REVIEW

A model for streamlining psychotherapy in the RDoC era: the example of 'Engage'

GS Alexopoulos[1] and P Arean[2]

A critical task for psychotherapy research is to create treatments that can be used by community clinicians. Streamlining of psychotherapies is a necessary first step for this purpose. We suggest that neurobiological knowledge has reached the point of providing biologically meaningful behavioral targets, thus guiding the development of effective, simplified psychotherapies. This view is supported by the Research Domain Criteria (RDoC) Project, which reflects the field's consensus and recognizes the readiness of neurobiology to guide research in treatment development. 'Engage' is an example of such a streamlined therapy. It targets behavioral domains of late-life depression grounded on RDoC constructs using efficacious behavioral strategies selected for their simplicity. 'Reward exposure' targeting the behavioral expression of positive valence systems' dysfunction is the principal therapeutic vehicle of 'Engage'. Its first three sessions consist of direct 'reward exposure', but the therapists search for barriers in three behavioral domains, that is, 'negativity bias' (negative valence), 'apathy' (arousal) and 'emotional dysregulation' (cognitive control), and add strategies targeting these domains when needed. The end result is a structured, stepped approach using neurobiological constructs as targets and as a guide to personalization. We argue that the 'reduction' process needed in order to arrive to simplified effective therapies can be achieved in three steps: (1) identify RDoC constructs driving the syndrome's psychopathology; (2) create a structured intervention utilizing behavioral and ecosystem modification techniques targeting behaviors related to these constructs; (3) examine whether the efficacy of the new intervention is mediated by change in behaviors related to the targeted RDoC constructs.

INTRODUCTION

Evidence-based psychotherapies are rarely used and sustained in the community.[1–4] A major barrier to their implementation is their complexity, which makes them inaccessible to a large number of mental health professionals.[5–8] Streamlining and simplification of psychotherapies is a necessary first step for their large-scale use.

A MODEL FOR STREAMLINING PSYCHOTHERAPY

Ideally, to develop a simplified, efficacious psychotherapy, one should rely on accepted concepts and findings on the *neurobiology of the targeted domains of function*. In theory, using neurobiological constructs to guide the selection of targets would assure that the streamlined psychotherapy addresses biologically driven, core aspects of psychopathology that perpetuate maladaptive behavior and suffering. Identifying distinct, biologically driven behavioral targets could *sharpen the selection of behavioral interventions* from a larger list of interventions that earlier psychotherapy research has found effective in changing behavior. Simplifying *the language and delivery* of such interventions can make them accessible to community clinicians. Further, biological constructs of function can be used to structure the *personalization* of psychotherapy. Personalization using a stepped approach can start with interventions targeting psychopathology driven by the core biological disturbance of the targeted disorder. Depending on the response to early interventions and on the nature of

remaining psychopathology and its presumed biological determinants, new targeted interventions can be added. Of course, a central question is: 'Is our neurobiology strong enough to support this process?'

We argue that advances in neurobiology have reached a point that can meaningfully guide psychotherapy development. This view is supported by the Research Domain Criteria (RDoC) Project, which reflects the field's current consensus and recognizes the readiness of neurobiology to guide research on mechanisms and treatment of mental disorders.

The role of the RDoC Project

The RDoC Project's intent has been to develop a research program to promote knowledge on pathophysiology, identify targets for treatment development, detect subgroups for treatment selection and facilitate the use of neurobiology findings in clinical decision-making.[9] Its principal assumptions have been that mental illnesses are disorders of brain circuits and that dysfunction of relevant brain circuits can be identified by tools of clinical neuroscience. Accordingly, the RDoC research program focuses on circuitry, with levels of analysis progressing upwards from measures of circuitry function to clinical manifestations or downwards to the genetic and molecular/cellular factors influencing such functions.

