Running head: THE METABOLIC MIND

The metabolic mind: A role for leptin and ghrelin in affect and social cognition

Jennifer K. MacCormack [a] & Keely A. Muscatell [a,b]

[a] Department of Psychology & Neuroscience, University of North Carolina at Chapel Hill

[b] Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill

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Correspondence concerning this article should be addressed to:

Jennifer MacCormack, University of North Carolina at Chapel Hill, Department of Psychology and Neuroscience, 124 Howell Hall, Chapel Hill, NC 27599 E-mail: jkmaccor@unc.edu

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Abstract

Leptin and ghrelin are metabolic hormones central to energy regulation in the body. Theories of allostasis suggest that metabolism could matter for more than just food-intake and weight-regulation, but also ultimately for psychological processes, such as affect and social cognition. *Allostasis* is the process by which the brain monitors ongoing physiological states and, in turn, regulates physiology based on expectations about how a given situation will impact the self. Motivated by this allostatic perspective, we argue that leptin and ghrelin may be influenced by and even contribute to psychological processes like affect and social cognition. Specifically, we review literature suggesting that leptin and ghrelin may be sensitive to social affective signals and related contexts (e.g., social status; social threat vs. support), given that these signals and contexts may represent access to tangible physical and psychological resources that support allostasis and metabolic needs. We then review literature showing that leptin, ghrelin, and associated metabolic states may feed into the construction of social affective states and behaviors (e.g., emotion, risk-taking), in order to motivate behaviors in line with allostatic needs. We close by offering guidelines for researchers interested in contributing to this emerging field and highlight opportunities for future research. We believe that leptin and ghrelin offer exciting new directions for social and affective scientists interested in linking the mind, brain, and body.

Keywords: allostasis; emotion; ghrelin; leptin; metabolism; social cognition

Leptin and ghrelin are metabolic hormones central to energy regulation in the body. Leptin is an *adipokine* hormone produced by adipose cells (the body's largest energy reservoir), signaling satiety or energy sufficiency to the brain (Maffei et al., 1995; Ramsay, 1996). Leptin supports long-term appetite and energy regulation, shifting slowly with weight gain or loss. For example, in rodents, leptin administration reduces feeding behavior, increases physical activity, and stimulates the innate and adaptive immune systems, presumably in part because higher leptin indicates that the body has sufficient energy stores to engage in metabolically-costly activities (Bernotiene, Palmer, & Gabay, 2006; Houseknecht, Baile, Matteri, & Spurlock, 1998). These findings also replicate in humans (e.g., Licinio et al., 2007). Alternately, ghrelin is a peptide hormone produced by gastrointestinal cells, acting on the central nervous system to signal hunger or energy depletion (Kojima et al., 1999). Ghrelin supports short-term appetite and is secreted when the stomach is empty (Cummings et al., 2001, 2004). Animal models show that ghrelin administration increases feeding behavior (Nakazato et al., 2001), and in humans, ghrelin injected into the bloodstream increases self-reported hunger within approximately 30-min, although ghrelin and hunger are not necessarily coupled in a one-to-one fashion (Wren et al., 2001).

But why should psychologists care about leptin and ghrelin if these hormones are primarily involved in food-intake and energy regulation? Well, a small but growing literature suggests that they may also matter for social affective processes. At first glance, this idea that metabolic hormones could be influenced by or even contribute to affect and social cognition may seem counterintuitive. However, perspectives on *allostasis* (i.e., how the brain monitors and manages physiology) argue that metabolism is fundamental for psychology (Barrett, Quigley, & Hamilton, 2016; McEwen & Wingfield, 2003). As such, metabolic hormones leptin and ghrelin may, by extension, be implicated in people's experiences, perceptions, and behaviors beyond motivations to eat. Below, we briefly discuss allostasis and how it can guide hypotheses about the role of leptin and ghrelin in social affective processes. Next, we review literature suggesting that leptin and ghrelin may be sensitive to social affective signals and related contexts perhaps because these signals and contexts are "metabolically salient." In other words, social affective signals (e.g., interpersonal conflict, social status) and their associated psychology (e.g.,

perceptions of threat vs. belonging) may impact leptin and ghrelin because these signals and contexts inform the brain's predictions about anticipated energy needs. Second, we review literature showing that leptin and ghrelin may also feed into the construction of social affective processes (e.g., mood, risk-taking), as a way of motivating behaviors that support anticipated energy needs. We close by sketching potential mechanisms that could guide future research and offer practical guidelines for psychologists wishing to incorporate leptin and ghrelin into their own work.

The metabolic mind: A framework connecting leptin, ghrelin, and social affective processes

Energy is a fundamental principle of biological life. In mammalian cells, energy is derived from food and oxygen to power cellular electrochemical processes (Nicholls & Fergusson, 2013). Metabolism refers to this process of energy maintenance, including the breakdown of food into energy (measured in kilojoules or calories) and the management of fat tissue for energy storage. Because the acquisition and use of energy is central to sustain life and reproduce (Wallace, 2010), theories on allostasis suggest that metabolism should matter for more than just food-intake and weight-regulation, but also for psychological processes, such as affect and social cognition. *Allostasis* is the active process by which the brain predicts how past, present, and future life circumstances may impact an organism, in turn coordinating physiological changes (e.g., metabolic, autonomic, neuroendocrine, immune) to meet actual or anticipated environmental demands and to support the organism's movement, growth, reproduction, and survival (Kleckner et al., 2017; McEwen & Stellar, 1993; Picard, McEwen, Epel, & Sandi, 2018; Schulkin, 2011; Sterling & Eyer, 1988). Coordinating physiological changes and enacting behavioral responses to life events each require energy expenditure, suggesting that the anticipation and regulation of energy needs are important facets of allostasis. Metabolic messengers like leptin and ghrelin help communicate an organism's energy availability to the brain and in turn mediate efferent brain-to-body commands in support of states and behaviors that assist with energy intake and regulation (Ahima & Antwi, 2008; Seeley & York, 2005). Leptin and ghrelin's role in metabolic signaling suggests that they may contribute to predictions about the current energy state of the brain and body, guiding how the brain adjusts states and behaviors in line with expectations about the world.

