Cognitive Therapy and Research
https://doi.org/10.1007/s10608-020-10132-1

REVIEW

Cognitive Therapy in the Treatment and Prevention of Depression: A Fifty-Year Retrospective with an Evolutionary Coda

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Abstract

In the 50 years since it was first introduced, cognitive therapy has been shown to be as efficacious as antidepressant medications (on average) in the acute treatment of nonpsychotic depression, although some patients will do better on one than on the other. Moreover, patients treated to remission with cognitive therapy are less than half as likely to relapse following treatment termination as patients treated to remission with medications. However, a recent study suggests that adding medications interferes with any such enduring effect and medications themselves may have an iatrogenic effect that suppresses symptoms at the expense of prolonging the underlying episode. Neural imaging suggests that cognitive therapy works from the "top down" to facilitate cortical regulation of affect processes whereas medications work from the "bottom up" to dampen the stress response. Adaptationist theory suggests that depression is an evolved adaptation that served to keep our ancestors ruminating about complex social problems until they arrived at a solution; if true then any intervention that facilitates problem solving is likely preferable to one that merely anesthetizes distress.

Keywords Cognitive therapy · Enduring effects · Antidepressant medications · Iatrogenic effects · Evolved adaptation

Depression is the most prevalent of the psychiatric disorders and the second leading cause of burden worldwide (Ferrari et al. 2013). Cognitive therapy is the most extensively tested of the psychosocial interventions and has been found to be as efficacious as and more enduring then antidepressant medications (ADMs). Depression appears to be an evolved adaptation that enhanced reproductive fitness in our ancestral past. This means that depression may have been selected for because it served a function. If true, then any intervention that furthers that function is likely to be more beneficial than interventions that only provide symptomatic relief.

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In this article we first review the efficacy of cognitive therapy relative to ADMs both with respect to acute response and the prevention of subsequent relapse and recurrence, as well as indications regarding which works best for different patients (moderation) and the causal mechanisms underlying each (mediation). We then consider evidence suggesting that depression is an evolved adaptation, what functions it evolved to serve, and the implications that may have for choosing between treatment options.

Acute Response and Subsequent Prevention

It has been over 50 years since Beck first published his cognitive theory of depression (Beck 1963) and a closely associated cognitive therapy for depression (Beck 1964). Both articles appeared in the *Archives of General Psychiatry* but had little impact on that profession other than to get him drummed out of the Philadelphia Psychoanalytic Society. He used this time to write his classic treatise on depression in which he expanded on both theory and therapy (Beck 1967), and his subsequent presentation at the Association for Advancement of Behavior Therapy in Denver in 1970 that described the way he used behavioral experiments to

Published online: 16 July 2020

test the accuracy of beliefs brought his work to the attention of the psychology community (Beck 1970).

In 1975 the Beck group presented preliminary findings at the Society for Psychotherapy Research of a study that compared cognitive therapy to antidepressant medication (ADM) that would eventually be published in the inaugural issue of this journal (Rush et al. 1977). Until that time no psychotherapy had ever held its own vis-a-vis ADM, or even bested pill-placebo, but in that trial cognitive therapy appeared to be superior to ADM (it was not for reasons we describe below) and when Blackburn et al. (1981) published similar results in a study out of Edinburgh, cognitive therapy was off to the races.

The reason that cognitive therapy was not truly superior to ADM in Rush et al. was that we did a poor job of implementing medication treatment; doses were too low, and we started medication withdrawal in two weeks before the end of treatment. Both were honest mistakes (convention at that time limited imipramine doses to 300 mg/day and we wanted patients off both treatments at the week 12 assessment), but we ended up overestimating differences in acute response in favor of cognitive therapy and underestimating its enduring effect relative to prior ADM (Kovacs et al. 1981). Starting ADM withdrawal 2 weeks early counted several patients as having not responded when in fact they relapsed early.

We corrected those mistakes in a subsequent trial at the University of Minnesota that found that cognitive therapy and ADM were comparably efficacious (on average) in terms of acute response (Hollon et al. 1992) but that cognitive therapy cut risk for relapse by half relative to ADM following treatment termination (Evans et al. 1992). Another group at Washington University found similar results with respect to both acute response (Murphy et al. 1984) and the prevention of subsequent relapse (Simons et al. 1986) and Blackburn et al. also found evidence for an enduring effect for prior cognitive therapy relative to prior ADM (Blackburn et al. 1986). Not all studies find cognitive therapy comparable to ADM in terms an acute response, but when they do not, there are problems with the implementation of either ADM (Rush et al. 1977; Blackburn et al. 1981) or cognitive therapy (Dimidjian et al. 2006; Elkin et al. 1989, 1995). As shown in Fig. 1, what does appear to be robust is that cognitive therapy has an enduring effect that reduces risk for relapse by more than half (seven of eight trials), and that the magnitude of that effect is at least as great (if not greater) than keeping patients on continuation ADM (Cuijpers et al. 2013).

Evidence of comparable acute effects notwithstanding, there was the perception in the field that psychosocial interventions like cognitive therapy were not enough for nonpsychotic patients with more severe depressions, and that such patients needed to be medicated (American Psychiatric Association 2000). However, a placebo-controlled trial conducted across two sites (Penn and Vanderbilt) found that patients with more severe depressions were as likely to respond to cognitive therapy during acute treatment as to ADM, and that both were superior to pill-placebo (DeRubeis et al. 2005). Moreover, prior exposure to cognitive therapy cut risk for subsequent relapse and recurrence by more than half relative to medication treatment following treatment termination (Hollon et al. 2005a, b). Cognitive therapy (adequately implemented) was at least as efficacious as antidepressant medications and more

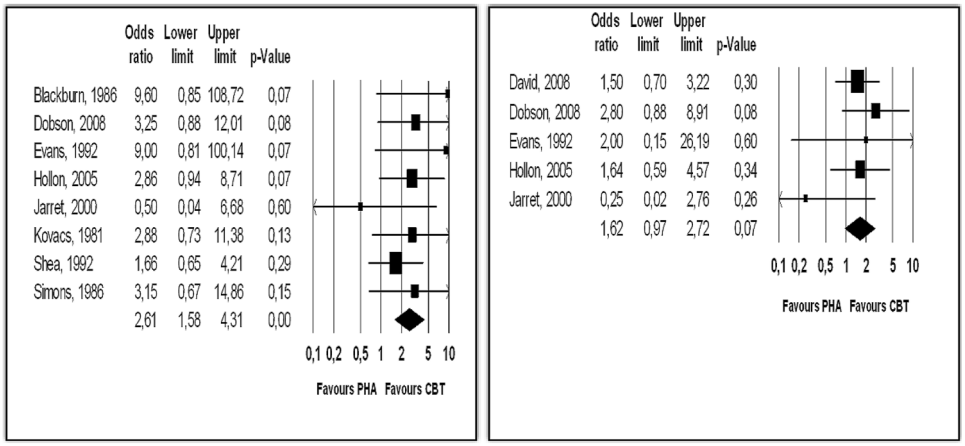

Fig. 1 Cognitive therapy has an enduring effect following treatment termination: *Relative to Medication Discontinuation (left panel):* Long-term effects of prior treatment with cognitive therapy provided in the absence of medication relative to medication discontinuation following acute treatment with medication alone: Forest plot of Odds Ratios (ORs) of response. *Relative to Medication Continuation (right panel:* Long-term effects of prior treatment with cognitive therapy provided in the absence of medication relative to medication continuation following acute treatment with medication alone: Forest plot of Odds Ratios (ORs) of response. *Reprinted with permission from* Cuijpers et al. (2013)

enduring than ADM following treatment termination even among patients with more severe depressions.

