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Inflammation, Self-Regulation, and Health: An Immunologic Model of Self-Regulatory Failure

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Abstract
Self-regulation is a fundamental human process that refers to multiple complex methods by which individuals pursue goals in the face of distractions. Whereas superior self-regulation predicts better academic achievement, relationship quality, financial and career success, and lifespan health, poor self-regulation increases a person's risk for negative outcomes in each of these domains and can ultimately presage early mortality. Given its centrality to understanding the human condition, a large body of research has examined cognitive, emotional, and behavioral aspects of self-regulation. In contrast, relatively little attention has been paid to specific biologic processes that may underlie self-regulation. We address this latter issue in the present review by examining the growing body of research showing that components of the immune system involved in inflammation can alter neural, cognitive, and motivational processes that lead to impaired self-regulation and poor health. Based on these findings, we propose an integrated, multilevel model that describes how inflammation may cause widespread biobehavioral alterations that promote self-regulatory failure. This *immunologic model of self-regulatory failure* has implications for understanding how biological and behavioral factors interact to influence self-regulation. The model also suggests new ways of reducing disease risk and enhancing human potential by targeting inflammatory processes that affect self-regulation.

Keywords
cytokines, self-regulation, cognition, motivation, executive function, development, behavior, disease, health

The social and physical worlds that individuals inhabit are filled with temptations and demands that distract people from goals and challenge their best intentions. A fundamental aspect of successfully navigating such an environment thus involves managing impulses that arise as people attempt to engage in short-term behaviors (e.g., skipping dessert) that are consistent with longer term goals (e.g., losing weight). The method by which humans work to maintain such alignment is generally referred to as *self-regulation* (Muraven & Baumeister, 2000), and its relevance for shaping peoples' lives is difficult to overstate. Indeed, whereas closely controlling one's thoughts and actions can help an individual maintain long-lasting relationships, foster incredible talents, and accomplish remarkable feats, failing to self-regulate can lead to behaviors that have the potential to cause tremendous personal and collective harm.

Self-regulation is an important psychological construct in part because it is relevant for many different outcomes (see Table 1; Baumeister & Vohs, 2005). For example, self-regulation plays a key role in shaping lifelong health by influencing the extent to which people engage in many different actions that can have serious consequences, such as adhering to a healthy diet, scheduling annual visits to the doctor, taking prescribed medications, exercising regularly, and practicing good health behaviors, including eating, sleeping, and brushing one's teeth on a consistent schedule (Bandura, 2005; Schwarzer, 1999). Self-regulatory abilities also greatly affect peoples' interpersonal and

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Table 1. Multifaceted Benefits of Better Self-Regulation by Life Domain

Benefits	Example Reference(s)
Education	
Higher grade point average	Tangney, Baumeister, & Boone, 2004
Decreased likelihood of failing in school	Blair & Diamond, 2008
Career	
Better job performance	Porath & Bateman, 2006; Stajkovic & Luthans, 1998
Greater career success (e.g., salary, job satisfaction)	Ng, Eby, Sorensen, & Feldman, 2005
Social relationships	
Better social skills and status	Eisenberg et al., 1993
Better social relationship quality	Tangney et al., 2004
Quality and length of life	
More positive affect, well-being, and life satisfaction	Hofmann, Luhmann, Fisher, Vohs, & Baumeister, 2014
Reduced occurrence of psychopathology	Tangney et al., 2004
Better overall health	Atherton, Robins, Rentfrow, & Lamb, 2014; Bandura, 2005
Longer lifespan	Friedman et al., 1993

work life by shaping their friendship and romantic relationship quality, academic achievement, and overall career success (Diamond, 2013). Finally, although psychosocial stressors are a part of many peoples' lives and can increase risk for life-threatening diseases, self-regulatory abilities have been found to buffer individuals against negative health outcomes that are frequently caused by stress (G. W. Evans & Fuller-Rowell, 2013).

In contrast, failures of self-regulation are known to contribute to a variety of personal and societal maladies (Baumeister, Heatherton, & Tice, 1994). For example, failing to self-regulate can result in succumbing to negative social influences (Burkley, Anderson, & Curtis, 2011), debt-procuring impulsive spending (Baumeister, 2002), poor self-presentation (Vohs, Baumeister, & Ciarocco, 2005), relapsing in smoking cigarettes (Muraven, 2010), and committing crimes (T. D. Evans, Cullen, Burton, Dunaway, & Benson, 1997; LaGrange & Silverman, 1999). As a result of these effects, poor self-regulation is a very strong, independent predictor of both disease-specific and overall mortality (Friedman et al., 1993; Kröz et al., 2011).

Given the critical importance of self-regulatory abilities for human behavior and health, a large number of studies have been conducted over the past four decades to elucidate social, environmental, and cognitive processes that contribute to self-regulatory failure and the consequences that such failures have for individuals over the life course. Moreover, this body of work has been evaluated in several excellent reviews (e.g., Heatherton & Wagner, 2011; Muraven, Tice, & Baumeister, 1998; Vohs & Baumeister, 2011; Vohs & Heatherton, 2000; Wagner & Heatherton, 2015). At the same time, comparatively little attention has been paid to the roles that specific biologic processes might play in self-regulation, even though elucidating such mechanisms could help refine thinking about self-regulation and possibly lead to the identification of new strategies for enhancing self-regulation and improving the human condition (Klein, Shepperd, Suls, Rothman, & Croyle, 2015; Moffitt et al., 2011; cf., Heatherton & Wagner, 2011). Discussion of the biological bases of self-regulation has been limited in part because researchers have lacked the types of methodological tools that are necessary to study the full range of biologic processes that might underlie self-regulation. Recent advances in neuroimaging and immunologic techniques have since been developed, though, and one of the most interesting and potentially important discoveries in this area of research has involved the finding that specific neural and immune system processes may interact to directly influence self-regulatory ability.

The purpose of the present review is to examine neural and immune system processes that are relevant for self-regulation, behavior, and health. In doing so, we hope to generate new ideas for future research that use concepts and methods from psychology, neuroscience, and immunology to elucidate the psychological and biological bases of self-regulation. To achieve this goal, we first summarize contemporary thinking and research on self-regulation. Second, we provide an overview of immune system processes that are involved in human behavior and health. Third, we describe pathways by which the immune system can affect neural structure and function. Fourth, we examine how aberrant neural and immune system dynamics can impact processes that are required for effective self-regulation. Fifth, based on this information, we propose an integrative, multilevel model of self-regulation, behavior, and health. Finally, we discuss the possible implications of this work and suggest some possible avenues for future research. Because evidence linking immune system dynamics and self-regulation is more well-developed in some contexts than

others, our overarching goal is to provide a comprehensive assessment of what is presently known and a framework for future research on these important issues.

Self-Regulation

We define self-regulation as the *ability through which people create and maintain alignment with distant or abstract goals*, especially when immediate motivations and desires compete with those goals. Self-regulation is not a singular process but rather a set of multiple interrelated processes that enable individuals to control their thoughts, behavior, and future in concrete and abstract ways by managing goals, strategies, plans, intentions, and impulses (Coutlee & Huettel, 2012). Numerous proximal factors have been proposed to influence self-regulation, such as stress, motivation, cognitive resources, and self-regulatory strategies (Hagger, Wood, Stiff, & Chatzisarantis, 2010; Vohs & Baumeister, 2011). Several distal factors have also been proposed, including brain structure, trait-like tendencies to appraise situations as more positive or negative, and individual differences in cognitive abilities (Heatherton & Wagner, 2011). Despite the complex ways in which these many factors can interact to ultimately influence self-regulation, though, a substantial body of research points to the fact that individual acts of self-regulation—resulting in either self-regulatory success or failure—depend to a great extent on the balance between executive control and the strength of an impulse, emotion, or reward. A graphical representation of these dynamics is depicted in Figure 1.

Many factors also interact to ultimately influence human behavior and health (G. Miller, Chen, & Cole, 2009; Toussaint, Shields, Dorn, & Slavich, 2016). In this context, self-regulation has been regarded as an important and sometimes critical factor to the extent that it contributes to cognitive, emotional, and behavioral outcomes that shape individuals' lives and well-being (Scheier, Carver, & Armstrong, 2012). Self-regulation may influence how individuals in a society live and interact through cognitive means by, for example, enabling them to consider the consequences of being conflictual or verbally combative or through behavioral means by promoting prosocial actions. Self-regulation can also influence individuals' lives through emotional means by facilitating effective coping strategies for dealing with negative affect or preventing aggressive or depressive behavior.