Affective and social cognitive processes also play an important role in allostasis, as they are viewed as arising from and contributing to the brain's allostatic predictions. This is in part because all behaviors and even cognitive functions require metabolic energy beyond our resting energy expenditure (Magistretti & Allaman, 2015), and some behaviors and situations are more metabolically costly than others (e.g., a stressful job interview or threatening social altercation vs. relaxing on the sofa with a romantic partner). Furthermore, afferent signals from the body provide important information about whether or not one has the energy reserves to engage in different behaviors (e.g., should I seek out new social connections or stay at home to conserve energy? Barrett et al., 2016; Touroutoglou et al., 2019). Thus, leptin and ghrelin could contribute to our social affective experiences and behaviors in a causal way. Following this idea that the mind is built upon metabolic motivations, we review early evidence from both animal and human literatures linking leptin and ghrelin to affective and social cognitive processes.

From mind to body: Social affective impacts on leptin and ghrelin

Given that efficient allocation and regulation of metabolic energy is crucial for any aspect of an organism's functioning and survival, life events or environmental signals that might impact an organism's allostasis should also impact metabolic functions, including leptin and ghrelin. For social species like humans, social affective signals may serve as an *additional* type of allostatic signal, indicating whether a current or upcoming context or stimulus is safe vs. threatening and whether there are sufficient physiological resources to respond accordingly. Humans long lived in hunter-gatherer bands (Hill et al., 2011), wherein the presence of others (especially close supportive others) improved chances of survival compared to living alone. In this way, social affective signals and contexts, such as whether an individual is high or low status, liked or disliked, socially integrated or isolated may serve as signals about access to tangible physical and psychological resources that support allostasis and metabolic needs. For example, an individual living without social support would likely have higher metabolic needs not only because they have to individually complete more tasks for daily functioning and survival, but also because they may be more susceptible to physical and psychosocial threats without a buffer of supportive others. In

line with this idea, we hypothesize that leptin and ghrelin, as key metabolic signals, may be sensitive to social affective signals and contexts. For example, social isolation, threat, and conflict may upregulate ghrelin, as a means of supporting energy-intake for active coping. Below, we explore existing literature relevant to this hypothesis with regard to social isolation and conflict, social status, and chronic vs. acute stressors.

Social isolation and conflict. Initial work demonstrated that social isolation was associated with higher leptin in men (Häfner et al., 2011). A more targeted study (Jaremka et al., 2015) investigated whether loneliness increases ghrelin and appetite. Forty-two women ate standardized meals, with ghrelin sampled before the meal, immediately post-meal, and 2- and 7- hours post-meal. Women also rated feelings of chronic loneliness and social isolation. Lonelier women had stronger ghrelin spikes post-meal (during the 2- to 7-hour period) as hunger again increased, but only for leaner participants (computed at -1SD from sample mean BMI compared to heavier BMI at +1SD). This finding suggests the possibility that, in leaner women, feelings of loneliness or "threats to belonging" promote greater food-intake, with ghrelin as a key mediator (Jaremka, Lebed, & Sunami, 2018). Experimental rodent work provides stronger causal evidence: healthy mice subjected to social isolation showed significant ghrelin increases after one week relative to group-housed controls (Yamada et al., 2015). Social isolation may also interact with diet choices to alter leptin. For example, rats exposed to chronic social isolation showed an exacerbated effect of high-fat diet on long-term leptin levels (Toniazzo et al., 2018). This early work suggests that social isolation and loneliness may elicit shifts in leptin and ghrelin.

Besides social isolation and loneliness, leptin and ghrelin may be sensitive to interpersonal conflicts or distress, given that such conflicts could signal the onset of threats or changes in support networks that could compromise allostasis. In one study (Jaremka et al., 2016), 43 married couples ate a standardized meal before completing a marital problems discussion, during which marital distress was coded. Leptin and ghrelin were assayed before the meal and again at 2, 4, and 7-hours post-meal. Results showed that greater marital distress in either spouse was associated with higher post-meal ghrelin (but not leptin); this effect only held for leaner individuals (again, -1SD from sample mean BMI). This null leptin

effect is curious, given that circulating leptin tends to increase by 4-6 hours post-food ingestion (Havel, Townsend, Chaump, & Teff, 1999). Perhaps leptin is less sensitive to interpersonal conflicts than ghrelin, but future investigations are needed.

Social status. Besides social connection, social status may be especially metabolically-relevant to allostasis. For social animals, low status means reduced access to food and mating partners, more frequent aggressions, and altered immune functioning (e.g., Sapolsky, 2004; Snyder-Mackler et al., 2016). As such, leptin and ghrelin may be sensitive to social status. Jarrell et al. (2008) found that female rhesus monkeys who moved to high-status positions showed a boost in leptin, perhaps indicating that higher-status individuals do not need to build up metabolic reserves thanks to easier food access. Follow-up studies (Michopoulos et al., 2010; Michopoulos & Wilson, 2011; Michopoulos, Higgins, Toufexis, & Wilson, 2012) found that dominant female monkeys showed increased leptin and improved weight-maintenance during social threat relative to subordinates, suggesting that leptin may promote more effective metabolic adaptation to status-related stressors. On the other hand, low-status monkeys showed ghrelin upregulation in the face of social threat, perhaps to motivate food-intake to support coping.