Moderation of Treatment Response

Although cognitive therapy and ADM appear to be about comparably efficacious (on average) with respect to acute response, there are indications that different subsets of patients show differential response to each. The question then becomes whether we can predict which treatment will be best for a given patient. In the Penn-Vandy study previously described, patients who met criteria for personality disorders did better on ADM than on cognitive therapy whereas patients without personality disorders showed the opposite pattern (Fournier et al. 2008). The number of prior exposures to ADM predicted poorer response to medication treatment but not to cognitive therapy (Leykin et al. 2007) whereas being married or unemployed or having more precipitants predicted better response to cognitive therapy than to ADM (Fournier et al. 2009). DeRubeis et al. pulled these moderators into a single algorithm to predict differential response and found that if each patient had gotten his or her optimal treatment outcomes would have been improved by twice the drug-placebo difference (DeRubeis et al. 2014).

The DeRubeis et al. have since moved to the use of machine learning to produce their prescriptive algorithms, aka precision treatment rules (PTRs) (Cohen and DeRubeis 2018). These PTRs promise to revolutionize the field. To the extent that we can determine the optimal treatment for a given individual, we should be able to improve outcomes even in the absence of improving treatments just by making treatment selection more efficient. Moreover, only those patients who show a specific response to a given treatment are adhering to the causal mechanisms underlying that intervention (Kazdin 2007). Therefore, we should be able to make our tests of causal mediation more precise by including those PTRs in interactions with our purported mediators. This is the essence of moderated mediation and will be discussed in the subsequent section of the article.

Causal Mediation of Treatment Effects: Process and Mechanism

There are two types of causal process involved in the generation of treatment effects; the active ingredients of treatment (often referred to as treatment process) and the mechanisms that those active ingredients engage in the patients treated (Hollon et al. 1996). With respect to treatment process, DeRubeis et al. found that adherence to specific techniques early in cognitive therapy drove early response that in turn drove the quality of the therapeutic alliance (DeRubeis and Feeley 1990; Feeley et al. 1999). In essence, the best way to generate a good working relationship with your client in cognitive therapy is to jump right into the process of using specific behavioral and cognitive strategies to provide rapid symptom relief. Not all therapies hit the ground running, but cognitive therapy works best when relationships develop in the process of producing symptomatic change.

In the earlier Minnesota trial, both cognitive therapy and ADM showed comparable overall change in cognition and depression, but change in cognition drove change in depression in cognitive therapy whereas change in depression drove change in cognition in ADM (DeRubeis et al. 1990). In a series of trials, Mayberg and colkagues have shown that ADM tends to produce specific changes in brain stem and limbic system functions whereas cognitive therapy tends to produce specific changes in the cortex in areas involved in emotional regulation (Goldapple et al. 2004; Kennedy et al. 2007; Mayberg 2009; Mayberg et al. 2000, 2005; McGrath et al. 2013). What this suggests is that ADMs work from the "bottom up" to dampen the stress response whereas cognitive therapy works from the "top down" via cortical affective regulation mechanisms (DeRubeis et al. 2008). Strunk et al. (2007) have shown that those patients who best internalize the strategies taught in cognitive therapy are least likely to relapse following treatment termination and Tang et al. (2007) have shown that the same holds true for patients who show a pattern of "sudden gains" (a rapid drop in symptom scores) that often follows "insight" into the cognitive model.

All of these indices suggest that cognitive therapy works via changing beliefs and behaviors, with the latter often set up as "experiments" to test those beliefs. These indices are suggestive at best; it is easier to detect an effect than it is to explain it. But they are consistent with the notion that cognitive therapy and ADM work through different process and mechanisms (top down vs bottom up) to bring about change in depression.

One similarity that cognitive therapy and ADM both share is that specificity of response to each appears to be moderated by severity (Driessen et al. 2010; Fournier et al. 2010). Patients who are less depressed appear to respond to treatment regardless of its nature whereas patients with more severe depressions appear to need a treatment that mobilizes a specific mechanism such as cognitive therapy or ADM, as well as other efficacious treatments like behavioral activation or interpersonal psychotherapy. To the extent true one would expect specificity of response clustered among patients with more severe depressions.

Does Adding ADM Interfere with Cognitive Therapy's Enduring Effect?

In earlier times the consensus was that combining cognitive therapy with ADM retained the specific benefits of each (rapid response to ADM and enduring effects for cognitive therapy) (Hollon et al. 2005b). Now that is not so clear. As shown in Fig. 2, we found that patients assigned to combined treatment were about 10% more likely to remit and recover than patients treated with ADM alone (Hollon et al. 2014) (an effect that was itself heavily moderated such that almost all of that advantage was concentrated among the third of the patients who were more severe but not chronic), but no evidence of any enduring effect for patients who had all been treated with cognitive therapy in combination with ADM (DeRubeis et al. 2020). We had not anticipated this lack of effect since we had observed an enduring effect for cognitive therapy provided in the absence of ADM in two of the three study sites using many of the same therapists in our earlier trial (Hollon et al. 2005a). Previous trials with considerably smaller samples were mixed with respect to adding ADM to cognitive therapy; one trial found evidence of an enduring effect (Evans et al. 1992) whereas another did not (Simons et al. 1986), and a third was too muddled to interpret clearly (Blackburn et al. 1986).

Barlow et al. (2000) found something similar in the treatment of panic disorder. In that multi-site trial, patients treated to remission with cognitive behavior therapy (CBT) were less likely to relapse following treatment termination than patients treated to remission with ADM. Patients treated to remission with combined treatment with active medication were as likely to relapse following treatment termination as patients treated to remission with ADM alone, whereas patients treated to remission on combined treatment with pill-placebo were no more likely to relapse than patients treated to remission with cognitive therapy alone. ADM interfered with CBT's enduring effect and the mechanism was pharmacological.