Given these far-reaching effects, a large body of research has investigated methods for enhancing self-regulation as a means of improving self-regulation-related outcomes. Studies on this topic have examined a variety of different intervention strategies, given self-regulations' multifaceted nature, and this work has suggested that some strategies may improve self-regulation despite the fact that self-regulatory abilities are largely stable over time (e.g., Berman et al., 2013; Casey et al., 2011; Meichenbaum & Goodman, 1971; Sultan, Joireman, & Sprott, 2011; Verbeken, Braet, Goossens, & van der Oord, 2013). One notable limitation of this work, however, is that it has identified methods for enhancing self-regulation abilities that are broad and nonspecific and that vary greatly with respect to their efficacy (Berkman, Graham, & Fisher, 2012). Indeed, there is debate as to whether the self-regulation training methods developed to date are effective (e.g., Simons et al., 2016). Understanding the biological mechanisms that underlie self-regulation may

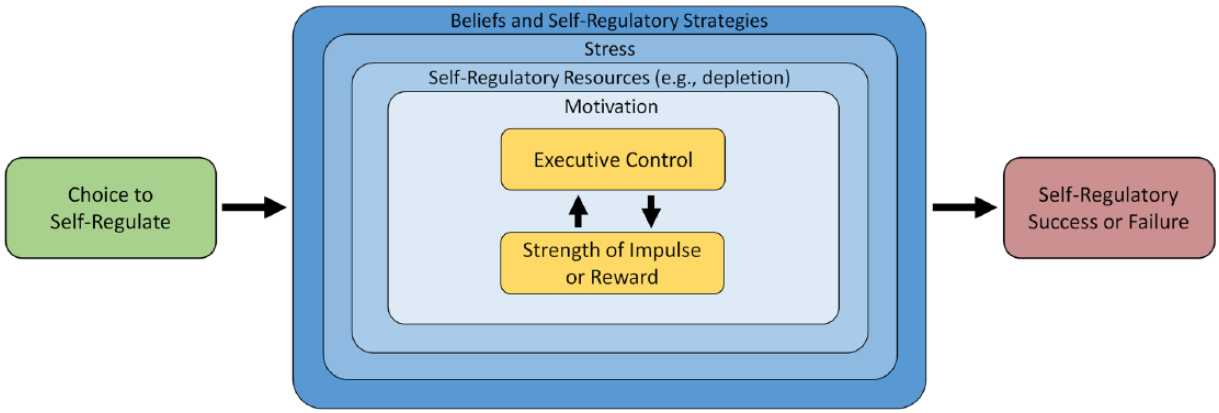

Fig. 1. Processes involved in self-regulation, arranged by their proximity to individual self-regulatory acts. Acts of self-regulation depend most proximally on the strength of an impulse, emotion, or reward, which both influence and are influenced by executive control abilities. This interplay is influenced by a person's motivation to self-regulate, as motivation to self-regulate is crucial if sustained executive control is needed. Motivation is then in turn influenced by self-regulatory resources, as motivation to self-regulate will be low if one knows self-regulation is ultimately a futile effort. Self-regulatory resources are in turn affected by stress, as stress reduces self-regulatory resources. Finally, and most distally, beliefs and self-regulatory strategies can have an influential impact on self-regulation, due in part to how these factors may alter perceptions of both stress and self-regulatory resources.

address some of these issues and help inform the development of more effective interventions for promoting self-regulation, but research on this topic has been limited, especially compared to the amount of work that has focused on identifying cognitive, emotional, and behavioral aspects of self-regulation.

Biologically informed theories of self-regulation

With respect to the few biological formulations of self-regulation that have been proposed, two models stand out that provide an initial picture of how specific biological mechanisms may lead to self-regulatory failure. The first model argues that self-regulation depends in part on glucose and that temporary reductions in self-regulatory ability are mediated by temporary depletions of circulating or focal brain glucose (Gailliot & Baumeister, 2007). Although this model has been challenged (i.e., Hagger & Chatzisarantis, 2013; Job, Walton, Bernecker, & Dweck, 2013; Molden et al., 2012), some of its tenants may hold up to criticism (Baumeister, 2014; Chatzisarantis & Hagger, 2015; although see Baumeister & Vohs, 2016; Dang, 2016; Hagger et al., 2016). The second noteworthy biologically informed model of self-regulation posits that the glucocorticoid hormone cortisol, which is released during stress, alters brain function in ways that may impair self-regulation (Blair et al., 2011; Raio, Orederu, Palazzolo, Shurick, & Phelps, 2013; cf., Shields, Bonner, & Moons, 2015). These theories provide important initial accounts of biologic mechanisms that may underlie self-regulatory successes and failures. However, for reasons that we outline below, it is unlikely that cortisol and glucose are the only biological factors that influence self-regulation. Moreover, cortisol and glucose may not represent the most critical factors to focus on in this context.

The Immune System, Inflammation, and Their Relevance for Self-Regulation

One system that may be intimately involved in self-regulation, but which has received virtually no attention to date, is the human immune system. As we discuss below, immune system activity—especially components of the immune system involved in inflammation—appear to impair numerous facets of self-regulation. In addition, health conditions that are associated with aberrant immune system activity, such as obesity, are also characterized by poor self-regulation. Moreover, like the nervous system (Knudsen, 2004), the immune system exhibits sensitive periods during which time environmental inputs, such as life stress, can shape the reactivity of the immune system for years to come, thus providing a potential explanation for why early life stress is associated with both poor self-regulation and worse health over the lifespan (Bilbo & Schwarz, 2009; see also John-Henderson, Rheinschmidt, Mendoza-Denton, & Francis, 2014). Consequently, multiple reasons exist for examining the role that the immune system plays in self-regulation.

The primary responsibility of the immune system is to rid the body of foreign pathogens and help the body recuperate during physical injury and infection (Daruna, 2012; Murphy, 2014). One key player in immune system activity is a class of proteins called *cytokines*, which facilitate communication between immune cells. Cytokines come in several different types and serve many functions (Daruna, 2012). Most relevant for the present discussion, though, is a class of cytokines called *proinflammatory cytokines*, which upregulate inflammatory activity throughout the body (Slavich & Irwin, 2014).

Proinflammatory cytokines are released from immune cells usually after a microbial invader or tissue injury has been detected (Irwin & Slavich, 2017; Medzhitov, 2008). Under these circumstances, cytokines signal to attract other cells to target locations and can also cause blood vessels to expand to increase trafficking of immune cells to sites of injury or microbial invasion (Barton, 2008). These dynamics in turn cause redness, heat, pain, and swelling at the affected area(s) and can also cause systemic changes including the induction of fever, fatigue, altered sleep and eating, and social-behavioral withdrawal (Curfs, Meis, & Hoogkamp-Korstanje, 1997; Slavich & Irwin, 2014). Collectively, these effects are referred to as *inflammation*.

Immune system activity in general and inflammatory activity in particular are coordinated by thousands of complex physiochemical interactions that have numerous biobehavioral effects. The immune system, therefore, does not *only* influence self-regulatory behavior (as described above), nor is it the only system that influences self-regulation. As we have already mentioned, however, components of the immune system involved in inflammation can have very powerful effects on cognition, motivation, and behavior, making this system potentially critical for understanding self-regulatory failure.

As we describe in greater detail below, support for the idea that inflammation can degrade self-regulatory ability comes from numerous studies showing that inflammatory activity can impair both cognitive and emotional self-regulation (e.g., Frydecka et al., 2015; Gianaros et al., 2014; A. H. Miller, Capuron, & Raison, 2005; Mooijaart et al., 2013; Prossin et al., 2011; Reichenberg et al., 2001; Trompet et al., 2008). Therefore, although there is very little cross-talk between studies on self-regulation and inflammation, extant evidence suggests that self-regulation influences immune system activity and vice

versa. Such effects may be surprising, as inflammation is still typically thought of as the body's primary response to physical injury or infection (Slavich, 2015). However, biological mediators of the inflammatory response can also have neural, cognitive, and motivational effects, making the immune system highly relevant for self-regulatory behavior (Dantzer & Kelley, 2007; Maier & Watkins, 1998). To describe how the immune system can influence self-regulation, we next provide a brief overview of how the brain and immune system interact in ways that are relevant for self-regulation.

Bidirectional pathways linking the immune system and brain

Like other bodily systems, the immune system and brain have the ability to bidirectionally communicate, and the pathways that underlie these links enable the brain to steer the activity of the immune system and vice versa (Irwin & Cole, 2011; Nusslock & Miller, 2016; Slavich & Irwin, 2014; Slavich, Way, Eisenberger, & Taylor, 2010). One pathway by which the brain regulates immune system activity involves the hypothalamic-pituitary-adrenal (HPA) axis, which, through the anti-inflammatory actions of cortisol, functions as a key down-regulator (but also up-regulator) of proinflammatory cytokine activity (Busillo & Cidlowski, 2013). Another pathway by which the brain can regulate immune system activity is the sympathetic-adrenal-medullary (SAM) axis, which, once activated, up-regulates proinflammatory cytokine production through the release of epinephrine and norepinephrine (Daruna, 2012). In brief, therefore, the brain can modulate the immune system through at least two main pathways: Whereas the HPA axis primarily (but not exclusively) reduces inflammation by inhibiting the release of proinflammatory cytokines, SAM axis activity ultimately increases inflammation by promoting the release of proinflammatory cytokines.