To organize research on brain circuits, the RDoC Project identified five broad domains of function (negative valence, positive valence, cognition, social processes and arousal/

[1]Weill Cornell Institute of Geriatric Psychiatry, Weill Cornell Medical College, White Plains, NY, USA and [2]Department of Psychiatry at the University of California San Francisco, San Francisco, NY, USA. Correspondence: Dr GS Alexopoulos, Weill Cornell Institute of Geriatric Psychiatry, Weill Cornell Medical College, 21 Bloomingdale Road, White Plains, NY 10605, USA.
E-mail: gsalexop@med.cornell.edu

modulation). These domains of function may contribute to psychopathology in varying degrees across a range of clinically defined psychiatric disorders. Accordingly, they serve as areas in which circuit functions and their determinants may be investigated. Measures in such investigations range from genetic, molecular, cellular, circuitry and physiological functions to observed behavior and self-reports.[10] The ultimate aim of this process is to integrate behavioral and neurobiological findings.

Beyond proposing an organized research approach, the RDoC Project initiated workshops and a consensus development process. This process led to the identification of constructs encompassed within each domain of function. Each construct is a behavioral function with evidence that it has behavioral validity and that it maps onto a specific biological system such as a circuit.[10] The RDoC recognizes that understanding the role of brain circuits is a work in progress. However, the consensus development process led to an agreement of what constitutes valid knowledge at this point and where to start further research. It also signified an agreement that there is adequate readiness for neurobiology to play a role in treatment development.

Bottom-up, top-down

Optimally, an intervention for a mental disorder and its neurobiological contributors should be built from the bottom-up. In theory, drugs, direct electrical or magnetic stimulation and gene therapies can target specific brain circuits implicated in abnormal behaviors. Such 'surgical precision' has not been accomplished so far. Most of treatments have broad targets and their putative mechanisms of action are based on *post hoc* interpretations once there is a signal of efficacy. Psychotherapies face even greater challenges in targeting distinct brain circuits. Even the simplest techniques consist of complex interventions processed by interacting brain circuits. For this reason, the available psychotherapies cannot be viewed as treatments targeting specific brain circuits promoting psychopathology.

We argue that a 'reduction' process is feasible and may result in a psychotherapy targeting neuroscience-driven constructs of function (RDoC domains) that have a biological basis. Such a reduction can be achieved in three steps:

Step 1: Identification of RDoC constructs driving the psychopathology of the targeted syndrome.

Step 2: Creation of a structured psychotherapy utilizing behavioral and ecosystem modification approaches targeting these constructs.

Step 3: A study examining whether the efficacy of the new psychotherapy is mediated by change in behaviors related to the targeted RDoC constructs. Identification of such behavioral mediators of efficacy would open the field to biological investigations using measures (units of analysis) at the physiology, circuit, cell, molecule and gene levels. The results of such studies can clarify the new psychotherapy's mechanism of action.

THE EXAMPLE OF 'ENGAGE'

'Engage' was conceived as a streamlined psychotherapy using neurobiological constructs to identify behavioral targets; select behavioral interventions; and structure a stepped, personalized approach to the treatment of late-life depression. 'Engage' relied on the RDoC workshop proceedings and related findings to select behavioral targets. Accordingly, 'Engage' theorized that dysfunction of Positive Valence Systems (especially in Reward Valuation, Effort Valuation, Action Selection, Preference-based Decision-Making and Reward Learning) is a central process perpetuating late-life depression. For this reason, 'Engage' used 'reward exposure' (reactivation and retraining of positive valence systems) as its principal intervention. Barriers to direct 'reward exposure' may be posed by the behavioral expression of neurobiological

system dysfunctions frequently occurring in late-life depression. 'Negativity bias' (a behavioral expression of Negative Valence Systems dysfunction; construct: Loss), 'apathy' (an expression of the Arousal and Regulatory System dysfunction; construct: Arousal) and 'emotional dysregulation' (an expression of Cognitive Systems Dysfunction; construct: Cognitive Control) have both a neurobiological basis and occur in large numbers of depressed older adults. To address behavioral abnormalities related to the above neurobiologically based domains of function, 'Engage' selected cognitive-behavioral and ecosystem modification strategies that literature has found efficacious. The end result is a streamlined psychotherapy consisting of simple to learn strategies targeting domains of function grounded on accepted neurobiological constructs in late-life depression.

