's arousal to such objective measurements.

Another use for physiological monitoring is in facilitating the therapeutic alliance. The generalized unsafety theory of stress (GUTS) model proposes that physiological stress responses are deployed automatically unless they are inhibited by the perception of the sense of safety (Brosschot, Verkuil, & Thayer, 2018). It is argued that HRV is enhanced when safety is experienced and is reduced if not. Safety is a critical variable in the establishment of an effective therapeutic alliance. Monitoring of client HRV might be useful for this purpose.

Yet another domain would be to examine physiological similarities and correspondences in client and therapist, in both observable (facial expression) and hidden (e.g., HRV) domains and relate them to client and therapist ratings of psychological attunement. Such "biofeedback" research could potentially be used to enhance or maintain attunement during therapy sessions.

Following Jessica Payne's chapter (see Chapter 7 of this volume), emotional arousal in the moment (e.g., as measured by skin conductance or HRV) appears to tag experience for later memory consolidation. Perhaps it would be possible to examine instances of arousal in sessions and determine whether, in the context of a good night of sleep, those experiences are better remembered the next day compared to events in sessions not associated with arousal. Similar to other evidence that neural patterns associated with learning during the day are replayed at night (Ricci et al., 2018; Stickgold, 2005), it is conceivable that there is a physiological signature of a CEE that gets replayed at night during sleep, potentially contributing to (re)consolidation.

Resting State fMRI to Assist in Psychotherapy

Resting state fMRI is relatively easy to perform in contrast to task-based studies that require presentation of experimental and control stimuli. Andrews-Hanna and colleagues point out in their chapter that connectivity within neural networks at rest provides information about the tendency to be focused on internal thoughts vs. the external environment (see Chapter 5 of this volume). This raises the issue of whether brain imaging with resting state fMRI could be useful for clinicians in helping to determine what type of treatment might be most beneficial for a given client depending on their presenting problem, their goals for treatment, their motivation and their resources. It could conceivably provide evidence in support of certain psychotropic medications as well as particular types of therapy depending upon the findings of excessive or diminished resting state connectivity within specific networks. Perhaps this could be studied in the context of intensive retreat-style interventions in which one or two weeks are devoted to optimizing treatment outcomes as well as in routine clinical care settings that are currently widely available.

Conclusions

A goal of this work has been to bring coherence and integration to the broad field of psychotherapy practice based on the constraints of brain science. This goal was articulated over 100 years ago (Freud, 1895, 1920) but is one that can now can be realistically envisioned due to advances in neuroscientific knowledge.

In this book and in this chapter we have "translated" the mechanisms of change into brain terms. It is possible now to create the first neural circuitry models of the IMM and LRNG models. This is meant to be a first step in model specification that must be updated by empirical research. This model helps identify where gaps exist and where research is most urgently needed.

We now know that MR is a real phenomenon in humans and very relevant to enduring change in psychotherapy. MR principles (e.g., the LRNG model) are of value now in tweaking current approaches to psychotherapy to optimize clinical outcomes. MR has the potential to revolutionize and transform how clinical care is provided. How to exploit this mechanism for optimal clinical advantage—in different clinical contexts—is a huge issue and potentially of great importance to human welfare.

The future agenda is to refine our understanding of how MR works at the neural systems and molecular levels and to use this knowledge to optimize its application in different clinical contexts. The possibility exists that eventually the way psychotherapy is done could be radically transformed—in terms of duration of sessions, content of sessions, frequency of sessions, presession and postsession mental activity, napping, attention to sleep quality and duration to promote reconsolidation, avoidance of medications that might disrupt REM, use of medications to prolong the effects of psychotherapy, duration of treatment, the outcome measures used, and the outcome periods assessed.

The clinical and basic science literature converge in highlighting the importance of schemas— superordinate knowledge structures that reflect abstracted commonalities across multiple experiences (Gilboa & Marlatte, 2017)—which are a type of semantic memory. We know very little about the basic neurobiology of semantic memory destabilization and reconsolidation; hence, we know little about how schemas can be changed. Elucidating the relevant neurobiology may make it possible to use psychotropic agents in novel ways in conjunction with psychotherapy to promote enduring change.

A focus on MR highlights that while enduring change is highly desirable, considerable clinical benefit can often be obtained through techniques that promote change that is more short-lived or even reversible. After all, should relapse occur clients can return for further treatment. Techniques that target other memory mechanisms such as extinction (Craske, Hermans, & Vervliet, 2018) and new learning in competition (Brewin, 2006) with the old remain valuable approaches. The goal of our project, however, has been to delineate the mechanisms involved in optimizing the degree and duration of clinical improvement. By translating psychotherapy interventions into brain-based processes, delineating different memory processes and the mechanisms of change associated with each, and understanding the role of emotion in effecting change in interaction with these memory mechanisms, the potential exists to develop a new taxonomy of clinical interventions based on what problems are being targeted, how long they have been in place, how intractable they are, and whether an important goal is to achieve enduring change.

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