Conversely, the immune system can also influence brain activity via several pathways. In brief, proinflammatory cytokines can directly stimulate neurons via cytokine receptors on neurons (Hopkins & Rothwell, 1995; Louveau et al., 2015; Raison, Capuron, & Miller, 2006; Rothwell & Hopkins, 1995). Such effects can occur through direct interaction between the immune system and brain (Louveau et al., 2015) but also through indirect interactions, such as when neural activity is influenced by stimulation of the vagus nerve or by alterations in the synthesis and degradation of various neurotransmitters (Garcia-Oscos et al., 2015; Maier, Goehler, Fleshner, & Watkins, 1998; Thayer & Sternberg, 2010). Ultimately, via these and other nonmutually exclusive pathways, proinflammatory cytokines can exert strong modulatory effects on the structure and function of brain regions that support self-regulation, such as the prefrontal cortex (PFC; Audet, Jacobson-Pick, Wann, & Anisman, 2011; de Pablos et al., 2006; Garcia-Oscos et al., 2015; Poh, Yeo, Stohler, & Ong, 2012).

Neurocognitive and Behavioral Pathways Linking the Immune System and Self-Regulation

So far, we have reviewed evidence indicating that the brain and immune system interact. Next, we examine psychological processes that support self-regulation and how immune system activation may impact these processes. In particular, we summarize research demonstrating how cytokines and other immune system mediators can influence beliefs about self-regulation, self-regulatory depletion, motivation and reward, appraisals of stress, and executive function. Evidence relating immune system activity to each of these self-regulatory processes varies, and some self-regulatory processes, such as executive function, have a stronger body of evidence linking them to immune system activity than others. Nevertheless, because these processes all represent mechanisms that may underpin successful self-regulation, we describe known connections when appropriate and identify the need for future research when warranted.

Beliefs about self-regulation

Personal beliefs exert strong effects on self-regulatory abilities. Beliefs about self-control, self-regulatory capacity, and the efficacy of agency, for example, modulate several self-regulatory abilities, including error monitoring in cognitive tasks (Rigoni, Wilquin, Brass, & Burle, 2013), preconscious action-initiating processes (Rigoni, Kühn, Sartori, & Brass, 2011), self-control (Rigoni, Kühn, Gaudino, Sartori, & Brass, 2012), and the effects of glucose supplementation on self-regulation (Job et al., 2013). Moreover, individuals' belief that their self-regulatory abilities are limitless attenuates the detrimental effects of prior self-regulatory exertion on subsequent self-regulatory behavior (Vohs, Baumeister, & Schmeichel, 2012). Indeed, a recent meta-analytic review examining the effects of beliefs about self-regulation found that beliefs about self-regulatory abilities have a small-to-moderate effect on the efficacy of self-regulation (Burnette, O'Boyle, VanEpps, Pollack, & Finkel, 2013). This is notable given that numerous factors influence self-regulation.

Similarly, the use of regulatory strategies contributes to effective self-regulation (Burnette et al., 2013). Self-regulatory strategies are the preplanned methods by which individuals attempt to attain their goals, such as by deciding to walk out of a room if one sees cupcakes on a table at a party. Although these methods are often dependent

on the adequate functioning of more immediate methods of self-control, such as response inhibition, they contribute a unique part of the variance in overall self-regulatory success (Burnette et al., 2013) and may even facilitate more immediate methods of self-control if these strategies are indeed predefined (Crockett et al., 2013). Thus, beliefs about self-regulation and strategies both appear to have a prominent impact on the effectiveness of self-regulatory efforts.

A substantial body of research has examined the effects of different beliefs on cytokines and other immune system mediators. Existing studies support the idea that beliefs related to self-efficacy (Mausbach et al., 2011), spirituality (Ai, Pargament, Kronfol, Tice, & Appel, 2010), and religion (Koenig et al., 1997) may be associated with reduced basal proinflammatory cytokine activity as well as cytokine reactivity to stress. Interestingly, positive beliefs about one's self-efficacy, as well as religious beliefs, have been shown to promote self-regulation (Burnette et al., 2013; McCullough & Willoughby, 2009). Although correlational, these data indicate that certain beliefs of the self or God may create psychological states that lead to decreased levels of proinflammatory cytokine activity, which may have implications for self-regulation.

An additional possibility is that proinflammatory cytokines influence neural systems in ways that shape the development of beliefs that impair self-regulation. Put another way, rather than certain beliefs lowering circulating levels of cytokines and thereby enhancing self-regulation, heightened levels of proinflammatory cytokines may contribute to the development of beliefs that undercut successful self-regulatory strategies. Little direct support is presently available for this formulation (although see Papageorgiou et al., 2006). However, a robust finding pertaining to the cognitive and behavioral effects of inflammation is that proinflammatory cytokines can induce depressed mood (e.g., Eisenberger, Inagaki, Mashal, & Irwin, 2010; for a review, see Maier & Watkins, 1998). To the extent that negative beliefs that degrade self-regulatory abilities increase in salience during depressive mood states (Madigan & Bollenbach, 1986), these links may suggest that proinflammatory cytokine activity may promote self-regulation impairing beliefs in part by inducing depressive mood. One intriguing possibility, then, is that cytokines may help promote the development of beliefs that impair effective self-regulation, especially in individuals who are cognitively vulnerable.

Self-regulatory depletion

Another potential aspect of self-regulation that may be modulated by immune system activity is self-regulatory depletion. Research has suggested that exercising self-regulation impairs self-regulatory abilities (Baumeister & Heatherton, 1996; Hagger et al., 2010). This phenomenon has been given various labels, but it is most commonly referred to as *depletion*. It is important to note that the existence of self-regulatory depletion has been contested by a failed replication attempt (Hagger et al., 2016; for responses, see Baumeister & Vohs, 2016; Dang, 2016) and by meta-analytic techniques that account for publication bias (Carter, Kofler, Forster, & McCullough, 2015; for a response, see Inzlicht, Gervais, & Berkman, 2015). Nevertheless, evidence linking cytokines to alterations in brain regions that are thought to underpin depletion is persuasive, thus providing a justification for examining potential links between cytokine activity, self-regulatory depletion, and self-regulation.

Assuming that self-regulatory depletion exists in some form, there are several mechanisms that may underlie this effect. For example, depletion may be caused by reductions in a neural resource (Berkman & Miller-Ziegler, 2013; Persson, Larsson, & Reuter-Lorenz, 2013), resultant stronger emotions or impulses (Vohs, Baumeister, Mead et al., 2012), altered motivation and attention (Inzlicht & Schmeichel, 2012), or some combination of these processes. Depletion, if it exists, may also correspond to alterations in specific neural regions that are employed during self-regulation. For example, depletion may contribute to reduced activity in the anterior cingulate cortex (ACC; Inzlicht & Gutsell, 2007) and dorsolateral PFC (DLPFC; Friese, Binder, Luechinger, Boesiger, & Rasch, 2013; Hedgcock, Vohs, & Rao, 2012), increased activity in reward- or emotion-related brain regions, and reduced functional connectivity between reward or emotion-related regions and systems involved in top-down control (Wagner, Altman, Boswell, Kelley, & Heatherton, 2013; Wagner & Heatherton, 2013).

Depletion is hypothesized to impact self-regulation through these dynamics, but premature or more profound depletions of self-regulatory ability may occur as a result of proinflammatory cytokine activity. Cytokines, for example, can alter the function of brain regions that are thought to underpin self-regulatory depletion. More specifically, acute inflammatory challenges, such as typhoid vaccination, can cause an exaggerated DLPFC response when individuals engage in tasks that require self-control (Harrison, Brydon, Walker, Gray, Steptoe, Dolan et al., 2009). Because the DLPFC plays a central role in self-regulation and self-regulatory fatigue, excessive DLPFC activity may lead to a more pronounced self-regulatory depletion on subsequent tasks involving self-regulation. Consistent with this possibility, prior research has shown that DLPFC activation during a task requiring self-control mediates impairment on subsequent tasks requiring self-control, with greater activation during the first task predicting greater self-regulatory impairment on the second task (Richeson et al., 2003). Thus, cytokine-induced exaggerations in DLFPC activity during a self-control task

may lead to quicker and more pronounced self-regulatory depletion. In humans, acute inflammatory challenges have also been shown to reduce functional connectivity between the medial PFC (mPFC) and brain regions involved in mood and emotion (Harrison, Brydon, Walker, Gray, Steptoe, & Critchley, 2009), similar to that seen in self-control depletion (Wagner & Heatherton, 2013). Putting these links together, then, data suggest that proinflammatory cytokine activity may be one mechanism underlying quicker and more pronounced self-regulatory depletion.

Interestingly, an acute inflammatory challenge has been shown to reduce resting glucose metabolism in the ACC in humans (Hannestad et al., 2012), which is a brain region critically important in self-regulation that shows reduced activity during depletion (Inzlicht & Gutsell, 2007). As previously stated, a major theory of self-regulatory depletion is that focal reductions in glucose availability mediate effects of self-regulatory depletion (Baumeister, 2014). Because cytokine expression and production increases following self-regulatory depleting tasks (Brydon et al., 2005), these results suggest that cytokines may not only contribute to quicker and more pronounced depletion but that they may also alter glucose metabolism in ways that impair self-regulation. The data are thus consistent with glucose-dependent models of self-regulatory depletion but extend this work in an important new direction by identifying cytokines as a potential proximal biological mechanism that plays a key role in altering glucose metabolism in the ACC.