There is a possible biological explanation. Hebb's dictum holds that "cells that fire together wire together" (Hebb 1949). *Being on ADMs may suppress the nascent stress response necessary for a connection to form with the perception of control.* In a brilliant series of studies exploring the neural pathways underlying the phenomenon referred to as "learned helplessness", Maier et al. found a descending excitatory glutamatergic pathway from the cortex that synapsed on an inhibitory GABA neuron in the raphe nucleus (the site of all cell bodies using serotonin as a neurotransmitter in the brain) that fired when an animal could exercise control of shock (Maier et al. 2006). *In effect, when an animal detects control, its cortex signals the raphe nucleus not to trigger the stress response.* In an recent article Maier and Seligman (2016) suggest that they got helplessness all

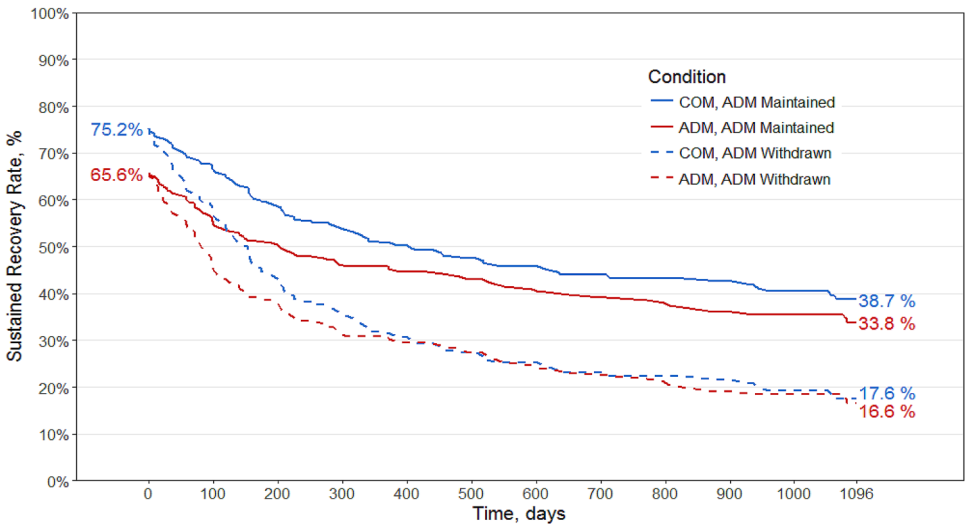

Fig. 2 Estimated Sustained Recovery as a Function of Phase I plus Phase II Condition: The x-axis represents time, in days, from random assignment to be maintained on or withdrawn from medications. The y-axis represents the estimated sustained recovery rates across the 3-year maintenance period. The beginning points for the CBT and ADM conditions from phase 1 reflect the percentage of patients with these conditions who met recovery criteria during phase 1. Sustained recovery was estimated as a function of phase 1 and phase 2 treatment conditions. *COM:* combination antidepressant medication and cognitive behavior therapy during phase 1; *ADM:* antidepressant medication alone during phase 1. *ADM Maintained:* antidepressant medication maintained across the three year phase II follow-up; *ADM Withdraw:* antidepressant medication withdrawn at the beginning of the three year phase II follow-up. Reprinted with permission from DeRubeis et al. (2020)

wrong; it is not that organisms learn that they lack control (what they exhibit is just the "species specific" stress response to uncontrollable negative events) but rather *those that have control learn to be resilient when confronted with subsequent lack of control*. Learning requires connectivity and connectivity requires synchrony; if taking ADMs dampens the stress response by reducing the propensity of the raphe to fire, impulses emanating from the cortex will not be needed to inhibit firing in the raphe and the fact one has control may not be learned.

Is Depression an Evolved Adaptation?

An adaptationist perspective on evolutionary theory suggests that depression may be an evolved adaptation that serves a functional purpose like anxiety or pain. Anxiety leads us to avoid situations that might be rife with danger and pain keeps us for doing additional damage to tissues that have already suffered an injury. Most nonpsychotic disorders revolve around strong negative affect and most have high prevalence and relatively low heritability (Keller and Miller 2006). To an evolutionary biologist this suggests that negative affects are adaptations that evolved because they increased the reproductive fitness of our gene lines in our ancestral past.

This can be illustrated by a study by Crook et al. involving surgically altered squid and their natural predator sea bass (Crook et al. 2014). Sea bass eat squid and squid try to avoid being eaten. Each species goes through an intricate series of maneuvers when they encounter one another that involve orientation and approach on the part of the sea bass culminating in attack and protective coloration and evasive maneuvers (including spurting out of an ink jet) on the part of the squid. Survival for the squid depends on how soon it starts its evasive maneuvers once a sea bass appears, something quantified as its "alert distance".

What Crook et al. did was to either surgically remove (or not) one of the squid's eight swimmers either with (or without) an analgesic. Quartets of four squids (one from each of the four cells in the 2×2 design) were then placed in a tank with a sea bass and rates of predation assessed. The surgeries were conducted six hours before the test of predation (more than enough time for the effects of the analgesic to have worn off). Human observers could not detect whether a given squid had been operated on or not, but the sea bass could (that is the kind of thing that predators are good at). Those squids that had not been maimed were less likely to be eaten (whether they had been anesthetized or not) but those that had been operated on without anesthesia started their evasive maneuvers sooner than those who were anesthetized and were more likely to survive. The conclusion was that pain functioned to help the squid survive.

Physical pain and emotional pain differ in some respects but from an adaptationist perspective they both are aversive experiences that serve to coordinate response to threat. Moreover, that very coordination of disparate bodily functions suggests that most instantiations of the adaptations represent neither disease (the brain is not "broken") nor disorder (the whole body is involved in a coordinated response). That is not to say that the biological mechanisms that subserve an adaptation may not breakdown (disease) or that the severity of the may not be so great as to interfere with normal function (dysfunction). Some people experience idiopathic pain in the absence of any detectable tissue damage and others become depressed in the absence of precipitating event or incapacitated by the severity of their depression. But most episodes occur in response to problems in living (Keller 2018).

If depression is an evolved adaptation, the question then becomes what function(s) it evolved to serve. A corollary question is whether an intervention that facilitates that purpose is to be preferred over another like ADM that simply anesthetizes the distress. Several competing evolutionary theories have been advanced and more than one may contribute to the process (Nesse 2000), but the one that we think has the greatest relevance to treatment selection is the analytical rumination hypothesis (ARH) proposed by Andrews and Thomson (2009). According to the ARH, clinical depression (especially melancholia) can be distinguished from other depression-like syndromes like infection and starvation by virtue of where energy is directed to meet the challenge at hand. All three involve lassitude and the loss of interest in hedonic pursuits, but each differs from the other in terms of where metabolic resources are directed. When someone is dealing with infection considerable amounts of energy is directed toward immune system function and when someone is starving energy is directed toward the maintenance of vital organs (Andrews et al. 2015). In melancholia, energy flows to the cortex and makes it resistant to distraction, presumably to keep the individual focused on the problem at hand (ruminating) until he or she arrives at a solution.