Despite these intriguing primate findings, little work tests the effects of social status on leptin and ghrelin in humans. One recent study (Sim et al., 2018) examined whether subjective social status impacts ghrelin: healthy men (N=48) showed greater circulating ghrelin and lower fullness/satiety ratings after a low subjective social status manipulation compared to their ghrelin and fullness ratings following a control task. Similarly, inducing low subjective status leads people to prefer high-calorie foods and consume more calories (Cardel et al., 2016; Cheon & Hong, 2017), although this work did not include assessment of metabolic hormones. Future studies should unpack how both objective (i.e., socioeconomic status or SES) and subjective social status can alter metabolic signaling, especially given that altered leptin and ghrelin may contribute to the link between low social status and downstream obesity and disease.

Chronic and acute stress. Ultimately, social isolation, interpersonal conflicts, and low social status can all be understood as types of chronic or acute social stressors. As such, another pathway for

social affective influences on leptin and ghrelin is via the psychological states and behaviors that such signals and contexts evoke. Within an allostatic framework, environmental pressures likely signal to the brain that more resources are needed to cope with demands (McEwen & Wingfield, 2010), which could lead to increases in metabolically-relevant behaviors such as greater food consumption that can in turn provide energy for coping. In this way, stress is an already-recognized mechanism underlying emotional eating (e.g., Tomiyama, Finch, & Cummings, 2015), which occurs when people cope with negative affect and stress by increasing food-intake (i.e., binging) or eating more of certain food types (Macht, 2008; Tomiyama et al., 2015). Indeed, work on emotional eating suggests that leptin and ghrelin may help facilitate stressors' impacts on feeding behaviors. For example, both emotional and non-emotional eaters show increased circulating ghrelin after an acute psychosocial stressor (Raspopow, Abizaid, Matheson, & Anisman, 2010). Alternately, lower leptin reactivity after an acute stressor is associated with greater consumption of high-sugar, high-fat "comfort" foods (Tomiyama et al., 2012). Finally, stress-induced cortisol release appears to stimulate ghrelin (Sinha & Jastreboff, 2013). Together, these findings suggest that stress may alter metabolic behaviors (e.g., eating), as one mechanism linking stress and obesity, and may do so in part via leptin and ghrelin. Below we review existing evidence linking chronic and acute stress to altered leptin and ghrelin.

First, as a type of chronic stressor, greater early life adversity is associated with higher circulating leptin in middle adulthood, even after controlling for physical activity, diet, and BMI (Joung et al., 2014). Leptin also helps explain the relation between childhood adversity and higher blood pressure (Crowell et al., 2016). Chronic stress effects may even be trans-generational. Both rodent and human studies show that chronically-stressed mothers bear children with higher leptin and body weight compared to low-stress mothers, with effects for children lasting even into adulthood (review in Entringer, 2013). But why would individuals with higher adiposity also have greater leptin, if leptin signals satiety and sufficiency of metabolic resources? One common explanation is *leptin resistance.* Despite obese individuals having excessive adipose tissue and proportionally high leptin, this higher leptin does not reduce appetite or support weight loss, suggesting that the brain and body may have become insensitive to leptin signaling

(Myers et al., 2012). More research is needed to unpack links between chronic stress, leptin, and weight gain/obesity.

Beyond chronic stressors such as early life adversity, leptin may also be sensitive to acute stressors. For example, Brydon et al. (2008) found a small increase in leptin 45-min after an acute stressor (Stroop and speech tasks). However, a second study using the Trier Social Stress Test (TSST; Tomiyama et al., 2012) found no change in leptin at 50- or 90-min post-stressor. This inconsistency may be due to task differences (e.g., the latter involved greater social evaluative stress) or because leptin's reactivity to acute stress is a small effect (e.g., as found in the former study). Given that leptin typically responds to food ingestion within 4-6 hours (Havel et al., 1999), a longer measurement window may be necessary. Future work should continue investigating the effects of acute stress on leptin reactivity in humans.

Similar to leptin, ghrelin may change in response to both chronic and acute stressors—although given its acute time-course, it may be especially sensitive to acute stress. Consistent with this, several studies in both humans and rodents have examined acute stress-related ghrelin reactivity. For example, as noted earlier, Raspopow and colleagues (2010) found that both emotional and non-emotional eaters (N=48) show ghrelin increases within 30-min after the TSST relative to baseline. Similarly, in a sample of overweight women (N=28), ghrelin increased in response to a stressful cold pressor task (Geliebter & Gluck, 2012). In another study (Monteleone et al., 2012), both women diagnosed with bulimia nervosa and healthy controls showed significant increases in ghrelin after the TSST relative to baseline. However, in healthy women, ghrelin peaked 25-min post-stressor and rapidly returned to baseline; women with bulimia showed elevated ghrelin as late as 60-min post-stressor, suggesting that acute stress effects on ghrelin's peak and recovery could vary depending on population. Further converging evidence finds that acute stress alters ghrelin in rats relative to sham stress (e.g., Kristenssson et al., 2006). Beyond acute stress, some rodent work suggests that ghrelin is sensitive to chronic stress (Ochi et al., 2008; Patterson et al., 2010). In humans, early life adversity may affect ghrelin: for example, Pakistani adolescents who experienced terrorist attack-related trauma in childhood showed a nearly two-fold elevation in ghrelin relative to adolescents without a trauma history (Yousufzai et al., 2018). Together, findings suggest that

stress (particularly acute stressors) can increase ghrelin, perhaps in part to motivate greater energy intake for active coping efforts that are metabolically-demanding.