In sum, existing data provide initial evidence suggesting that proinflammatory cytokines could contribute to a quicker or more pronounced self-regulatory depletion by altering neural activity in key brain regions. At the same time, we are not aware of any studies that have directly tested this mechanistic model to date, and alternative directional effects are possible. Rather than cytokine activity contributing to quicker and more pronounced self-regulatory depletion, for example, it is possible that cytokine activity alters processing in brain regions supporting self-regulation, which may in turn impair self-regulation. Additional research is thus needed to examine the nature and directionality of these effects and to further investigate whether self-regulatory depletion exists as it has been conceptualized to date.

Motivation and reward

Like self-regulatory beliefs and depletion, immune system activity may alter motivation and reward processing in ways that impair self-regulation. In recent years, substantial attention has also been paid to the ways in which motivation affects self-regulation. Self-regulatory failure can be overcome by increasing motivation, which indicates that inadequate motivation may be one of the critical components of self-regulatory failure (Baumeister & Vohs, 2007; Muraven & Slessareva, 2003). Reward has also been studied in the context of self-regulation. Perhaps counterintuitively, reward expectancy appears to bolster self-control in some situations (Schmidt, Lebreton, Cléry-Melin, Daunizeau, & Pessiglione, 2012), such as when expecting a reward that requires effort to obtain increases one's motivation to engage in self-regulation. Similarly, tasks that are interesting or have been previously rewarded require less self-regulatory resources and may even replenish those resources despite task demands (Goto & Kusumi, 2013; Thoman, Smith, & Silvia, 2011). These findings are qualified, though, by other data showing that the reward value of stimuli opposite from long-term goals, such as the reward value of a piece of cake when trying to lose weight, can drive self-regulatory failure (Wagner et al., 2013). Thus, although the relation between reward sensitivity and self-regulation is not as linear as is motivation, reward sensitivity can be beneficial for self-regulation insofar as it influences one's motivation to engage in self-regulation.

Importantly, motivation and reward sensitivity are both heavily influenced by proinflammatory cytokines. Some of the first behavioral effects observed along these lines involved the finding that proinflammatory cytokines induce anhedonia and relatively quick reductions in motivation and socially affiliative behavior, which are now included in the general constellation of behaviors known as *sickness behaviors* in both human and nonhuman animals (Dantzer & Kelley, 2007; Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Maier & Watkins, 1998). In addition, experimentally inducing an inflammatory state strongly reduces motivation in nonhuman animals (e.g., Haba et al., 2012) and reduces neural responses to motivationally salient stimuli in humans (Harrison, Cercignani, Voon, & Critchley, 2015). As such, the consensus is that sickness behaviors reflect a motivational state, wherein motivation is reduced to facilitate recovery from physical injury or infection (Dantzer & Kelley, 2007). This lack of motivation bears directly upon self-regulation, as self-regulatory failure often occurs from a lack of motivation to maintain goals (Heatherton & Wagner, 2011; Wagner et al., 2013).

A corollary of decreased motivation is decreased sensitivity to pleasure or reward. And indeed, inflammatory activity also impairs sensitivity to reward. Inducing an inflammatory state in mice, for example, reduces their pleasure-seeking behavior (Markou & De La Garza, 2005). Similarly in humans, an experimentally induced inflammatory state has been shown to decrease neural responding to reward in the ventral striatum, which is a brain region that mediates experiences of pleasure (Eisenberger, Berkman et al., 2010). As mentioned

previously, research has shown that decreased sensitivity to reward could either help self-regulation or contribute to its failure. If a goal relies on reward as an incentive, such as losing weight to look good in a new pair of pants, decreasing sensitivity to reward may impair self-regulation. Conversely, if a goal does not rely on reward for motivation, such as losing weight to avoid health problems, then decreasing reward sensitivity will leave those regulatory processes unaffected and may even guard against self-regulatory failure by decreasing the reward value of goal-opposing stimuli. In sum, then, inflammatory activity may impair self-regulation by reducing motivation and may either help or hinder self-regulation by decreasing sensitivity to reward.

Appraisals of stress

Immune system activation may also alter appraisals of stress, thereby impairing self-regulation. Perhaps the most commonly discussed cause of self-regulatory failure is exposure to stress. Although stress does not impair all cognitive processes (e.g., Shields, Lam, Trainor, & Yonelinas, 2016), failures of self-regulation are known to occur following several different types of stress, including difficult social interactions (Finkel et al., 2006; Vohs et al., 2005), social exclusion (Baumeister, DeWall, Ciarocco, & Twenge, 2005), academic stress (Oaten & Cheng, 2005), and emotional distress (Tice, Bratslavsky, & Baumeister, 2001). It should be noted, however, that the effects of stress on self-regulatory abilities are more nuanced than is often presented. For example, sex, biological and emotional reactivity to stress, and individual differences in susceptibility and resilience to stress can all moderate or attenuate the impairing effects of stress on self-regulatory abilities (Elzinga & Roelofs, 2005; Schoofs, Pabst, Brand, & Wolf, 2013; Shields, Moons, Tewell, & Yonelinas, 2016; Shields, Sazma, & Yonelinas, 2016; Sprague, Verona, Kalkhoff, & Kilmer, 2011). Still, reduction in self-regulatory abilities that occur following stress can create a cyclical pattern wherein exposure to stress impairs self-regulation, which in turn leads to further occurrences of stress and impairments in self-regulation (Arnsten, 2009; see also Hammen, Kim, Eberhart, & Brennan, 2009). This may potentially explain why stress is such a strong predictor of failures in self-regulation (Muraven & Baumeister, 2000). Conversely, appraising life events as stressful is a key factor shaping the effects of different life events on health (Haley, Levine, Brown, & Bartolucci, 1987; Slavich, 2016; Slavich & Cole, 2013).

Although inflammatory activity has not been shown to contribute directly to the occurrence of stressful life events, research has shown that inflammation can alter experiences of the social world and individuals' appraisal of stressors. In a sample of chronically stressed women, for example, circulating levels of proinflammatory cytokines were found to predict greater engagement of brain regions that process the affective valence of stimuli—specifically, the subgenual ACC (sACC) and parts of the orbitofrontal cortex (OFC)—in response to grief; moreover, neural activity in these regions was associated with behavioral indicators of grief (Lane, Wager, O'Connor, Irwin, & Wellisch, 2009). However, it should be noted that mere associations of cytokines with neural activity in regions related to appraisals and perceptions of stress do not necessarily imply that cytokines themselves alter these experiences of stress. More pointedly, experimentally inducing an inflammatory response triggers significant increases in self-reported feelings of social isolation, demonstrating that inflammation is intimately involved in contributing to negative appraisals of events (Eisenberger, Inagaki et al., 2010; see also Reichenberg et al., 2001). To summarize, then, experiences of stress may impair self-regulatory abilities (S. Cohen & Lichtenstein, 1990; Crescioni, 2012; Duckworth, Kim, & Tsukayama, 2012; Sprague et al., 2011), and proinflammatory cytokine activity contributes to greater experiences of stress (Eisenberger, Inagaki et al., 2010; Hannestad, DellaGioia, Ortiz, Pittman, & Bhagwagar, 2011). Proinflammatory cytokine-mediated alterations in appraisals of stress may thus play a role in impairing self-regulation.

Executive function

Perhaps the most important psychological resource necessary for effective self-regulation is executive function (Hofmann, Schmeichel, & Baddeley, 2012). There is some debate about whether executive function is distinct from (but supports) self-regulation or whether executive function and self-regulation are essentially the same construct (Diamond, 2013; Hofmann et al., 2012). For the present discussion, though, these constructs may be thought of as the same. For example, a common task assessing executive function, the Stroop task, is also commonly used to assess self-regulation. Taking a stance on this particular debate is not critical for the present discussion, although it is important to recognize that impairment in executive function indicates impairment in self-regulation.

Executive function refers to higher cognitive processes that enable flexible, stable, goal-directed, and adaptive thought, and it is crucial for appropriate functioning in contemporary society. Factor analysis studies have indicated that there are three primary, interrelated, yet slightly different executive functions—namely, updating, inhibition, and set shifting (Miyake et al., 2000). Updating is the active and intentional monitoring and updating of information, inhibition is the process of overriding prepotent responses or inhibiting impulses/distractions, and set-shifting refers to the ability to cognitively change one's

mental set or focus on tasks. Executive function abilities arise from the complex interactions of the PFC, other cortical structures, and subcortical structures (Alvarez & Emory, 2006; Heyder, Suchan, & Daum, 2004); still, prefrontal structures do seem to have some primacy (Mansouri, Tanaka, & Buckley, 2009). As the control processes of self-control are dependent upon the PFC, it is not surprising that these three basic executive functions (i.e., working memory, response inhibition, and mental set shifting) enable self-regulation (Hofmann et al., 2012). Working memory permits an active representation of goals and goal-relevant attentional control, inhibition enables the ability to respond to a given stimulus while overriding impulses or habits, and task-switching allows for flexible switching between different ways of meeting the same goal (Hofmann et al., 2012). The interrelated aspect of the three executive functions allows them to be usefully conceptualized as supporting a single construct and thus proves pragmatic for the purposes of this review. Numerous studies have been conducted examining how cytokines influence executive functions, and we now review this work, focusing on four types of studies: cross-sectional and longitudinal association studies, cytokine administration studies, experimental studies involving the induction of acute inflammation, and genetic studies.