Of particular interest in this regard is that serotonin is the primary mechanism directing energy distribution to meet with one challenge or another. Serotonin, like the other biogenic amines norepinephrine and dopamine, is an evolutionary ancient neurotransmitter with cell bodies buried deep in the brain stem. The raphe nucleus utilizes serotonin; the locus coeruleus is for norepinephrine; and the substantia nigra and ventral tegmental area manage dopamine. It is further of interest that norepinephrine is the neurotransmitter most involved in mobilizing the sympathetic nervous system in response to threat and dopamine is the neurotransmitter most involved in mobilizing the pursuit of hedonic reward. Serotonin regulates them both, moving energy back and forth between response to threat and the pursuit of rewards

(Belmaker and Agam 2008). Any organism must meet two kinds of challenges on an ongoing basis. It must get lunch (secure hedonic reward) while it keeps from becoming someone else's lunch (avoid risk). Each has an underlying neural organization: the behavioral activation system (BAS) for approaching reward and the behavioral inhibition system (BIS) for avoiding risk (Gray 1990). It must be more than an accident of nature that serotonin is the neurotransmitter targeted by nearly all ADMs, likely because it modulates energy distribution across different brain regions.

How does all this relate to the ARH? When the raphe nucleus fires it enervates the amygdala to pay attention to the current problem, the hippocampus to allocate working memory to the current problem at hand, the prefrontal cortex to make it resistant to distraction, the nucleus accumbens to shut down hedonic pursuits, and the hypothalamus to inhibit growth, reproduction, and physical activity (Andrews et al. 2015). In effect, it promotes rumination at the expense of hedonic pursuits. To an evolutionary biologist this suggests that rumination is the adaptation that depression evolved to produce.

But why rumination and what adaptive role could it possibly serve? Andrews and Thomson (2009) note that in our ancestral past being ostracized from the troop was a virtual death sentence and especially for females caring for offspring. They would either starve or be picked off by predators. Again, it must be more than chance that women are more likely to ruminate than men, even when they are not depressed, and nearly twice as likely to get depressed (Nolen-Hoeksema 2012). Rumination keeps one focused on complex social problems until they can be resolved. Not all problems that trigger depressions are inherently social; frustrations in non-social goal striving can trigger depressions as well. The rumination process appears to involve at least two sequential components, causal analysis and problem solving (Bartoskova et al. 2018; Maslej et al. 2019). According to the ARH, organisms are more likely to engage in slow deliberate problem solving (what Evans and Stanovich 2013 refers to as "system 2" thinking) when they are depressed, and that this facilitated the resolution of complex problems be they affiliative or achievement related in our ancestral past.

Depression is the most "temporal" of the nonpsychotic affective disorders. Persons are depressed across situations while in episode, but most episodes resolve on their own, even in the absence of treatment (spontaneous remission). *Any coherent theory of depression must account for this temporality and especially its tendency to spontaneously remit.* The ARH is not alone in doing so. Several other psychosocial models do as well, but the dominant biological theories do not. What we would propose is that the various psychosocial treatments do a better job of moving along the function(s) that depression likely evolved to serve than do the ADMs, since the latter merely anesthetize the distress. We think the reason that cognitive therapy not only holds its own with ADM with respect to acute response, but also has an enduring effect that reduces subsequent risk, is that it facilitates the process of adaptive rumination. It teaches people how to ruminate more productively in the service of solving complex life problems.

What Does Cognitive Therapy Diverge from Analytic Rumination?

Nonetheless, there are points of divergence that need to be worked through. Much of what we do in cognitive therapy is predicated on the notion that it is "errors in thinking" that lead to distress and that helping clients become more accurate in their thinking will provide relief (Beck et al. 1979). That is at best tangential to the ARH and at worst in conflict with the notion that people who are depressed are dealing with an accurate perception of a real-life problem. These seemingly different perspectives may not be that hard to reconcile. Not all episodes have clear-cut precipitants, but many do, and when they do, conducting a causal analysis regarding the source of the problem and coming up with an effective strategy for its solution is compatible with both cognitive theory and the ARH. Evidence emerging from studies that follow birth cohorts suggests that depression is far more prevalent and less likely to be recurrent than once realized (Monroe et al. 2019). These estimates suggest that two thirds of all women and one third of all men will experience one or more episodes of major depressive disorder by the time they are in their mid-thirties, typically in response to major life events, but most will have only one or at most two episodes. Only a minority of people will have three or more episodes, often in the absence of precipitants.

This led Monroe et al. (2019) to question the prevailing notion that each episode of depression increases risk for subsequent episodes within any given individual (sensitization or kindling) in favor of the notion that what we have is a mixture model in which any of us would get depressed in response to a major life stressor ("depression possible") versus a smaller subset of individuals with a preexistent diathesis that predisposes them to frequent episodes in response to minor stress ("recurrence prone"). ADMs should reduce distress in all (it even works to reduce distress in uncomplicated grief) but do nothing to resolve an underlying predisposition. Cognitive therapy does and should; the existing evidence is that those patients who best internalize the skills taught in the approach and who learn to attribute negative outcomes to failed strategies rather than stable defect in the self are the ones least likely to relapse or recur following treatment termination (Strunk et al. 2007; Tang et al. 2007).

Some forms of rumination are more likely to be productive than others. Most patients in trials are "recurrence prone" (we get few first episode patients) and most have stable latent diatheses (cognitive schema) activated in response to stress. They often enter treatment with the notion that they are defective in some way (usually that they are incompetent or unlovable) and that that is the source of their life problems (the source of their distress). They make global stable internal attribution for whatever ills afflict them and longitudinal research shows that such an explanatory style increases risk in response to negative life events (Alloy et al. 2006). In essence, they get "stuck" making a characterological attribution that points to no ready solution.

One of the first things that we do when working with patients is to encourage them to formulate at least one alternative hypothesis to the notion of personal defect (what Salkovskis 1996 refers to as "theory A vs theory B"). In most instances that rival alternative is that they simply chose the wrong strategy for dealing with their problems. What this does is to pit a stable trait theory that is difficult to change against a more remediable behavioral explanation that can be resolved by the application of the appropriate behaviors. Some patients already know what to do but forget to do so under strong states of emotion whereas others lack the necessary skills and need to be taught. This is especially true with assertion skills in important relationships.

If the ARH is correct then most people will arrive at workable solutions in a matter of months but others may stay "stuck" much longer. One of the authors once worked with an sculptor who had lost his job teaching in a liberal arts college three years earlier and viewed his distress as a "reality-based" given that he was stuck working as a handyman in a condominium complex (Hollon and Beck 1979). What he had not done in the interim was to apply for another teaching job because every time he thought about doing so he got overwhelmed with the magnitude of the task and concluded that he was an "incompetent loser" who had an "unconscious need to fail" (he had had several sessions of dynamic therapy). His "theory A" was that he was incompetent (a belief he developed as a young teen when his father forced him to compete for paternal attention with his brother) and doomed to fail no matter what he did. What this core belief did was to interfere with even starting to apply for a new job in his profession.