The focus on positivity valence systems

'Engage' conceptualizes depression as a dysfunction of the positivity valence systems leading to inadequate experience of pleasure or meaning from rewards. In animals, precipitants of depression, including chronic stress, alter gene expression and the morphology, functional activity and connectivity of networks mediating reward-related depression-like behaviors.[11] The molecular and cellular basis of these behaviors includes changes in glutamatergic and GABAergic synaptic plasticity, dopamine neuron excitability, epigenetic and transcriptional mechanisms and neurotrophic factors.[12–18] Tools, such as mutations in mice, gene transfer and optogenetics, have made it possible to identify specific proteins acting within specific cells within reward circuits in mediating depression-like behavior.

Depressed young adults have abnormalities in reward processing. Delay discounting studies showed high impulsivity and time inconsistency in intertemporal action for gain and loss in depression suggesting a dysfunction in the RDoC construct of reward valuation.[19] Depressive symptoms were associated with deficits in reward-based decisions and high variability in selection of action[20] consistent with impairment in the RDoC constructs of action selection and preference-based decision-making. Further, small caudate volume has been observed in depressed patients as well as low activation of the nucleus accumbens and the caudate during rewarding outcomes in a monetary gain paradigm,[21] impaired reward reversal accuracy and attenuated response of the anteroventral striatum to unexpected reward during reward reversal learning.[22,23]

Aging influences reward processing.[24] Older adults present impaired learning under reward uncertainty because of inability to update value (outcome) representations using prediction error signals. Aging influences the flexibility of adaptation to changes in stimulus-reward contingencies during reversal learning. Furthermore, older adults have high sensitivity to loss (punishment) in learning tasks when the acquisition of behavior depends on outcome processing. In depressed older adults, history of suicide attempts was associated with lower putamen gray matter volume and high delay discounting of rewards.[25] These observations are consistent with impairment in the RDoC constructs of action selection and preference-based decision-making.

'Reward exposure': the principal treatment vehicle

Impairment in the positivity valence systems leads to the abandonment of rewarding activities, strengthening the conviction that little meaning or value is left in life and promoting depressive symptoms. Accordingly, 'reward exposure' is the principal treatment vehicle of 'Engage'. It is devoted to reinforcing engagement of patients in once rewarding social and physical activities that have been abandoned during depression.

'Reigniting and retraining' the positivity valence systems has been the goal of drug treatment and psychotherapy for depression. On a behavioral level, there are least three reasons

to focus on 'reward exposure': (1) Increasing rewarding activities has been a central component of most psychotherapies for depression.[26–29] (2) Pleasant Activity Scheduling is an effective component of integrated care models for depression; the IMPACT treatment model is one such example.[30,31] (3) Depressed elders understand and often respond to direct attempts to encourage their social and physical activities.[29,31]

Based on this view, the first three sessions of 'Engage' are devoted to *direct facilitation* of rewarding activities. In the context of a supportive relationship, therapists guide patients to develop a list of rewarding social and physical activity goals and select two to three activities in which to engage between sessions. Facilitation of rewarding activities utilizes a simplified problem-solving approach. During sessions, they: (1) select a goal (i.e., a rewarding activity); (2) develop a list of ideas on what to do in order to meet this goal; (3) choose one of these ideas; and (4) make an 'action plan' with concrete steps to address obstacles to implementation.

Reward exposure serves both as the principal therapeutic tool and as a behavioral probe to identify depressed patients who cannot be engaged or who fail to experience the value of reward engagement. Throughout the first three sessions, therapists conduct a structured assessment to determine whether 'action plans' progress well or are inhibited by *barriers* in three behavioral domains, that is, 'negativity bias,' 'apathy' leading to behavioral inertia or 'emotional dysregulation'. Each of these constructs is related to impairment in domains of function identified by the RDoC workshops, and each has been the target of learning-based therapies of depression. If a barrier is identified, therapists choose strategies to mitigate it so that 'reward exposure' can progress unhindered.