Relatedly, daily life stressors (which can encompass both chronic stressors such as financial worries and acute stressors such as a recent interpersonal altercation) may also impact metabolic hormones. Jaremka et al. (2014) recruited 50 women to complete three laboratory visits each two or more weeks apart. During each visit, women fasted before eating a standardized meal, with blood samples for leptin and ghrelin collected 45-min post-meal. They also completed the self-reported Daily Inventory of Stressful Events. Results revealed that, even when controlling for BMI, women reporting more social stressors showed elevated ghrelin and reduced leptin profiles post-meal relative to women reporting fewer social stressors. Non-social stressors did not relate to leptin and ghrelin. The elevated ghrelin and reduced leptin post-meal suggests that socially-stressed women may feel hungrier and less satiated sooner after eating than women with fewer social stressors. This suggests that social stress may be particularly metabolically-taxing (above and beyond other types of stressors), lending additional support to the hypothesis that leptin and ghrelin may be sensitive to social affective signals and contexts.

Future questions. Despite an initial literature suggesting that social affective signals and contexts influence leptin and ghrelin, more work is needed to replicate and extend these findings. For example, future studies could clarify the mechanisms linking acute stress to ghrelin reactivity, including the neural, autonomic, glucocorticoid, and immune processes that may mediate effects of acute stress on ghrelin. Similarly, researchers could experimentally manipulate stress appraisals (e.g., wherein a stressor is perceived to be a challenge vs. threat; Jamieson, Hangen, Lee, & Yeager, 2018) to determine if these evoke different metabolic profiles. Another idea is to manipulate social support during a stressful task—with the prediction that social support could buffer against stress effects on leptin and ghrelin. Beyond stress, future work could test whether the social isolation findings reviewed above extend to acute social exclusion paradigms like Cyberball (Williams & Jarvis, 2006), consistent with the idea that social exclusion should have allostatic implications for metabolism and safety. Altogether, future work is needed to verify these speculations and establish the boundary conditions by which social affective

signals and contexts modulate leptin and ghrelin.

In sum, there appears to be initial support for the idea that leptin and ghrelin may be sensitive to social affective signals and contexts. It is also possible that leptin and ghrelin may "bottom-up" contribute to affect and social cognition, motivating behaviors in line with allostatic needs. We explore this possibility next.

From body to mind: Leptin and ghrelin may contribute to affect and social cognition

Across animals, the brain anticipates energy demands (Kim, Seeley, & Sandoval, 2018; Seeley & York, 2005), in turn orchestrating physiological and motivational changes to meet those demands, including with the help of metabolic hormones leptin and ghrelin. For example, during important life events that require intense energy use like migration, hibernation, puberty, and pregnancy, both human and animal feeding behaviors increase to intake energy while weight status, via adipose tissue, signals how much energy is set aside for anticipated demands, e.g., a winter famine (reviews in Kaplan & Gangestad, 2005; McEwen & Wingfield, 2003). As such, the brain includes receptors for metabolic chemicals from the periphery to signal how much effort or risk is required to meet anticipated energy needs and guide behaviors in a "bottom-up" fashion.

Accordingly, leptin and ghrelin receptors are widely distributed throughout the brain, especially in the hypothalamus and other subcortical limbic structures (reviews in Ferrini, Salio, Lossi, & Merighi, 2009; Howick, Griffin, Cryan, & Schellekens, 2017; Myers, Münzberg, Leinninger, & Leshan, 2009). For example, there are extensive leptin receptors in key reward regions like the ventral tegmental area and substantia nigra (Elmquist et al., 1998; Hommel et al., 2006), and animal models show that ghrelin is a crucial mediator in brain phasic dopamine signaling, especially in nucleus accumbens and ventral striatum dopamine receptors (Abizaid, 2009). These patterns of receptor distribution suggest that leptin and ghrelin may play a role in motivating reward-seeking more generally. Specifically, there are receptors for leptin and ghrelin in regions that regulate more than just hunger and satiety, responding to multiple types of reward and risk, including non-food related rewards and risks (see meta-analyses: Krain et al., 2006; Liu, Hairston, Schrier, & Fan, 2011; Sescousse, Caldú, Segura, & Dreher, 2013). As such, although leptin and

ghrelin at their core help regulate metabolism, we suggest that they may do so in part by supporting domain-general states and behaviors in service of energy regulation, such as affective states, social cognition, and behaviors. We explore this possibility below.

Affect. Affective states involve feelings of pleasure-displeasure (valence) and activation-quiescence (arousal) and are thought to be fundamentally *motivating* for behavior. In line with this idea, we suggest that leptin and ghrelin may contribute to the generation of affect, as such affect would help motivate behaviors for energy intake and maintenance (Chuang & Zigman, 2010; Zarouna, Wozniak, & Papachristou, 2015). More specifically, the affective dimensions of metabolic states likely not only reinforce future appetitive behaviors as is already suggested (Dagher, 2009), but these feelings could also serve as an allostatic "barometer" (Duncan & Barrett, 2007)—helping organisms identify when metabolic energy is low (e.g., feeling hungry, tired) vs. sufficient or in surplus (e.g., feeling full, energized). In line with this hypothesis, the theory of constructed emotion suggests that moods (longer lasting affective states) and emotions (more transient states) reflect the brain's interoceptive predictions about an individual's ongoing allostasis (Barrett, 2017). Affective changes in valence and arousal likely reflect an integration of metabolic, immune, cardiovascular, and autonomic afferent signals into conscious awareness (Barrett & Bliss-Moreau, 2009; MacCormack & Lindquist, 2017). As such, feeling anxious or depressed, angry or sad, may similarly reflect more chronic or acute signals about anticipated energy supply and demand. If leptin and ghrelin indeed play a domain-general affective role, then it is important to demonstrate that they do so even when food is not necessarily involved.