What we did was to generate an alternative "theory B" (that he was choosing the wrong strategy) and got him to test that proposition by "chunking" up big tasks into a series of smaller steps that he implemented one at a time. In most instances, it is not that someone who is depressed cannot do, it is that they do not start, a phenomenon referred to as response initiation deficit (Miller 1975). It became apparent that this simple behavioral expedient helped him achieve his goals (he first took his wife out to a traveling art exhibit and then in rapid succession readied his portfolio to submit to several different teaching jobs and resolved three years of unpaid taxes with the IRS). He had spent the last three years ruminating unproductively about the cause of his depression (he was not globally incompetent just someone who got overwhelmed by the magnitude of the task when he tried to do it all at once) but was able to resolve his distress (and his employment situation) within a matter of weeks by formulating a competing theory (that he was using the wrong strategy) and testing it out in a series of behavioral experiments.

The same author worked with a teacher in the placebo-controlled comparison to ADM who had spent the better part of the past fifteen years clinically depressed and suffering from PTSD in the aftermath of a traumatic event that had occurred during her teens (DeRubeis et al. 2005). When she first entered therapy she informed her therapist that, as a consequence of that event (something she did not want to talk about in therapy), she had become a "bad" person who "ripped apart" anyone that she got close to and that what she need was for him to see her on a nearly every day for the rest of her life to keep her malignant propensities in check (she also informed him that treatment would not last all that long since she was already twenty-nine and did not plan to live past thirty and that she was an incorrigible liar such that he could not believe anything she said). She was more than able to provide examples of males that she had "ripped apart" (her soon to be ex-husband just the latest) although in each instance it seemed more a matter of engaging in a series of interpersonal "safety behaviors" (lying about her past and manipulating her partner to get what she wanted without taking the risk of asking for it) that served as compensatory strategies that were intended to protect her from rejection but had the opposite effect. "Theory A" then became her notion that she was "a bad person that ripped others apart" that we pitted against "theory B" that she simply engaged in "self-defeating (bad) strategies" in relationships in an effort to protect herself from rejection.

As might have been expected the traumatic event turned out to have been a rape at age fifteen made all the worse by her father's lack of concern in its aftermath (her mother had recently passed away) from which she took away the notion that she was "damaged goods" and that no decent male would ever commit to a relationship with her. It took three months of nearly daily sessions to get her to relive the trauma. In addition to the notion that she was somehow "defiled" she also described herself as being so frightened by the notion that something so awful could happen to someone who did nothing to deserve it that she found it comforting to come to think of herself as a "predator" in relationships (the clearest example we have ever seen of the "just world" hypothesis in action). Once it became clear that she was engaging in compensatory strategies (lying and manipulating) in an effort to protect her self from rejection

(that actually had the opposite effect of bringing it about) it was evident that the best experiment for her to run was to describe what happened to her current boyfriend to see if that led him to reject her.

It took several months (and a heart-to-heart with a female friend from her youth and an anonymous survey of a dozen young male European soccer coaches that she had her therapist run at his young son's indoor soccer tournament) before she was ready to do so, but when she did she found that the boyfriend was nothing but supportive (he was sorry that it had happened to her but it had no impact on how he felt about her). That was more the beginning of therapy than the end (old habits like lying and manipulating die hard) but the ultimate resolution was quite satisfying. Fifteen years of rumination had not resolved the problem (nor had 3 years of rumination for the sculptor) largely because both got stuck blaming some supposed defect in their character when it was the strategies chosen to deal with the situations that were to blame.

The teacher was so sure that she would be rejected (because she was unlovable) that she relied on compensatory strategies (safety behaviors) that undercut the quality of her relationships and kept her from learning that her fears were unfounded. Her core beliefs led her to act in ways that undermined her relationships and her fear of rejection prevented her from testing her beliefs. The sculptor also fell prey to self-fulfilling prophecies, although it was his inability to anticipate that he could work things out (because he was incompetent) that undercut his motivation to start.

Most episodes of depression resolve on their own even in the absence of treatment and for the majority of those depressions it is quite reasonable to assume that the ***rumination leads to resolution***. It is certainly the case that cognitive therapy would not work if our clients' "brains were broken"; it is an approach that assumes that clients can think clearly, just that they forget to under strong states of emotion. Hollon and Garber (1990) speculated that what we do in cognitive therapy is not so much to teach clients to think like people who are not depressed (their thinking is dominated by the kinds of heuristics and biases that Kahneman 2011 refers to as "thinking fast") but rather to process information in a more deliberate fashion ("thinking slow") so as to focus on correctible errors in their behavioral strategies rather than stable defects in the self. This is wholly compatible with the evolutionary model proposed by the ARH.

Are ADMs Iatrogenic?

Current theory in psychiatry suggests that ADMs work by redressing a deficit in synaptic serotonin. The problem with this hypothesis is that serotonin levels in the synapse likely are not in deficit but rather in excess. It is exceedingly difficult to measure serotonin levels in the brain, but Barton et al. measured 5-HIAA (the serotonin metabolite) levels in the jugular vein (the most direct "downstream" indicator of serotonin levels in the brain) and found them to be elevated in persons who were currently depressed (Barton et al. 2008). ADMs initially increase levels of neurotransmitter in the synapse; how is it that increasing something that is already in excess reduces the levels of symptoms in an already existing depression?

That likely is because the initial increase in neurotransmitter levels triggers internal homeostatic mechanisms to shut down neurotransmitter synthesis in the presynaptic neuron and decrease sensitivity post-synaptically (Andrews et al. 2015). It takes a week or two for those changes to take effect (about the length of time it takes for ADMs to bring about symptom reduction) but levels of synaptic serotonin come down as a consequence. In effect, taking ADM is like holding a match up to a thermostat to turn the furnace down; ADM drives up synaptic serotonin levels to four times normal levels ever found in nature and as a consequence forcing internal homeostatic mechanisms to push back and drive those levels down.

What this does in turn is to lock down the very homeostatic mechanisms that otherwise would have led to spontaneous remission for so long as the medications are kept in place, something that Andrews refers to as oppositional perturbation (Andrews et al. 2011). Andrews further posits that the degree to which a given medication class perturbs the underlying neurotransmitter systems predicts the likelihood of relapse once those medications are taken away and that is exactly what happens (Andrews et al. 2012). Patients who remit on pill-placebo have about one chance in five of relapsing after discontinuation; selective serotonin reuptake inhibitors that affect only serotonin double that risk to over 40%; tricyclics that affect both serotonin and norepinephrine increase that risk to nearly 60%; and monoamine oxidase inhibitors that affect dopamine as well increase risk to about 75%. Some suggest that evolutionary theory cannot be tested, but in this instance an adaptationist perspective provides a clear prediction of rates of relapse following ADM termination that is wholly consistent with the data.

What we think may be going on is that ADMs work to suppress symptoms by virtue of driving levels of extracellular neurotransmitter(s) so high that it triggers the homeostatic regulatory mechanisms to "push back" and turn the system down. The problem is that the same homeostatic mechanisms that would have brought about spontaneous remission if left to run their course are "locked down" by the medications. In essence, patients are brought to remission but kept in episode so that they are at elevated risk for relapse (three times as great as risk for recurrence following recovery) so long as they are kept on medications. We suspect psychiatry also views ADMs as purely palliative since

recommendations call for keeping all patients on continuation medications for up to a year following medication-induced remission and patients with a history of recurrence on medications indefinitely (Frank et al. 1991; Rush et al. 2006).