Mitigating negativity bias

Negativity bias refers to selective attention to negative rather than positive information and experiences, and it is a behavioral expression of the construct of loss of the RDoC negative valence domain. According to classical cognitive theorists, negativity bias constitutes a 'cognitive vulnerability' factor for depression.[32] Several biological correlates of negativity bias have been identified. Negativity bias is associated with greater psychophysiological reactivity and early neural excitation to signals of potential danger, heightened startle amplitude and higher heart rate responses to conscious and non-conscious fear conditions.[33–35] Correlates of negativity bias include high activation of the brainstem, amygdala, anterior cingulate cortex (ACC) and ventral and dorsomedial prefrontal cortex (dmPFC) to conscious and non-conscious fear probes and differences in electrical brain measures of working memory and electroencephalograph theta power.[33,35] Hyper-reactivity of the amygdala in carriers of the short allele of the 5-HTTLPR (serotonin-transporter-linked polymorphic region) serotonin transporter has been associated with sensitivity to negative stimuli[36] and negative bias in the processing or interpretation of emotional stimuli.[35,37,38]

Strategies for coping with negativity bias teach patients to recognize when they are excessively focusing on negative cues and to redirect their attention to neutral or positive aspects of the situation. 'Engage' uses simplified cognitive behavioral strategies to overcome negativity bias when patients encounter difficulties with 'reward exposure'. These include Playing Devil's Advocate, Weighing the Evidence, Practicing Positivity Bias, keeping a 'Negative Thought Log', writing Alternative Positive Explanations to negative thoughts and noticing and learning how positive people respond to negative situations.

Remedying apathy

The geriatric literature is replete with descriptions of apathy syndromes of depression (depression without sadness, masked depression, etc). Apathy is defined as 'lack of motivation not attributable to diminished level of consciousness, cognitive impairment or emotional distress'.[39–41] Apathy affects more than one-third of non-demented individuals with major depression, is most prevalent in older adults[42–44] and is associated with poor treatment response of depression.[45–47]

Apathy is a clinical expression of dysfunction in arousal/modulation, a construct of the RDoC part of the Arousal and Regulatory System. Apathy occurs in various conditions impairing the ventral striatum, dorsal ACC, ventral globus pallidus and medial thalamus.[48] In Parkinson's disease, apathy was inversely correlated with dopamine and norepinephrine transporter binding (^{11}C-RTI-32) in the ventral striatum.[49] In frontotemporal dementia, apathy was associated with abnormal metabolism in the ventral striatum, ACC, orbitofrontal cortex and caudate.[50] More than 60% of patients with focal frontal lobe lesions had apathy, whereas apathy was identified in 40% of patients with basal ganglia lesions.[50] Apathy of late-life depression is accompanied by low resting functional connectivity of the NAcc with the amygdala, caudate, putamen, globus pallidus and thalamus, and increased functional connectivity with the dmPFC, superior frontal cortex and the insula.[51] Persistence of apathy of late-life depression after serotonin-specific reuptake inhibitor treatment was correlated with smaller posterior subgenual cingulate gray matter volume and lower uncinate fasciculus white matter integrity (by diffusion tensor imaging) (Yuen *et al.*[52] *ACNP* 2012).

Apathetic patients have difficulty initiating activities and, when they do, they cannot maintain interest and stay on task. Creating an action plan may help patients with mild apathy. However, patients with prominent apathy need prompts to trigger their action plan.[53,54] Examples of prompts include checklists for action plans, placing signs and equipment for daily activities in full view around the patient's home, using labels and electronic devices (e.g., tape recorders and menu-driven electronic instructions) to get the plan started, calling the patient during the week to prompt the action plan, engaging family and friends to prompt patients to start an action plan and starting the action plan in session. Easily distracted patients may respond to the removal of distracting items from their environment and to the designation of a place where they can review their action plans and other assignments.