Some early evidence in nonhuman rodent models supports this possibility. For example, leptin administration in rodents increases self-stimulating behaviors beyond food (e.g., pressing a lever that stimulates an implanted electrode), likely via interaction with dopaminergic systems (Carr, 2002; Fulton, Woodside, & Shizgal, 2000). A growing body of evidence in both rodents and humans implicates ghrelin and its receptors in drug-related reward responses (e.g., Wenthur et al., 2019; Zallar et al., 2019; see also Morris, Voon, & Leggio, 2018 for review). For example, in humans, individuals with higher fasting ghrelin appear to be more reward-sensitive and report experiencing more intense, longer-lasting

subjective effects in response to intravenous alcohol administration relative to saline placebo (Ralevski et al., 2017, 2018; this work used ethanol rather than alcohol ingestion which contains carbohydrates in order to disentangle the pleasure induced by ethanol from alcohol's caloric value). In the context of addiction wherein reward is highly conditioned, blocking ghrelin receptors in rodent brains can reduce the craving component of nicotine-dependence and alcoholism (review in Panagopoulos & Ralevski, 2014). Similarly, leptin and ghrelin—via their interactions with other systems such as the immune and autonomic nervous systems may further potentiate rewarding vs. aversive states and help generate subjective arousal. For example, peripheral leptin administration in rats and mice subjected to thermal pain leads to greater nociceptive pain sensitivity than placebo controls (Kutlu et al., 2002), perhaps given that leptin is a pro-inflammatory mediator (Bernotiene et al., 2006) and may exacerbate the pain associated with injury-induced inflammation. On the other hand, ghrelin administration in rodents and humans mediates the release of several arousal-associated hormones like cortisol and adrenaline (Mihalache et al., 2016). Further, peripheral ghrelin administration in humans elicits reports of highly aroused, unpleasant feelings and can increase sympathetic muscle activation during a stressor relative to placebo saline, suggesting that ghrelin may increase physiological and subjective arousal, alertness, tension, and action-readiness even in contexts where food-intake is not the primary outcome (Garin, Burns, Kaul, & Cappola, 2013; Lambert et al., 2011).

Beyond acute emotion experiences, leptin and ghrelin may also be implicated in the etiology of chronic mood states. A recent meta-analysis showed that individuals with major depression have lower levels of leptin (Cao et al., 2018), although findings were correlational, leaving the causal relation unclear. Similary, leptin administration in rodents exerts antidepressant effects, wherein leptin performs as well as fluoxetine at reducing depressive symptoms (Liu et al., 2010). Ghrelin, on the other hand, is implicated in anxiety. For example, both central and peripheral administration of ghrelin in mice produces behaviors consistent with anxiety (Asakawa et al., 2001; Carlini et al., 2002). Thus, it appears that leptin and ghrelin may contribute to psychopathologies like depression and anxiety, although both clinical trials and experimental work in humans are greatly needed.

Altogether, these early findings are consistent with our hypothesis that leptin and ghrelin may support the construction of broader affective processes beyond just food-related reward and motivation. However, most research in this area has been conducted in nonhuman animals, and significant efforts are needed to replicate and extend findings in humans. Given that affective states can motivate behavior, leptin and ghrelin's effects on reward, arousal, and mood may exist in part because these states arguably motivate an organism to engage in behaviors that support metabolic needs. We next discuss evidence that metabolic states and leptin/ghrelin can impact risk-taking, impulsivity, and aggression.

Risk-taking, impulsivity, and aggression. Cross-species studies suggest that when hungry or under nutritional stress, small animals with high metabolic rates tend to choose a "risk-prone" strategy. For example, frogs and fish in the fasted state are more likely to forage outside typical ranges into riskier (more variable) predator- or competitor-laden zones (Carlson, Newman, & Langkilde, 2015; Damsgird & Dill, 1998; Godin & Crossman, 1994). On the other hand, in large-bodied omnivores like chimpanzees, energy deficits (e.g., hunger, malnourishment) may elicit divergent risk behaviors. For example, an observational study over 14 years (Gilby & Wrangham, 2007) found that chimpanzees were more likely to adopt risk-prone foraging behaviors (e.g., hunting red colobus monkeys) when nutrients were abundant but more likely to adopt risk-averse foraging strategies (e.g., feeding on plants) when environmental resources were scarce. This supports the notion that metabolic states may facilitate either risk-prone or risk-averse behaviors, depending on broader scarcity vs. abundance in the surrounding environment. As humans are also large omnivores, leptin and especially ghrelin may play a similar contextualized role in risk assessment and decision-making, an idea explored below.

Symmonds and colleagues (2010) examined risky economic decisions in healthy-weight men. In different randomized sessions (14 hours post-fasting vs. immediately after eating a controlled meal vs. 1 hour after eating a meal), males (N=24) completed a lottery choice task with leptin and ghrelin assayed each session. Results demonstrated that participants were most risk-averse for about 1 hour post-meal, associated with significant declines in ghrelin—suggesting that higher ghrelin could support risk-taking in a metabolically-depleted state but that declining ghrelin, as a signal of nutrient intake, may temporarily

induce risk-aversion as the body digests food. However, higher baseline leptin was also correlated with riskier choices post-meal relative to fasting, suggesting that although ghrelin declines may temporarily induce risk-aversion, individuals' prior leptin status could moderate these effects. Similarly, Levy and colleagues (2013) found that fasted participants were more risk-tolerant, not just in the context of food and water but also monetary decisions, providing converging evidence that these metabolic effects on risk are not limited to food. However, here, ghrelin or leptin were not measured, so more work is needed to examine if metabolic hormones mediate the link between hunger and risk-seeking behaviors in food vs. non-food domains.