Does Cognitive Therapy Truly Have an Enduring Effect?

As previously noted, cognitive therapy reduces risk for subsequent relapse by more than half relative to medications following treatment termination (Cuijpers et al. 2013) and the two trials that have extended follow-ups through 24 months suggest that that enduring effect extends to the prevention of recurrence after continuation medications are stopped (Dobson et al. 2008; Hollon et al. 2005a, b). The problem with this interpretation is that it is largely based on comparisons between patients treated to remission with cognitive therapy versus ADM and there is reason to think that different sets of patients may respond to each. For example, patients with depressions superimposed on underlying personality disorders were more likely to respond to ADM than they were to cognitive therapy in the DeRubeis et al. 2005 trial previously described (patients free from personality disorders showed the opposite pattern) and it was exactly those patients who were most likely to relapse when ADM was discontinued (Fournier et al. 2008). It is possible that cognitive therapy's enduring effect may be an artifact of differential mortality; high risk of relapse patients who need medications are more likely to respond to ADM and low risk of relapse patients who do not are more likely to respond to cognitive therapy (Klein 1996).

Cognitive-based interventions do appear to have a preventive effect in at-risk adolescents who are not currently depressed (Garber et al. 2009; Brent et al. 2015) or when they are applied after medication treatment is withdrawn (Bockting et al. 2015). However, we cannot rule it out with respect to follow-ups of acute treatment trials in which only about 50–60% of the patients initially randomized enter the follow-ups.

What is needed is a design that provides a "no specific mechanism" baseline; a randomized controlled clinical trial in which patients are treated to remission and recovery in a condition that neither works through the biogenic amines (like ADMs) nor targets changes in thinking and behavior (like cognitive therapy). What is needed is a nonspecific control (pill-placebo) that mobilizes neither of the mechanisms thought to be responsible for change in either ADM or cognitive therapy. Such a trial should be possible to do in an ethical fashion since at the less severe half of the patients who meet criteria for major depressive disorder do as well on pill-placebo as they do on active medications (Fournier et al. 2010) or psychotherapy (Driessen et al. 2010) and about half of the patients with more severe depressions will respond as well to nonspecific controls as they do to active interventions (DeRubeis et al. 2005; Dimidjian et al. 2006; Elkin et al. 1989, 1995). Moreover, cut-scores can be established based on earlier trials that define expected improvement so that patients who are not getting better in a timely fashion can be withdrawn from the trial and provided some alternative treatment.

The nonspecific control should still be less efficacious than either active intervention (we can estimate that only about three-quarters of the patients randomized to that condition will remit and recover relative to either cognitive therapy or ADM) making it susceptible to differential mortality, but that can be handled by using something akin to propensity analysis to identify patients who recover in the nonspecific control and restricting comparisons vis-a-vis prior ADM or prior cognitive therapy to only the recovered patients in those conditions who most closely match the patients who recover in the nonspecific control (see Coffman et al. 2007). If cognitive therapy truly has an enduring effect than the subset of recovered patients most similar to the recovered patients in placebo should be less likely to recur following treatment termination than those who recover on placebo. If ADM truly has an iatrogenic effect then the subset of recovered patients most similar to those patients who recover on placebo should be more likely to recur following treatment termination. Comparisons between those two subsets of recovered patients (the ones most like the recovered patients in the nonspecific control) should give us a "true" read of the magnitude of the difference between prior cognitive therapy versus prior medication treatment unbiased by differential mortality. This is a study that not only could be done but one that should be done and one that we very much hope to do and one that draws on evolutionary theory.

Coda: An Evolutionary Perspective on Depression and Cognitive Therapy

Cognitive therapy has considered depression from an evolutionary perspective, but largely as an adaptation designed to conserve energy after the perceived loss of an investment in a vital resource such as a relationship or group identity or personal asset (Beck and Bredemeier 2016). However, such past efforts at integration were accompanied by notions that inaccurate depressogenic beliefs about the self, world, and future that amplify perceptions of loss. In effect, conventional cognitive theory would agree that depression leads to rumination but would not regard rumination as part of the solution but rather as something that might have been adaptive in our evolutionary past but that has become maladaptive in contemporary times.

The field of psychiatry largely considers depression to be a "disease" in which something is malfunctioning in the brain. Cognitive theorists are more likely to point to errors in information processing (a problem in the "software" rather than the "hardware") but still view depression as a "disorder" in response to stressors that becomes a problem in itself. Apart from the fact that no reliable malfunctions have been discovered in the depressed brain, and the fact that the disorder narrative has a difficult time explaining spontaneous remission, there is at least one other reason why cognitive therapists should be wary of tying themselves to that notion. *Specifically, the various cognitive therapies all require the depressed brain to work relatively well.* As one example, cognitive therapy requires the depressed person to be willing to analyze the evidence underlying negative self-concepts, consider alternative hypotheses for them, and test them. Moreover, the patient is encouraged to develop and test these alternative hypotheses themselves through the use of Socratic questioning (Braun et al. 2015). Patients are not told what to think—they are asked questions and encouraged to reason out the answers themselves, which facilitates long-term learning. Finally, cognitive therapy works best for people with a greater capacity to learn (Bruijniks et al. 2019).

The ARH largely conceives of depression as a response to complex problems (be they affiliative or achievement related) that promotes a cognitive style that attempts to learn how to solve these problems. It is a normal part of human nature to face difficult, complex problems and learn how to solve them. We start off life as infants with a very simple understanding of the world, and as we grow older our mental models become more sophisticated. We think it is no coincidence that depression begins to increase substantially in frequency during adolescence—precisely the time when social relationships become much more complicated. We also think that it is no coincidence that this is the time when the sex difference in depression begins to develop, because the social challenges facing young reproductively aged women arguably increase in complexity more than those facing young men (Andrews and Thomson 2009). In short, we suggest that depression increases in a gender-biased way during adolescence because this is a time when people, and particularly newly reproductively capable young women, must learn how to deal with complex social challenges linked to sex and reproduction.

Under the ARH, the role of the cognitive therapist is to help the depressed individual learn the complex information required to solve the problem. However, there are several possible explanations for instances when rumination appears to be maladaptive without relying on either a disease or a disorder narrative. We will show that these possibilities are not mutually exclusive.

Evolutionary Mismatch

First, evolved adaptations are traits that exist now because they were shaped or modified by selection pressures that occurred in the past (Tooby and Cosmides 1990). For this reason, they are expected to perform adaptively (meaning better than average but not necessarily perfectly) when operating in the evolutionarily relevant environments. Modern environments may deviate substantially from ancestral environments, and adaptations may not be perfectly adapted to modern conditions (the *evolutionary mismatch hypothesis*). In this context, it is possible that some rumination produces maladaptive outcomes, not because it is the result of a mental disorder, but because it is an ancient adaptation operating in modern environments. In the case studies above, both patients had developed stable self-images that they were flawed, incompetent or unlovable, In both cases, the patients experienced stressful or abusive interactions indicating that they were not valued by their parents and in each instance the therapist helped the patient see that they could develop alternative strategies that worked better (the sculptor) or relationships with people who valued them more (the teacher).