Improving emotional dysregulation

Emotional dysregulation is a behavioral correlate of the cognitive control construct of the RDoC Cognitive System domain of function. Classical theories suggest that emotional regulation depends on an interaction between the mPFC, implicated in the governance of emotional functions,[55] and the subcortical circuits associated with emotion processing.[56,57] Recent findings suggest that rostral areas of the mPFC/ACC participate in conscious threat appraisal and mid regions of the dmPFC/dACC are part of a 'core' fear network that is activated irrespective of how fear was learned.[58–60] Ventral–rostral portions of the ACC and mPFC have a regulatory role of limbic regions generating emotional responses.[58] Anxiety is associated with increased dmPFC–amygdala connectivity during the processing of fearful faces and with faster behavioral responses.[61] Normal elders react less than younger adults to negative situations, ignore irrelevant negative stimuli better and remember relatively more positive than negative information.[62] A potential explanation is that older adults are less influenced by interoceptive cues, have lower amygdala and higher prefrontal activation in response to emotional stimuli[63] and have greater medial prefrontal control over negative input as demonstrated in multimodal studies.[64] However, when vascular disease leads to additional prefrontal white matter damage, older adults have fewer cognitive control mechanisms available to regulate their emotions.[62]

Strategies for emotional dysregulation interfering with 'reward exposure' aim to modulate emotions, for example, overwhelming
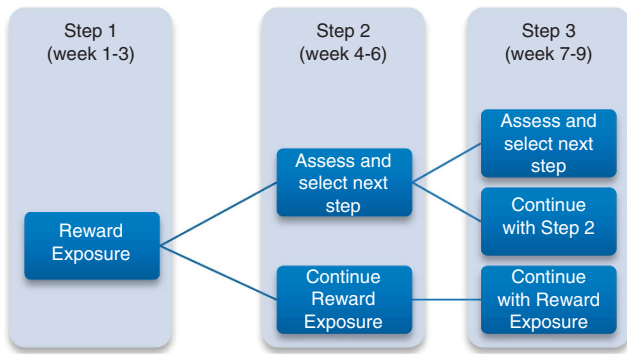
Figure 1. Steps of 'Engage'.

disappointment, anxiety, and so on. Effective emotion management strategies are distraction, meditation, relaxation exercises, deep breathing and imagery.[65–68] Therapist and patient select the most appropriate strategy based on the patient's previous experiences. Patients practice their selected strategy first in session and then on their own, so that they master it and can use it when they sense an emotional overflow while pursuing 'reward exposure'.

Personalization

'Engage' uses a stepped approach to personalization and relies on two principles of stepped care. First, the initial step should be the easiest for clinicians to deliver and for patients to adhere to. Second, the intervention should be self-correcting;[69] this approach is analogous to the 'measurement-based care' of STAR*D (Sequenced Treatment Alternatives to Relieve Depression).[70–74]

Accordingly, the first three sessions of 'Engage' are devoted to 'reward exposure' (Figure 1). The therapist guides patients to select rewarding, meaningful activities (e.g., social engagement, exercise, intellectual exchange) and form 'action plans' for their pursuit. Simultaneously, therapists assess whether patients: (1) learned how to form 'action plans'; (2) engaged in planned activities; and (3) showed improvement of depression. If all conditions are met, patients continue with 'reward exposure' (Step 1). If not, therapists identify the most prominent barrier to 'reward exposure' by session 3 and proceed with Step 2 by adding strategies to mitigate the identified barrier. A similar assessment is made between session 3 and the end of session 6. Patients doing well in Step 2 (e.g., 'reward exposure' plus strategies for negativity bias) continue with the Step 2. For those still experiencing difficulties, therapists assess whether another barrier exists and add a strategy to counteract it (Step 3). Starting with direct facilitation of rewarding activities is parsimonious and instructive. Obstacles to rewarding activities that are not immediately apparent may emerge after attempts to pursue these activities (Manual in Supplementary files).

Executive dysfunction has been associated with poor and/or slow response of late-life depression to pharmacotherapy.[75–77] However, patients with depression and executive dysfunction respond well to problem-solving therapy.[78,79] Problem-solving therapy does not use direct 'reward exposure', but trains patients to problem solve and indirectly offers the skills to reengage in rewarding activities. 'Engage' offers direct 'reward exposure', and uses additional strategies in patients with emotional dysregulation or apathy with assumed Cognitive Control or Arousal and Regulatory System abnormalities. Thus, 'Engage' offers a personalized approach to barriers imposed by behaviors related to executive dysfunction.