Given the relevance of impulsivity for risk-taking, some studies has also begun to look at associations between metabolic hormones on trait impulsivity; for example, initial work shows a positive correlation between higher fasting ghrelin and dimensions of impulsivity in humans (e.g., Ralevski et al., 2018). Experimental rodent work further suggests that centrally-administered ghrelin injection increases impulsive behavior in rats on behavioral impulsivity measures such as the go/no-go task (Anderberg et al., 2016). Future work should clarify the impacts of leptin and ghrelin on risk-taking and related behavioral tendencies such as impulsivity across different time-courses (e.g., when hungry vs. immediately after eating) and contexts, especially in humans. For example, high- vs. low-resource contexts may support divergent risk-prone vs. risk-averse behaviors in humans that are mediated in part by leptin and ghrelin signaling.

Related to ghrelin's impact on risk-taking and relation to impulsivity, there is also the possibility that it could, in some contexts, motivate aggressive behaviors, consistent with predation and competition for resources. To our knowledge, only one study has yet explored this possibility. Specifically, when the ghrelin-inhibiting enzyme *butyrylcholinesterase* is knocked out in mice, fighting and other aggressive behaviors significantly increase, mirrored by significant increases in circulating ghrelin (Chen et al., 2015). Given that hunger and low blood sugar (including manipulation thereof) is associated with aggressive behaviors in humans (e.g., Benton, 1988; Bushman, DeWall, Pond, & Hanus, 2014), ghrelin as a more proximal hunger-mediator may also play a role in human aggression, although this speculation

remains untested. Finally, most work examining effects of metabolic hormones on risk-taking and aggression focus on ghrelin, limiting our knowledge of the role of leptin in these processes.

Future questions. In sum, preliminary evidence suggests that both leptin and ghrelin may contribute to affect, risk-taking, impulsivity, and perhaps aggression. Future work should use experimental manipulations to test these causal connections more rigorously in humans. Of note, metabolic contributions to social cognition and behavior remain underexplored, although we believe that leptin and ghrelin's importance for reward, emotion, risk-taking, and aggression suggests that they should also matter for social cognitive processes like prejudice, empathy, and person perception. For example, in interpersonal contexts, leptin and ghrelin may shape motivations to meet strangers or initiate new relationships, contingent on metabolic state. Leptin, a key signal for pubertal onset (Sanchez-Garrido & Tena-Sempere, 2013), may also be implicated in adolescent risk behaviors. Finally, given that resource-sharing vs. competition is metabolically-relevant, individuals' metabolic states, alongside leptin and ghrelin as central metabolic signals, may shape in-group/out-group biases, especially under conditions of scarcity vs. abundance. These ideas remain untested in the literature but may be worth pursuing in future.

Methodological considerations

Although our understanding of the relation between psychological processes and leptin/ghrelin is nascent, the above evidence foreshadows exciting directions for future research. For psychologists wishing to adopt leptin and ghrelin measurements or manipulations, below we offer key methodological considerations. Key considerations are summarized in **Figure 1**.

Time-course. As noted throughout, leptin and ghrelin have different time-courses, such that leptin is more stable across multiple days (except for a few hours after a meal: Klok, Jakobsdottir, & Drent, 2007) and less sensitive to single acute events like missing a night of sleep (Pan & Kastin, 2014). Ghrelin, on the other hand, is highly sensitive to food-intake from the previous 12-24 hours (Spiegel et al., 2011) and is inversely related to the number of hours slept the previous night (Taheri et al., 2004). Further, both leptin and ghrelin have diurnal rhythms tied to sleep and meals. Leptin peaks during sleep and reaches its nadir upon awakening (Shea et al., 2005), while ghrelin increases from midnight to dawn,

appearing to peak mid-morning if no breakfast is eaten (Cummings et al., 2001). We also note that just as there are individual differences in fasting or baseline glucose levels, similar individual differences can be observed for other metabolic markers such as ghrelin (e.g., Ralevski et al., 2017). In light of these temporal and within-subject dynamics, researchers should (1) consider if the psychological phenomenon of interest is acute or chronic, (2) should assay or administer the hormones at the same time of day across participants (or control for time-of-day in analyses), (3) should always incorporate fasting or a standardized meal into the laboratory paradigm, (4) should include within-subject measures whenever possible (e.g., measure baseline and "reactivity"; use a randomized crossover design), and (5) should assess the last 24-hour's sleep and food history for possible inclusion as covariates.

Key Covariates. Body composition, sex, and age all predict variation in leptin and ghrelin functioning. Much work demonstrates that body composition extremes (obesity, eating disorders) alter leptin and ghrelin (Cui, López, & Rahmouni, 2017; Monteleone & Maj, 2013). As such, researchers should use healthy-weight samples unless interested in comparing effects across populations. Body composition matters most for leptin, given that leptin is proportional to adipose tissue, and thus some metric (e.g., BMI, body fat percentage) should be included as a statistical covariate in analyses. Sex is another key moderator. For example, leptin and ghrelin vary across the menstrual cycle (e.g., Dafopoulos et al., 2009), suggesting that sex and menses stage be used as statistical covariates. Finally, leptin and ghrelin change with age and often mark, even facilitate, critical changes across major life thresholds, like pubertal onset, fertility, and menopause (Garcia-Galiano, Allen, & Elias, 2014; Tena-Sempere, 2013). Leptin accumulates and ghrelin declines with age, partially underlying age-related shifts in appetite and weight status (Mishra et al., 2015; Nass et al., 2014). Studies with leptin and ghrelin should consider developmental stage when forming hypotheses.