From an evolutionary perspective, people have evolved to pay undue attention to how they are treated by family members, particularly parents. Parents usually have the greatest interest in the welfare of their children because they share genes in common and usually provide many years of investment in their children. If your own parents don't love you or invest in you, that does not bode well for your future. Statistically and evolutionarily, interactions with parents are more diagnostic of one's social value than interactions with more distant relatives, other members of your community, or strangers. So, we can understand how a long history of poor familial interactions may lead people to develop stable, negative self-schemas without relying on a disorder narrative, and without concluding that it is necessarily adaptive in a modern context.

Adaptive Search Strategies are Imperfect

Second, we conceive of rumination as a process by which depressed people search for solutions to the problems that triggered their episodes (Andrews and Thomson 2009). Even good search strategies are imperfect at finding solutions. As an analogy, natural selection causes a species to incrementally increase its fitness, without foresight or purpose. Figure 3 depicts a hypothetical fitness landscape in which the species starts off in the valley between peaks A and B. Peak B has the higher fitness, but the routes to peak A and B are both possible for the species because both paths involve incremental increases in fitness from its starting point. Let us suppose that, by chance, the species travels up to peak A.

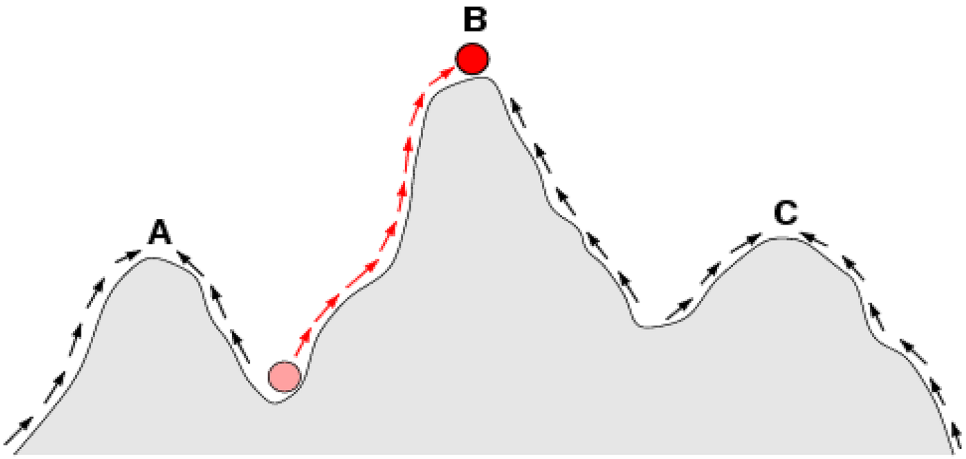

Fig. 3 A Hypothetical Landscape for Searching for a Solution: Natural selection can get stuck in local fitness optima (peak A or peak C) without reaching the highest fitness peak (B). Similarly, statistical optimization techniques can get stuck in local optima when searching through the parameter space for the best solution. Reprinted with implied permission from: Created by Claus Wilke in the public domain

It would be better off if it could get to peak B, but that would require the species to travel back down to the valley where it started—going in the direction of decreasing fitness—before it could climb up the other side. In other words, the species can find itself stuck on a less adaptive peak, because there is no viable path (one favored by natural selection) that would allow it to get to the higher, more adaptive peak. Rumination focuses on the causes of the problem but it does not guarantee that people will not get stuck on stable characterological ascriptions.

Search-based optimization techniques are useful and often find the optimal solution, but they are not perfect and do not guarantee that the optimal solution will be found. We suggest that rumination is a process by which depressed people use a slow, deliberate "system 2" processing style to search through the parameter space of their own problems to try to find an optimal solution (Evans and Stanovich 2013). This technique is very useful and often leads to good or optimal solutions given the constraints, which can explain why most depressive episodes eventually resolve on their own. However, like a species stuck on a suboptimal fitness peak, depressed people sometimes find themselves stuck in a suboptimal place of their problem solution space, with no clear way to a better outcome. The role of the cognitive therapist in this context is to provide strategies that can help the patient out of the suboptimal parameter space and find a better solution.

None of this requires endorsing a disease or disorder narrative for most episodes of depression. It simply means understanding something that evolutionary psychologists have long recognized. Natural selection has imbued our nervous systems with many adaptations that help deal with adaptive challenges. But these adaptations are not perfect. *There is no such thing as an adaptation that can maximize fitness under all possible circumstances* (Tooby and Cosmides 1990). We find it interesting that most dictionaries define rumination as "thinking deeply about something" whereas medical dictionaries define it as "obsessively thinking about an idea, situation, or choice, especially when it interferes with normal mental functioning" It is not clear that rumination is necessarily pathological, but it is clear that modern medicine considers it so.

Normal Anxiety Can Disrupt Rumination

Third, many people are relatively good at getting unstuck from a suboptimal place in their problem solution space because they are willing to incur a short-term cost (i.e., they are willing to go down from a suboptimal peak) for a long-term gain (because they can see how it will help them get to a taller peak). But if they have a great deal of anxiety, that can impair their willingness to leave the suboptimal peak. Anxiety is often co-expressed with depression, but its effect on cognition is different. Essentially, anxiety promotes a better-safe-than-sorry approach, which is often an adaptive response to potentially dangerous situations (Bateson et al. 2011; Nesse 2005a). People with higher levels of anxiety may be less willing to leave a suboptimal peak in their solution space because it requires taking some risks or incurring a cost. In fact, the co-expression of anxiety with depression can make it extremely difficult to determine exactly what is adaptive and what is not. Is it more important to get to a more optimal peak in the problem solution space or is it more important to avoid the risks that come from leaving the suboptimal peak? There is no easy answer to such questions and adopting a mental disease or disorder narrative is unlikely to be helpful. A more useful clinical approach is to help the patient devise strategies for achieving long-term goals in ways that minimize their risks. The role of the therapist is best characterized as that of a trusted ally helping patients manages complex problems.

The teacher who thought that her prior trauma undercut her value as a potential mate provides an example. She was reluctant to let anyone in whom she had an interest

know what had happened to her because she expected to be rejected and her fear of making things worse and the associated anxiety led her to engage in compensatory strategies ("safety behaviors") intended to protect her from rejection but that instead poisoned her relationships and generated exactly the outcomes that she most feared. Anxiety essentially generated self-fulfilling prophecies.