Cross-sectional and longitudinal associations of cytokines with executive function. Our understanding of how inflammatory activity influences executive function is gradually becoming clearer. Impairments in executive function in healthy individuals have been associated with several mediators of inflammatory activity, including the cytokines interleukin (IL)-1β (Simpson et al., 2013; Trompet et al., 2008), IL-6 (Marsland et al., 2015; Marsland et al., 2006; Simpson et al., 2013; Trollor et al., 2012), TNF-α (Jefferson et al., 2011), and IL-12 (Trollor et al., 2012), as well as the markers of systemic inflammation haptoglobin (Teunissen et al., 2003) and C-reactive protein (CRP; Marsland et al., 2015; Wersching et al., 2010). In addition, a variety of cytokines and markers of systemic inflammation have been associated with brain alterations that negatively impact executive function in humans. These brain alterations include reduced total brain white matter tract integrity (Marsland, Krajina, & Gianaros, 2012), reduced frontal lobe white matter tract integrity (Wersching et al., 2010), white matter hyperintensities, total brain gray matter atrophy (Satizabal, Zhu, Mazoyer, Dufouil, & Tzourio, 2012), PFC gray matter atrophy, and hippocampal gray matter atrophy (Marsland, Gianaros, Abramowitch, Manuck, & Hariri, 2008), thus supporting the abovementioned associations between cytokines and poor executive function. It is impossible to establish a causal effect from these correlational data alone; however, the aforementioned effects have been found to be significant after controlling for multiple potentially confounding factors, including age, body mass index, and smoking status. In addition, many of these studies longitudinally examined associations between these factors and found that higher levels of proinflammatory cytokines at baseline predict lower executive function over time (e.g., Jefferson et al., 2011; Teunissen et al., 2003; Trompet et al., 2008).

One longitudinal study that examined associations between cytokines and executive function over time attempted to partial out other components of the stress response by investigating perioperative immune system activity during cardiac surgery and then examining longitudinal associations between inflammatory activity and postoperative neurocognitive decline (Ramlawi et al., 2006). Although anesthesia can cause cognitive impairment, this study may help to explain why this cognitive impairment occurs. In particular, the study found that increases in CRP, IL-1β, and IL-10 during surgery were all significantly associated with neurocognitive decline, which suggests that longitudinal associations between inflammatory markers and impairments in executive function could be causal in nature. These data thus provide evidence that inflammatory activity is strongly associated with, and also increases prior to, executive function impairments, which impair self-regulation.

Administration of cytokines and executive function. Although the aforementioned correlational and longitudinal studies do not themselves establish that inflammatory activity impairs executive function, they do provide evidence that at least some cytokines may contribute to executive function impairments. Other evidence comes from studies in which cytokines have been carefully administered for medical purposes. For example, multiple studies have found that the use of cytokine therapy for medical treatment, such as exogenous administration of IL-2, leads to deficits in both cognition and executive function in humans (Capuron, Ravaud, & Dantzer, 2001; Meyers & Abbruzzese, 1992; Meyers, Valentine, Wong, & Leeds, 1994; Pavol et al., 1995; cf., Fontana et al., 2007). Research has also shown that cytokine therapy results in functional deficits in the frontal lobes (Juengling et al., 2000; Meyers et al., 1994), although the relation of these neurobiological effects to executive function has only been examined in one study to date (Meyers et al., 1994). These studies provide evidence that excessive peripheral inflammatory activity contributes to cognitive deficits. At the same time, additional research is necessary to determine whether extant alterations in the immune systems of individuals receiving cytokine therapy modulate the neurocognitive effects seen following cytokine administration.

Experimental inductions of acute inflammation and executive function. Despite the potential limited generalizability of studies employing clinical cytokine administration, a small number of studies have investigated executive function in conditions of experimentally induced acute inflammatory and glucocorticoid activity via endotoxin injection in otherwise healthy individuals. Generally, findings have been mixed. Two small studies (20–24 participants) failed to find support for the idea that endotoxin injection impaired working memory, which is one component of executive function (Grigoleit et al., 2010; Reichenberg et al., 2001). An additional small study (i.e., 10 participants) found that endotoxin administration actually increased working memory (O. Cohen et al., 2003), while another small study found that endotoxin administration either impaired or enhanced cognition and working memory depending upon the dose of endotoxin given (Grigoleit et al., 2011). Although human studies examining the effects of subclinical cytokine administration on executive function are rare, multiple rodent studies have found that endotoxin injection induces deficits in working memory (e.g., Chen et al., 2008; Sparkman et al., 2006). Notably, one of these rodent studies found that IL-6 was necessary for deficits in working memory (Sparkman et al., 2006).

These mixed findings may be due in part to the fact that endotoxin, which induces acute inflammatory activity, also leads to increased circulating cortisol, which has anti-inflammatory properties. Moreover, several recent human studies have suggested that increases in cortisol may enhance executive function (Henckens, van Wingen, Joëls, & Fernández, 2011; Schwabe, Höffken, Tegenthoff, & Wolf, 2013; Shields et al., 2015) and may be responsible for improving cognitive performance under endotoxin (van den Boogaard et al., 2010). Indeed, exogenous administration of cortisol leads to enhancements in working memory performance during the time at which working memory testing is done following endotoxin administration (Shields et al., 2015). Consistent with these findings, the only study conducted to date that assessed executive function and also employed a vaccine that does not increase cortisol obtained different results than prior studies, although it should be noted that the task employed in this study primarily assessed inhibition, not working memory (see Brydon, Harrison, Walker, Steptoe, & Critchley, 2008). Nevertheless, even with a total sample of 16 participants, this study found that reaction times on the Stroop task varied as a function of IL-6 levels, with higher IL-6 levels predicting slower reaction times. There was also a tendency for participants receiving the typhoid vaccine in this study to commit more errors on incongruent Stroop trials, which indicates poorer executive function, but the study's small sample size limited the statistical power available to detect significant effects. Given these findings, more research is clearly needed to understand the effects of experimentally induced inflammatory activity on executive function and self-regulation. These studies could use an improved paradigm of inducing acute inflammatory activity—such as one that does not up-regulate cortisol—but they will also need to employ larger sample sizes.

Genetic differences in immune system genes and executive function. Although genetic studies cannot elucidate cause, they provide a unique opportunity for studying associations between inflammatory activity and executive function insofar as they can help isolate effects of proinflammatory cytokines that are not entangled with the effects of stress, cortisol, illness, or behaviors that up-regulate inflammation. One cytokine that has been examined in neurogenetic studies of humans is IL-1β. In this context, a genetic variant that results in reduced expression of an enzyme converting IL-1β to its active form in humans—namely, the gene that codes for the IL-1β-converting enzyme (ICE)—has been found to predict lower levels of circulating IL-1β and also longitudinally predict better executive function compared to a genetic variant that is associated with higher levels of ICE and IL-1β (Trompet et al., 2008). Similarly, a genetic variant in the promoter region of the human *IL-1*β gene that results in increased IL-1β has been found to be associated with reduced working memory in healthy elderly males (Tsai et al., 2010) and females (Sasayama et al., 2011). These last two results may be explained by the fact that this genetic variant predicts reduced functional connectivity between neural regions involved in executive function, including the anterior midcingulate cortex, multiple areas in the PFC, and the putamen (Tu et al., 2013). However, additional research is needed to examine whether activity in these brain regions mediates the effects of variation in the human *IL-1*β gene on executive functions.

In addition to this research, one population-based study investigating the relation between cognitive factors and various cytokine-related genetic polymorphisms including *IL-1*β in elderly individuals did not find associations between *IL-1*β polymorphisms and executive function (Marioni, Deary, Murray, Fowkes, & Price, 2010). However, this study only looked at elderly Scottish citizens with asymptomatic atherosclerosis, and it is possible that this null effect is due to subtle effects of atherosclerosis on cognition or undiscovered and possibly culturally related confounds. In general, studies suggest that IL-1β is associated with poorer executive functioning, independent of other biological dysregulation, which indicates that IL-1β contributes to impairments in self-regulation.

A few studies have examined associations between variation in genes coding for IL-6 and executive function in humans, and these studies also reveal conflicting

results. The Scottish elderly population-based study referenced above found no association between genetic polymorphisms related to IL-6 and executive function abilities (Marioni et al., 2010), although that study only examined individuals with atherosclerosis. Additionally, half of the sample was instructed to regularly take aspirin, which can influence cytokine activity. In contrast, a larger population-based study of elderly Americans found that levels of IL-6 and the genetic variant that influences IL-6 production (i.e., the *IL-6* −174 CC genotype) predicted poorer executive function and Stroop task performance (Mooijaart et al., 2013). These studies should be interpreted with caution, as the reasons for the conflicting results are not entirely clear. Nevertheless, the studies provide initial support for the notion that genetic variation in the gene that codes for IL-6 is associated with deficits in executive function and may thus impair self-regulation.