Manipulation vs. Measurement. Manipulation is the strongest approach to investigate leptin and ghrelin impacts on the brain and behavior, affording inferences about causality. Due to ghrelin's acute nature, it is typical to administer a single subcutaneous injection of ghrelin 15-30 minutes before measuring the outcome of interest (Garin et al., 2013). On the other hand, due to leptin's chronic nature,

some studies administer leptin in small doses via subcutaneous injection over a set time-period (e.g., two weeks, one month). Measurement, on the other hand, is useful in cross-sectional designs or instances where researchers care about leptin and ghrelin as outcomes. It is crucial to note that the time-courses within which leptin and ghrelin respond to *psychological* events and tasks are still largely unknown. For example, Brydon et al. (2008) found that leptin reacted to acute stress within 45-min (but this did not replicate in Tomiyama et al., 2012 even after 90-min). Other work reviewed herein found that ghrelin reacted to acute stress within 30-min. Whether these timeframes replicate with other psychological paradigms is less clear but could serve as initial estimates. Early investigations should sample multiple timepoints to map the response trajectory of leptin and ghrelin to social affective events. Finally, blood assay is the most common and reliable assessment of leptin and ghrelin, but researchers are actively developing other techniques using saliva, urine, and even breastmilk, suggesting that other measures may become available in time. Ultimately, a combination of manipulation and measurement will provide the most systematic evidence for bidirectional paths between psychology (e.g., stress, out-group biases, risk-taking) and leptin/ghrelin.

Conclusion: Mapping the metabolic mind

In sum, the mind is likely metabolic, making predictions about anticipated energy demands and creating feelings, perceptions, and behaviors accordingly. As such, metabolic hormones leptin and ghrelin may be implicated in people's social affective experiences, perceptions, and behaviors beyond motivations to eat. Yet much more work is needed to clarify leptin and ghrelin's relation with affect and social cognition. To close, we suggest three pathways as promising targets for future research, bridging leptin and ghrelin to the mind and behavior (**Figure 2**). First, leptin and ghrelin work closely with the immune system (Bernotiene et al., 2006; Chowen & Argente, 2017). The immune system is already implicated in wellbeing, mood disorders, and even social cognition (Gassen & Hill, 2019; Slavich & Irwin, 2014). Future studies could, for example, assess how leptin and inflammation interact in the context of poor social support, low SES, or situations of chronic discrimination. Second, leptin and ghrelin's relation with the autonomic nervous system remains underexplored, with small samples and

mixed findings. For example, ghrelin shows mixed impacts on heart rate, heart rate variability, blood pressure, and sympathetic nerve activation (Lambert et al., 2011; Matsumura et al., 2002; Soeki et al., 2014). Future work could systematically test the autonomic impacts of ghrelin, with implications for acute stress and the construction of emotions like anger. Recent experiments confirm that hunger can indeed induce negative affective feelings and perceptions (e.g., feeling "hangry"; MacCormack & Lindquist, 2018)—but it would be valuable to determine whether and how leptin and ghrelin might help mediate these affective consequences of hunger. Finally, given that leptin and ghrelin have distributed receptors throughout the brain, both hormones may feed into neural representations of affect and social cognitive processes. For example, ghrelin administration predicts greater functional activation in limbic regions like the amygdala, anterior insula, ventral striatum, and medial orbitofrontal cortex (Malik, McGlone, Bedrossian, & Dagher, 2008), hinting at possible implications for ghrelin in the neural representation of affect, pain, interoception, and mentalizing. We look forward to future investigations further revealing how leptin and ghrelin may matter for affect and social cognition.