NEUROBIOLOGY STUDIES

The Manual of 'Engage' offers guidance on how and when to evaluate patients for the four behavioral expressions of RDoC domain dysfunctions in late-life depression. Instruments for 'reward exposure' (e.g., Behavioral Activation for Depression Scale),[80] 'negativity bias' (e.g., Brain Resource Inventory for Social Cognition),[81] 'apathy' (e.g., Apathy Evaluation Scale)[40] and 'emotional dysregulation' (e.g., BRISC) exist. Such instruments can offer further guidance for focusing clinical evaluation. These instruments are also easy to use and are available on mobile platforms, further simplifying the process of targeting and tailoring treatment.

'Engage' conceptualizes reactivation and retraining of the Positive Valence Systems as its principal mechanism of action achieved through 'reward exposure', a treatment component that all depressed patients receive. Constructs of the Positive Valence System such as Reward Valuation, Effort Valuation, Action Selection, Preference-based Decision-Making and Reward Learning can be targets for mediation analysis aimed to identify 'How Engage works'. Measures at different levels of analysis may be used for this purpose.

Although some depressed patients require only reactivation of the Positive Valence Systems, others may need interventions targeting barriers to reward exposure, that is, negativity bias, apathy and/or emotional dysregulation related to Negative Valence, Arousal and Regulatory and Cognitive Control Systems, respectively. Mediation analysis of measures of these systems in depressed patients with specific barriers to 'reward exposure' may offer information on the question 'For whom does Engage work?'

CONCLUSION

The 'holy grail' of psychotherapy research is the creation of therapies that can be used by community clinicians and are acceptable to patients. The need for such therapies is urgent in late-life depression. The baby boomers are expected to overwhelm the health-care system and have been afflicted by depression more than past cohorts (NCS data). Late-life depression has a modest response to pharmacotherapy, promotes disability, worsens the outcomes of most medical illnesses, increases expense and undermines treatment adherence.[82] Two IOM reports[83,84] predict that the workforce in geriatrics will be overwhelmed by the aging population, a problem that will reach cataclysmic proportions when ACA programs come into being. Older adults seek services in community settings where the providers of initial care for depression are social workers and nurses without in-depth training in psychotherapies. 'Engage' is designed for such clinicians and settings and has potential for broad scalability (use by many professionals) and reach by offering many depressed seniors access to effective psychotherapy. Its derivation from neurobiology responds to the NIMH Council report 'From Discovery to Cure'[85] and its potential for scalability and reach to the 'Bridging Science and Service' report.[86] The focus of 'Engage' on behaviors related to the positivity bias systems may have neuroeconomic implications for suicide prevention, an area of particular concern in depressed elders who have a high suicide risk.[87]

'Engage' can serve as a template for streamlining therapies for patients with a variety of psychiatric syndromes. Key features in this process are:

(1) Identification of one or more domains of function central to the psychopathology of the targeted syndrome. Reliance on the RDoC Project or similar consensus processes would assure that the targets of the streamlined psychotherapy are consistent with currently accepted neurobiological constructs.
(2) Development of a hierarchy of these domains of functions giving higher status to domains commonly occurring in patients with the targeted syndrome and thought to be driving its psychopathology.
(3) Creation of a structured, personalized, stepped therapy in which the first step consists of techniques targeting the domain of function highest in the hierarchy. Additional

domains of function should be targeted with appropriate behavioral techniques but only in patients unresponsive to the first step.

(4) Selection of behavioral and ecosystem modification strategies to target abnormal domains of function based on evidence of efficacy and simplicity so that training of community clinicians is feasible.

(5) Use of each step of treatment both as a therapeutic intervention and as an assessment tool to identify whether other domains of function need to be targeted. The end result of this process is a stepped therapy that structures both the selection of behavioral strategies and the personalization process on the basis of accepted neurobiology rather than psychological theories.

Uptake of an intervention requires organization infrastructure changes, but an effective intervention is easier to implement and sustain it if it is feasible and acceptable to clinicians. For this reason, streamlined therapies based on the above principles may have potential for broad *scalability* (used by many professionals) and *reach* by offering many patients access to effective care.

CONFLICT OF INTEREST

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