Compared to the limited number of genetic studies on genes that code for IL-1β and IL-6, several studies have examined how genetic factors involved in TNF-α production relate to cognitive function in humans. Variations in a single nucleotide polymorphism (SNP) in the human *TNF-α* gene (AA/AG/GG) leads to differing transcriptional activity, with the −308A allele conferring a stronger transcriptional activity than the −308G allele, likely resulting in higher TNF-α levels for individuals with the AA or AG genotype (Hajeer & Hutchinson, 2001; Wilson, Symons, McDowell, McDevitt, & Duff, 1997). This SNP has also been found to result in changes in cognitive control. In particular, individuals with the AA/AG genotype exhibit both behavioral and neural evidence of enhanced attentional processes, but reduced conflict processing and action selection abilities, relative to their GG counterparts (Beste, Baune, Falkenstein, & Konrad, 2010). Similarly, another study found that individuals with the AA/AG genotype exhibit better response inhibition but reduced error processing functions, when compared with their GG counterparts (Beste et al., 2011). In sum, these studies have demonstrated that genetic variation that leads to higher circulating levels of TNF-α enhances attention and inhibition but impairs error processing, conflict monitoring, and action selection abilities. Thus, although *TNF-α* influences executive functions involved in self-regulation, the association between *TNF-α* and executive function—and thus self-regulation—is more complex than the association between self-regulation and *IL-6* or *IL-1β*.

In sum, data from several sources, including correlational, longitudinal, experimental, and genetic studies, converge to suggest that heightened proinflammatory cytokine activity contributes to poorer executive function. Each of these lines of research is not completely persuasive by itself. When considered together, though, they begin to provide a stronger case indicating that cytokine-related deficits in executive function are an important factor underlying links between the immune system and impaired self-regulation abilities.

Summary of links between cytokines and self-regulation

To summarize, cytokines appear to play a role in influencing several processes that are important for self-regulation. These processes include beliefs about self-regulation, self-regulatory depletion, reward sensitivity and motivation, appraisals of stress, and executive function. In each of these instances, more proinflammatory cytokine activity appears to be related to less self-regulatory ability. Importantly, cytokines may be bidirectionally related to beliefs about self-regulation—that is, they may be both modulated by self-regulatory beliefs and also play a role in shaping such beliefs. Similarly, cytokine activity alters neural processes in ways that appear to exacerbate self-regulatory depletion. In addition, cytokines influence both reward sensitivity and motivation, with cytokine activity reducing motivation and producing anhedonia. Cytokines also alter neurocognitive appraisals of stress, illustrating another pathway through which cytokines may impair self-regulation. Finally, excessive cytokine activity appears to impair executive function. When considered together, then, these findings provide multiple sources of support for the formulation that increased cytokine activity can impair multiple self-regulatory processes.

An Immunologic Model of Self-Regulatory Failure

Based on these findings, we propose an integrated, multilevel model of self-regulation, inflammation, and health, which describes how immunologic factors may influence self-regulation and how self-regulation may in turn shape human health and behavior. According to this *immunologic model of self-regulatory failure*, elevations in proinflammatory cytokine activity can occur as a result of several factors, including bacterial or viral infection, physical injury, poor diet or sleep, or psychological stress. These cytokines can be released centrally in the brain, but even when elevated in peripheral tissue, there are several mechanistic pathways (e.g., involving active and passive transport, and the SAM and HPA axes) by which peripheral inflammation can communicate with the central nervous system to alter neural activity in brain regions that are critical for self-regulation, such as the DLPFC and ACC. Altered neural activity in these brain systems in turn impairs self-regulatory capacity. These dynamics exert short-term effects on self-regulation. However, long-term

changes can also develop. Over repeated exposure to inflammatory triggers, for example, glucocorticoids lose their ability to effectively down-regulate inflammation (i.e., glucocorticoid resistance) and adequately regulate immune system activity. The resulting dysregulation leads to sustained increases in proinflammatory cytokine activity and alterations in immune-related gene expression. As discussed earlier, several pathways link aberrant immune system activity with functional and structural changes in the brain, including reduced prefrontal cortical volume. These changes can in turn have numerous cognitive and behavioral consequences that predispose a person to experience self-regulatory failure. There are also several neurocognitive and behavioral pathways that give the immune system the ability to influence self-regulation, including personal beliefs about self-regulation, self-regulatory depletion, reward sensitivity and motivation, executive function, and perceptions of stress. These pathways are illustrated in Figure 2.

Over brief periods of time, increases in immune system activity and decrements in self-regulatory ability will likely have only limited effects on health. As increases in inflammation and difficulties self-regulating become more frequent or prolonged, however, immune-related health problems and disease states can eventually arise. A primary driver of these effects involves the fact that inflammatory activity, self-regulatory problems, and the pathways linking these factors can become mutually self-promoting over time. For example, inflammation can lead to failures in self-regulation that cause individuals to choose food options or forego exercise routines in a manner that leads to more adipose tissue, which is pro-inflammatory (Fantuzzi, 2005). Likewise, increases in pro-inflammatory cytokine activity may heighten perceptions of stress, leading to further increases in inflammation and neural sensitivity to threat, and the evolution of a positive feedback loop in the cytokine-neural threat network that can have lasting effects on self-regulatory ability and health (Slavich & Irwin, 2014). From this perspective, a person's biological milieu, psychosocial life history, thoughts, and behaviors all influence one another and interact over time to shape self-regulatory capabilities and lifespan health.

One benefit of this immunologic model of self-regulatory failure is that it may have broad explanatory power. First, it may explain why self-regulatory failure occurs following stress and prior acts of self-regulation, as both stress (Steptoe, Hamer, & Chida, 2007) and self-regulation (Brydon et al., 2005; Brydon, Edwards, Mohamed-Ali, & Steptoe, 2004) increase circulating levels of proinflammatory cytokines. Second, it may explain why individuals with certain medical illnesses involving the immune system or inflammation—such as psoriasis, diabetes, hypertension, and arthritis—have poorer self-regulatory abilities (Brands et al., 2007; Dick, Eccleston, & Crombez, 2002; Fortune et al., 2003; Marek, Placek, & Borkowska, 2011; Saxby, Harrington, McKeith, Wesnes, & Ford, 2003; Schillerstrom, Horton, & Royall, 2005; van den Berg, De Craen, Biessels, Gussekloo, & Westendorp, 2006; Vicario, Martinez, Baretto, Casale, & Nicolosi, 2005). Similarly, the model may help explain why certain TNF-α inhibitors enhance executive function (Tobinick & Gross, 2008) and why several psychiatric disorders, including depression and ADHD, are frequently characterized by both elevated inflammatory activity and difficulties in self-regulation (Oades, Dauvermann, Schimmelmann, Schwarz, & Myint, 2010; Slavich, O'Donovan, Epel, & Kemeny, 2010). Finally, this model may help explain why rates of self-regulatory failure are elevated under conditions of chronic stress, even in the absence of acute stress (Hammen et al., 2009), due in part to the fact that elevations in inflammation can become self-promoting over time (S. Cohen et al., 2012; Slavich & Cole, 2013).

Looking forward, this research may provide clinicians with new ideas for how to treat medical problems that are influenced by both self-regulatory difficulties and inflammation, such as obesity. Obesity is a prototypic example because it is a leading public health problem (Lobstein, Baur, & Uauy, 2004) that is characterized by both chronic inflammation (Cazettes, Cohen, Yau, Talbot, & Convit, 2011) and persistent deficits in self-regulation (Wing, Tate, Gorin, Raynor, & Fava, 2006) that include poorer executive function and worse emotion regulation (Blanco-Gómez et al., 2015; Clyne & Blampied, 2004; Cook et al., 2014; Coppin, Nolan-Poupart, Jones-Gotman, & Small, 2014; Zijlstra et al., 2012). Because obese individuals have more adipose tissue, which is a storehouse for proinflammatory cytokines (Tilg & Moschen, 2006), the model outlined in this review suggests these individuals would typically have greater difficulties with self-regulation, which challenges their ability to make healthy food choices and adhere to a prescribed diet. We describe obesity here only as an example disease condition in which inflammatory activity may both contribute to, and be caused by, the disorder, but others exist, including (for example) Type 2 diabetes, tobacco-related diseases, and hypertension. Ultimately, to the extent that inflammation-related difficulties in self-regulation help sustain disease states like obesity, inflammation may be an important target for pharmacologic interventions aimed at improving self-regulation and lessening disease symptoms.