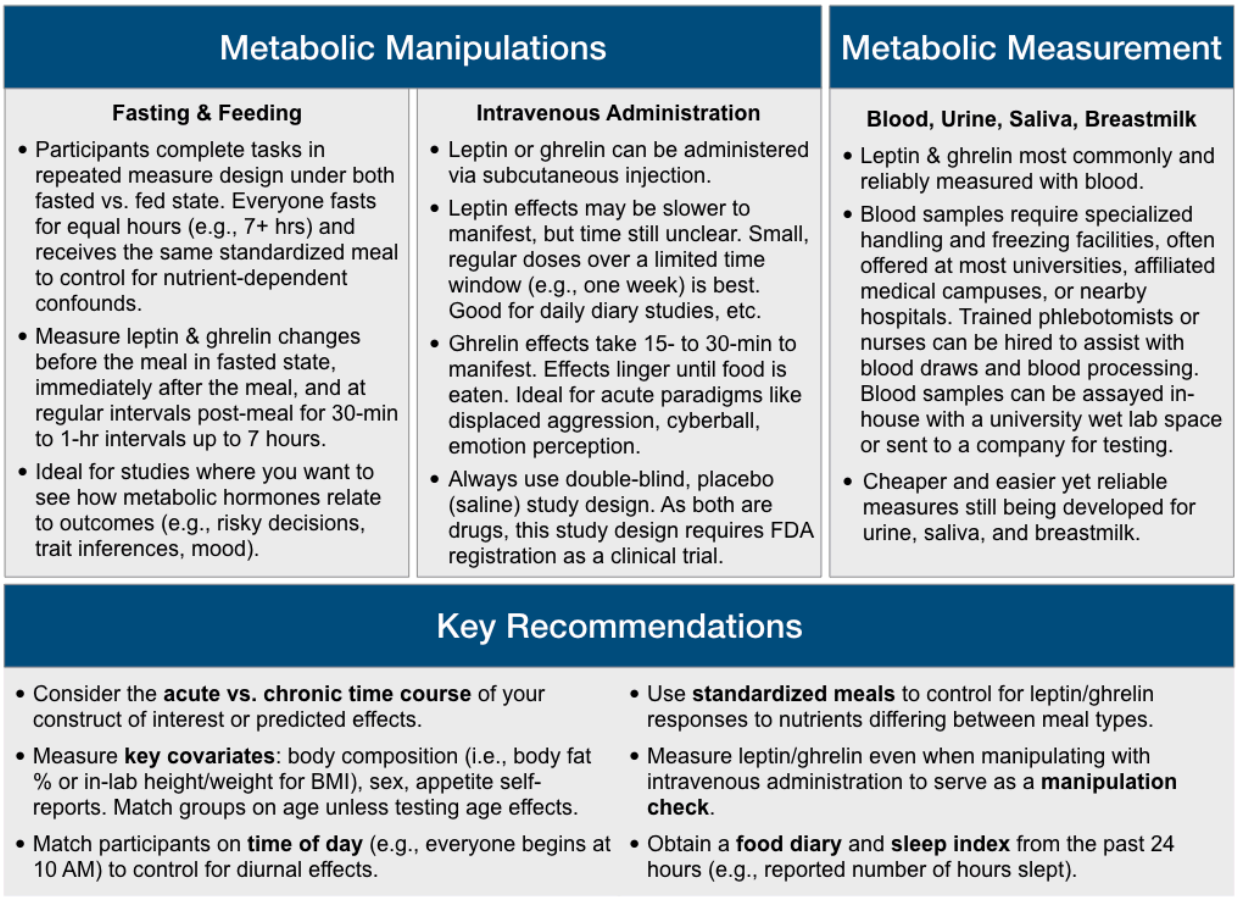

Figure 1. Methodological considerations for integrating leptin and ghrelin into study designs.

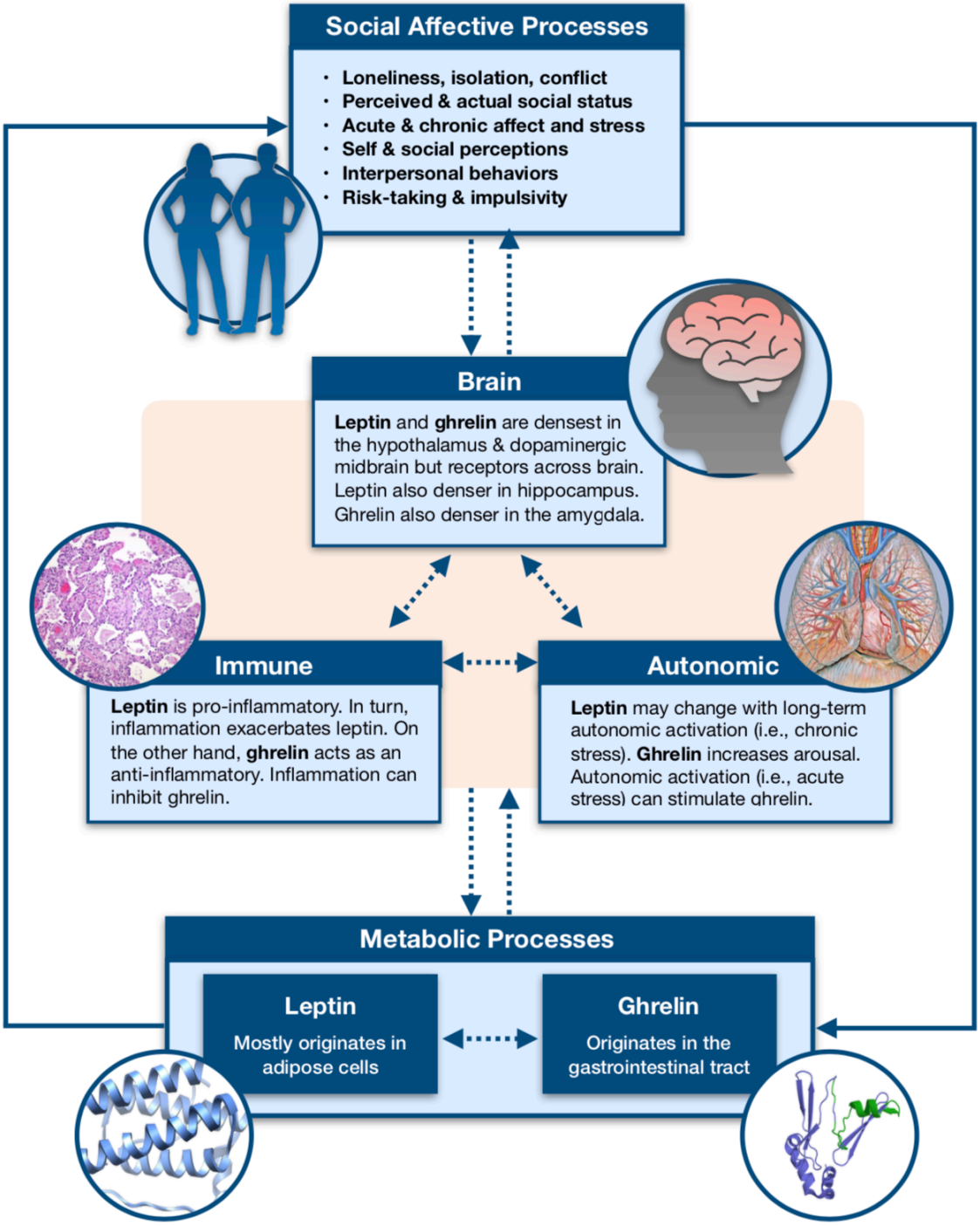

Figure 2. Leptin and ghrelin's bidirectional relations with social affective processes are likely mediated via the brain, autonomic, and immune system pathways, including interactions between these systems. For example, if leptin or ghrelin alters inflammation, subsequent inflammation-mediated effects of leptin and ghrelin may also be observed in the brain and autonomic nervous system. It is important to remember that cross-system relations with leptin/ghrelin are dynamic, with ghrelin responding more quickly on acute timescales and leptin over chronic timescales. Furthermore, leptin and ghrelin can also affect each other. Finally, it is important to note that the relations depicted herein develop and occur within the context of

broader environmental factors. For example, maternal and prenatal health, early life adversity, environmental pollutants, socioeconomic status, food insecurity and broader nutrition, weight and disease status, age, and lifestyle factors (e.g., smoking, exercise) likely also influence the bidirectional relations between leptin, ghrelin, and social affective processes.

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