Large Fitness Consequences Can Favor Seemingly Unproductive Cognitions

The fourth possibility is that the fitness consequences of harmful events can affect cognition. Consider a parent who is grieving the recent loss of a child. It is not uncommon for such parents to ruminate intensely over things that they might have done to prevent the child's death. To a clinician, the dwelling on the past may not seem very useful because the past cannot be changed. However, an understanding of the causes of a negative event can be useful in understanding how to prevent similar events in the future (Andrews and Thomson 2009; Roese and Epstude 2017). In natural fertility environments, women have, on average, about six children over their lifetimes and several of them die (Volk and Atkinson 2013). Effort spent on understanding the causes of a child's death might help prevent the deaths of other children (Nesse 2005b). There may be situations in which it seems obvious to the clinician that there was little or nothing that a parent could have done to prevent the child's death. In such situations, it may seem puzzling to see a parent engage in self-recriminating rumination, but the fitness value of a child is so great that natural selection can favor the expenditure of a great deal of cognitive effort even if it only has a small chance of increasing the survival chances of other children.

We have focused on parents ruminating over the loss of a child, but the principle is generalizable to any kind of situation in which large fitness consequences are at stake, such as social ostracism and romantic relationship difficulties. We suspect that clinicians will experience significant resistance if they try to convince patients that causal analysis is unproductive in such situations. A more productive approach might be to educate the patient that the depressed brain is designed to explore the causes of important problems on the off chance that preventive action could have been taken. Explicitly acknowledged, it might be possible to have a more productive conversation about the actual chances that corrective action would have made a difference.

Inclusive Fitness Theory

The last possibility is even more radical from a clinical perspective. One of the most important insights in evolutionary biology over the last century is that organisms are not designed by natural selection to maximize their own survival, or even their own reproductive success—they are designed to maximize the propagation of their genes (West and Gardner 2013). The difference between individual reproductive success and genetic propagation can be understood by the fact that organisms share genes in common with their biological relatives. Organisms can propagate their genes through their own direct reproductive efforts (direct fitness) or by enhancing the reproduction of their biological relatives (indirect fitness). The sum of direct fitness and indirect fitness is referred to as *inclusive fitness*, and that is what organisms are designed by natural selection to maximize (Hamilton 1964). Gene lines that do are favored by natural selection, not necessarily the specific individual. A detailed review of inclusive fitness is beyond the scope of this paper, but the concept is crucial to explaining many important biological events, including multicellularity, reproductive castes in social insects and mammals, apoptosis and other forms of programmed cell death, the evolution of social systems characterized by family groups, and parental behavior. An understanding of human physiology and psychology that fails to include inclusive fitness theory is impoverished and inaccurate.

Under certain situations, the maximization of inclusive fitness can occur through self-sacrificial or self-destructive behavior. The essence of the idea is captured by a famous quip made by the evolutionary geneticist J. B. S. Haldane who once said that he would not sacrifice his life for that of his brother, but he would for two brothers or eight cousins (Lewis 1974). Since siblings share half of their genes in common, and cousins share one-eighth in common, Haldane's quip actually denotes the breakeven point. Self-sacrifice to save the lives of three brothers or nine cousins would be a net genetic benefit. The quip assumes that all individuals within the family are equal in terms of their capacity to pass genes on to the next generation. However, selection can more easily favor self-sacrifice or self-destruction in a post-reproductive individual for the benefit of a reproductive or pre-reproductive family member. Even reproductively-aged individuals can engage in adaptive self-sacrifice for the benefit of family members if they are substantially impaired in their own ability to reproduce (e.g., chronic illness, developmental disorder, or uncompetitive in the mating market).

We suspect that many (if not most) instances in which people have developed stable, negative self-images reflect situations in which they are considering the pursuit of self-sacrificial or self-destructive indirect fitness strategies. The proclivity is so common (at least among the recurrence prone) that it deserves to be examined from an evolutionary perspective. As described above, self-destruction is more easily favored by natural selection among individuals who are defective or otherwise impaired in their ability to pursue direct reproduction. However, we predict that—at least among those of reproductive age—the development

of stable, negative self-schema usually requires a long history of feedback from the environment that one is impaired, uncompetitive, or devalued. This could explain why a history of childhood trauma and abuse and a history of failed romantic or marital relationships are risk factors for suicide during the reproductive years (de Catanzaro 1995; Luoma and Pearson 2002; Nademin et al. 2008). Inclusive fitness theory also offers an explanation for why people who die by suicide often believe that their family would be better off without them (Joiner et al. 2002).

Clinical notions of what is adaptive and what is diseased or disordered do not always coincide with what is adaptive from an evolutionary perspective. We have focused on self-blaming, self-deprecating rumination, and suicidal behavior to make this point, but it could be generalized to other behaviors that are of clinical interest, such as risk-taking and addictions.

If some of our readers—clinicians, researchers, lay people—feel a viscerally negative emotional response to the use of the word "adaptive" to describe suicide and other forms of self-destructive behavior, this is a sign that the evolutionary insight is novel and non-intuitive. *Clinicians need to understand the naturalistic fallacy. An 'is' is not an 'ought.' Cancer 'is' a collection of cells that are pursuing their inclusive fitness. It is hardly an "ought" and intervention is warranted.* Moreover, we should not let moral repugnance bias the scientific study of human behavior. Prolicide (killing one's offspring), the killing of conspecifics, and sexual coercion are commonly expressed throughout the animal kingdom, and humans are no different. We are not suggesting that clinical intervention is unwarranted in situations where people are engaging in self-destructive behavior as part of the pursuit of indirect fitness interests. Rather, we are saying that it is important to identify the evolutionary origins of seemingly maladaptive behaviors, such as rumination and suicide. Developing effective treatments will require differentiating psychological phenomena that result from some malfunction in the brain from those neurological mechanisms evolved to maximize inclusive fitness.

Summary and Conclusions

We think that depression is an evolved adaptation (like pain and anxiety) that served to increase fitness in our ancestral past and that those interventions that best facilitate the function that it evolved to serve are likely to prove to be superior to those that are purely symptom suppressive. Just as pain serves to signal to squids that have been maimed to begin their evasive maneuvers sooner, we think that depression signals to the individual that there are problems to be solved and that focusing attention on those problems (rumination) is the first step toward finding a solution. It is striking that so much energy in clinical depression is diverted to the cortex (as opposed to what happens in infection or starvation) and curious that serotonin (an ancient neurotransmitter with cell bodies deep in the brain stem that modulates that transfer) is the proximal target of most modern antidepressants. We think that cognitive therapy facilitates productive problem-solving (likely the reason why it has an enduring effect if indeed it has an enduring effect) and that ADMs may simply anesthetize distress and leave patients at elevated risk for relapse at whatever point they come off their medication. That is better than being eaten by a sea bass, but not the outcome most people would choose or that we would choose for them.

Compliance with Ethical Standards

Conflict of Interest Steven D. Hollon, Robert J. DeRubeis, Paul W.Andrews and J. AndersonThomson, Jr. declare that they have no conflict of interest.

Animal Rights No animal studies were carried out by the authors for this article.

Informed Consent Informed consent was obtained from all individual participants in this study.

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