Cytokine-specific effects on self-regulation

The empirical precedent for this model comes from the large body of research on inflammation and sickness behavior, which has demonstrated that increased inflammatory

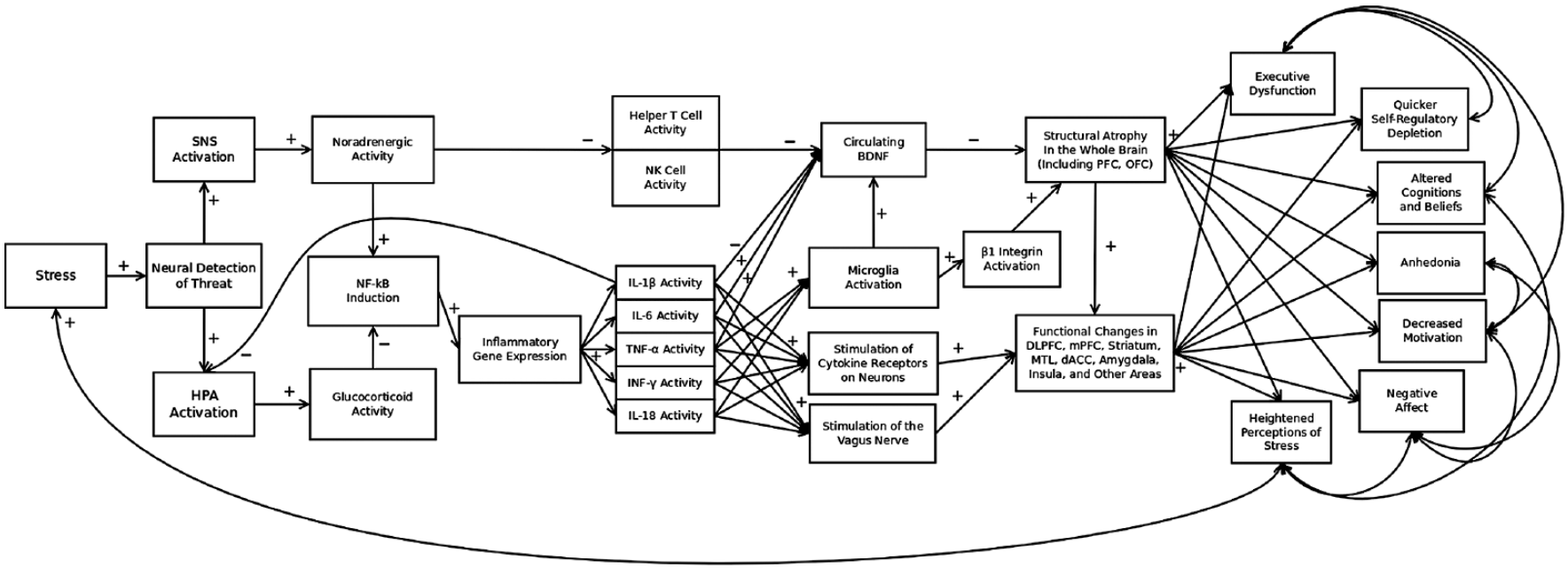

Fig. 2. Immunologic model of self-regulatory failure. Activation of the immune system is hypothesized to induce biological changes that alter neurocognitive and other biological processes that underpin self-regulation, leading to decrements in self-regulation. In particular, after a social-environmental stressor is neurally detected, the HPA and SAM axes increase in activity, leading to a decrease in natural killer (NK) cell and helper T-cell activity, and an increase in the release of numerous proinflammatory cytokines from immune cells. These immunologic dynamics then directly and indirectly influence neuronal activity, contributing to structural and functional changes in brain regions that support self-regulation. These neural alterations in turn produce an impaired self-regulatory phenotype, which leads to a decreased ability to successfully navigate stressful situations, ultimately increasing the likelihood of experiencing more stress in the future.

activity can have a variety of neurobehavioral effects on humans (e.g., Dantzer & Kelley, 2007; Dantzer et al., 2008; Maier & Watkins, 1998; Markou & De La Garza, 2005; Raison et al., 2006). Although sickness behaviors may influence some outcomes that are associated with poor self-regulation such as lack of motivation, sickness behaviors do not explain all of the inflammation-related deficits in self-regulation that are described in the model. If sickness behaviors were the primary mechanism linking proinflammatory cytokines and worse executive function, for example, then proinflammatory cytokine activity should be associated with worse *overall* cognitive performance, but this is not the case (Jefferson et al., 2011; Marsland et al., 2006; Trompet et al., 2008).

In addition, at least five lines of research presently support the notion that proinflammatory cytokines exert several specific effects on self-regulatory processes. First, peripheral administration of the proinflammatory cytokine IL-2 in humans selectively impairs the self-regulatory abilities of executive function and planning without influencing cognitive abilities that are unrelated to self-regulation (Capuron et al., 2001). Second, although circulating levels of the proinflammatory cytokines IL-6, IL-1β, and TNF-α are inversely associated with executive function, they are not associated with processes that are unrelated to self-regulation, such as visual immediate memory (Marsland et al., 2006; Trompet et al., 2008) and language processing (Jefferson et al., 2011; Trollor et al., 2012). Third, acute inflammatory challenges including endotoxin administration and typhoid vaccination do not influence processes that are unrelated to self-regulation, such as procedural memory (Harrison, Doeller, Voon, Burgess, & Critchley, 2014). Fourth, several studies have shown that it is specifically proinflammatory cytokines (and not other types of cytokines) that appear to influence self-regulatory abilities. Administration of antiviral cytokines such as interferon-α, for example, has no effects on executive function, even though antiviral cytokine therapy appears to decrease processing speed (Amodio et al., 2005; Capuron et al., 2001; Fontana et al., 2007). Finally, proinflammatory cytokines have some cognitive-behavioral effects that are more distantly related to self-regulation but still specific in nature. For example, proinflammatory cytokines can impair hippocampus-dependent delayed memory (Harrison et al., 2014), which is important for remembering personal goals and action steps that are necessary for self-regulation.

In sum, we do not suggest that proinflammatory cytokines are the *sole* biological cause of self-regulatory failure. Indeed, as reviewed above and as depicted in Figure 2, a multitude of other biological factors are also likely implicated (e.g., glucose, cortisol levels, etc.). However, proinflammatory cytokines do appear to play a very important and previously unappreciated role in self-regulatory abilities, and they also appear to exert several effects that are specific to self-regulation. We thus suggest that this immunologic model of self-regulatory failure may help shed new light on the biological bases of self-regulation in humans.

Testable predictions

Several testable predictions can be derived from this model. For example, if inflammatory cytokines exacerbate self-regulatory depletion, then the effects of self-regulatory depletion should be minimized in individuals who take a drug or supplement that reduces proinflammatory cytokine activity, such as a prescribed TNF-α inhibitor or the over-the-counter supplement stinging nettle (Riehemann, Behnke, & Schulze-Osthoff, 1999; Teucher, Obertreis, Ruttkowski, & Schmitz, 1996). Similarly, if inflammation reduces individuals' motivation, then taking an anti-inflammatory drug or supplement should increase motivation and enhance self-regulation abilities.

It is important to note that there are alternative interpretations of the findings reviewed here. For example, the physiologic stress response, which helps mobilize the body's resources to avoid physical harm and preemptively combat infection, could take up available glucose, thereby leaving less glucose available for proximal acts of self-control or self-regulation. Similarly, stress may require behavioral responses that utilize self-regulation—which may or may not be triggered by immune system activation—and in turn deplete a person's willpower. Importantly, however, these alternative interpretations of the available data are also testable. If immune system activation can impair self-regulation even when glucose is replenished, for example, then the idea that reducing local glucose is the sole mechanism through which inflammatory activity impairs self-regulation would be less parsimonious than the model presented here. Ultimately, these alternative theoretical conceptualizations of available data provide fruitful opportunities for future research.

Developmental Perspective on Inflammation, Self-Regulation, and Health

The above description of this immunologic model of self-regulatory failure presents a temporally static view of inflammation, self-regulation, and health. These interactions can also be viewed as developing over time, however, resulting from a complex interplay between stress exposure and ensuing changes in self-regulation and health (see Fig. 3). Moreover, these dynamics can have potentially enormous effects on behavior and health over long periods of time. For example, individuals experiencing early adversity, including maltreatment, abuse, or

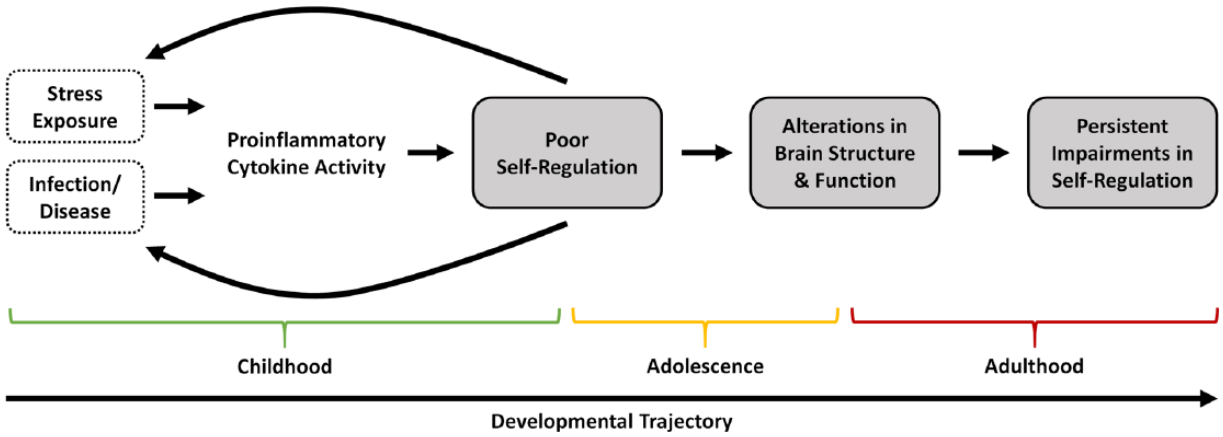

Fig. 3. Immunologic model of self-regulatory failure from a developmental perspective. Exposure to stress, infection, and disease in early life increases proinflammatory cytokine activity, which decreases an individual's self-regulatory ability. Poor self-regulation can in turn feed back to cause stress generation behaviors (e.g., saying a hurtful thing to a friend or loved one during an argument, not arriving on time to work) and poor health behaviors (e.g., not completing a course of antibiotics, not washing one's hands), which lead to greater exposure to stress and disease. As these dynamics continue over childhood and adolescence, more stable differences in brain structure and function can develop that ultimately produce persistent impairments in self-regulation in adulthood.

neglect or who are otherwise chronically or severely stressed, may exhibit structural and functional changes in neural systems that support self-regulation, as well as changes in stress-related biological axes (e.g., the HPA and SAM axis) that lead to persistent immune system dysregulation and related self-regulation difficulties. These difficulties can in turn cause social and behavioral problems, including conflictual relationships and problems at work or school, that engender additional life stressors and reinforce threat-related biases in neural and immune system functioning. Recent population-based studies have shown that self-regulatory abilities are crucial for interpersonal, educational, economic, and career success (Moffitt et al., 2011; see also Diamond, 2013). Consequently, over the long run, these effects may also become embedded in individuals' lives in the form of poorer social relationships, educational attainment, economic achievement, or professional development.

In addition to the cyclical nature of the effects described above, the influence of inflammatory activity on self-regulation may be amplified during sensitive or critical periods of development. Early childhood and adolescence are times of PFC maturation, but they are also times of greater risk for inflammatory activity because of a nascent and developing immune system and potential stress from a possible chaotic home environment. Because inflammatory activity appears to contribute to structural changes in the PFC among other brain regions (Marsland et al., 2015), it is possible that inequalities that predispose certain individuals to develop a more proinflammatory phenotype may have longer lasting health and behavioral consequences for those individuals.

As these developmental aspects of the model improve over time, its explanatory power may increase. At present, we believe the framework may help explain aspects of how socioeconomic disparities in health arise and widen over the lifespan. For example, the stress of low socioeconomic status during childhood is known to contribute to elevated inflammatory activity that can impair self-regulation, which is crucial for academic achievement (John-Henderson et al., 2014). This discrepancy in self-regulation may in turn affect individuals' ability to reach their fullest academic potential, which can limit their lifelong earning potential and increase their likelihood of remaining in a lower socioeconomic position. The stress associated with low socioeconomic status may also activate inflammatory processes that impair one's self-regulatory abilities, which underlie successful coping with stress (Vohs & Baumeister, 2011; see also Shields, Kuchenbecker, Pressman, Sumida, & Slavich, 2016). This reduced ability to cope, coupled with the increased stress burden that accompanies being in a lower socioeconomic position, may in turn promote immune system dysregulation that degrades individuals' ability to fight off infections and increases their likelihood of developing immune-related disorders. If this working model is substantiated, the framework could help explain how inflammation influences self-regulatory abilities that structure health disparities that are evident across individuals of differing socioeconomic positions.

Pressing issues and future directions

We believe that the model outlined above represents an important new perspective on how cytokines are involved in self-regulatory failure. At the same time, there are several issues that require future clarification. The most immediate issue involves the need to better understand

how proinflammatory cytokines interact with other potential biological mediators or moderators of self-regulation. Currently, no research has explicitly examined the conjoint influences of cytokines, cortisol, and glucose on self-regulatory processes. However, studies of endotoxin administration provide an opportunity to study conjoint influences of cytokines and cortisol on self-regulatory abilities, given that endotoxin administration strongly increases both cytokine and cortisol production (e.g., van den Boogaard et al., 2010). As reviewed above, these paradigms have generally failed to find effects of endotoxin administration on executive functions, indicating that cortisol may help prevent cytokine-induced decrements to executive functions in endotoxin administration studies (Shields et al., 2015; see also Weckesser, Alexander, Kirschbaum, Menningen, & Miller, 2016). Ultimately, future studies that experimentally manipulate cytokines, cortisol, and glucose within the same study design are necessary to elucidate the additive and interactive effects that these three mechanisms have on self-regulation.

A second important future direction is to extend this work by employing different inflammatory challenges. As reviewed above, for example, only a few studies have directly manipulated acute inflammatory activity in humans, which is a limitation of the extant literature. More importantly, many of these manipulations, such as endotoxin administration, also affect cortisol levels. It will thus be important for future studies to examine the effects of inflammatory challenges that do not influence cortisol (e.g., typhoid vaccination; Brydon et al., 2008).

A third important issue involves determining the reasons (adaptive or otherwise) for why proinflammatory cytokines affect self-regulation. To address this issue, researchers could draw from the sickness behavior literature. This work has often suggested that the cognitive and behavioral effects of cytokines are an adaptive response to injury or infection (Dantzer & Kelley, 2007; Dantzer et al., 2008; Maier & Watkins, 1998; Markou & De La Garza, 2005; Raison et al., 2006). For example, a lack of motivation and interest in rewarding stimuli may promote more stationary behavior, thus allowing bodily resources to be redirected toward fighting infection and promoting recovery. Impaired self-regulation would help to further limit exploratory behavior by making it difficult to remember goals, execute plans, and maintain a positive mood. Ultimately, these effects, coupled with a lack of motivation and a disinterest in reward, would help ensure that an individual remains as stationary as possible to help facilitate recuperation.

A final important question to consider is whether associations between inflammatory activity and self-regulation are similar in Western, educated, industrialized, rich, and democratic (WEIRD) populations versus non-WEIRD populations. On the one hand, several of the studies reviewed here suggest that these associations may be generalizable. For example, two studies on elderly Chinese men in Taiwan examined associations between *IL*-β genotype and executive function (Tsai et al., 2010) and *IL*-β genotype and brain structure (Tu et al., 2013), respectively, and a third study on elderly Japanese women in Japan examined associations between IL-β genotype and executive function (Sasayama et al., 2011). Notably, each study yielded results that are consistent with those obtained in WEIRD populations.

On the other hand, though, a growing body of research is showing that early physical and microbial environments influence individuals' inflammatory reactivity to different stimuli, such as social-environmental stressors (see McDade, 2012; McDade, Hoke, Borja, Adair, & Kuzawa, 2013). Therefore, it is possible that associations between inflammatory reactivity and self-regulation may differ in WEIRD versus non-WEIRD populations. Given the paucity of cross-cultural studies conducted on links between inflammation and self-regulation, additional research should examine how an early microbial environment moderates the effects of inflammation on self-regulation.

Summary and Conclusion

As described at the beginning of this review, self-regulation refers to the ability to act in goal-directed ways, which is especially important in the face of distractions. Self-regulatory success is the result of a complex interaction of different processes that are all oriented toward goal maintenance in either proximal or distal ways. Self-regulatory failure, in contrast, can result from alterations in several processes that support self-regulation, and the consequences of such failures can be catastrophic for an individual's life and the collective well-being of a society.

To elucidate mechanisms underlying these effects, we reviewed evidence showing that immune system factors can influence several neural, cognitive, and motivational processes that underpin self-regulation. We also described how dysregulated immune system activity can contribute to self-regulatory failure through multiple pathways, including by influencing beliefs about self-regulation, self-regulatory depletion, reward sensitivity and motivation, appraisals of stress, and executive function. Based on this work, we proposed an *immunologic model of self-regulatory failure*, which posits that proinflammatory cytokine activity plays a key role in altering neural, cognitive, and behavioral dynamics that can contribute to self-regulatory failure.

Despite evidence supporting this immunologic model, much more research is needed to test this formulation in both its static and developmental form, as well as to evaluate its predictive utility. This research would benefit from

identifying additional pathways linking inflammation, self-regulation, and health. Future studies should also aim to elucidate central mechanisms that give cytokines the ability to directly impact self-regulation. Finally, additional research is needed to examine how theoretical advances on these issues could help improve the treatment of disease conditions that cause substantial morbidity and mortality. In sum, the research reviewed here provides an important theoretical account of how the immune system influences self-regulation, but much more work is needed to fully realize the benefits of this research for improving health.

Author Contributions

G. S. Shields and G. M. Slavich developed the concept for this article and wrote the manuscript, W. G. Moons provided critical revisions to the paper, and all authors read and approved the final version.

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