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The feeling of anger: from brain networks to linguistic expressions

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Highlights

- Anger is an internal state that can be activated by threat provocation. Regardless of the situational trigger (e.g., perceived threat, unfair treatment), anger is couched in distinct internal states that can propagate and escalate in a positive feedback loop. (Figure 1).
- Four major neural networks activated during anger induction were identified in the review of functional MRI studies. These networks, mostly left lateralized, orchestrate feeling components of anger (Figure 2).
- Using the definition of feelings from The Human Affectome Project, language related to anger seems to convey the degree of arousal, the speed in which anger is experienced and displayed, and the different sources of threat (social: e.g., alienation, rejection)—which map on to neuroscience and anger components involving arousal, displays and regulation, and cognition.

Abstract

This review of the neuroscience of anger is part of The Human Affectome Project, where we attempt to map anger and its components (i.e., physiological, cognitive, experiential) to the neuroscience literature (i.e., genetic markers, functional imaging of human brain networks) and

to linguistic expressions used to describe anger feelings. Given the ubiquity of anger in both its normative and chronic states, specific language is used in humans to express states of anger. Following a review of the neuroscience literature, we explore the language that is used to convey angry feelings, as well as metaphors reflecting inner states of anger experience. We then discuss whether these linguistic expressions can be mapped on to the neural circuits during anger experience and to distinct components of anger. We also identify relationships between anger components, brain networks, and other affective research relevant to motivational states of dominance and basic needs for safety.

Keywords: anger, feeling, emotion, language, rage, aggression, brain, fMRI, prefrontal cortex, polymorphisms, genes

1. Introduction

A "feeling" is a fundamental construct in the behavioral and neurobiological sciences encompassing a wide range of mental processes and individual experiences, many of which relate to homeostatic aspects of survival and optimal life regulation (Buck, 1985; Damasio and Carvalho, 2013; LeDoux, 2012; Panksepp, 2010; Strigo and Craig, 2016). The feeling of anger is quite specific and practically universal, yet it remains one of the least studied of the basic emotions (Ekman, 2016). Provocation, a stimulus perceived as threatening or aversive, is a common activator of anger. Regardless of the provocation and situational triggers (e.g., perceived threat, unfair treatment), anger is couched in distinct internal states that can propagate and escalate in a positive feedback loop (see depiction in Figure 1). Unlike the sole reliance on aggression output to measure antagonism in other mammals, humans show multiple non-verbal and verbal expressions that can be readily recognized in the self and by others as *anger* (Potegal,

2010). Anger is reflected across distinct components, including the *arousal* component, as in stress reactivity with concomitant autonomic arousal; *cognitive* components, including heightened attention to threat, hypervigilance, and hostile attributions (Novaco, 2016). Outward *displays* embody specific facial expressions, bodily displays of threat, and vocal prosody as well as standard linguistic expressions which are used to reflect the subjective experience (e.g., feelings of being "mad", "enraged", etc). Thus, anger is experienced and expressed across these components, and self-regulation of anger can occur by altering some or all of these components. In modern society, as compared to ancient times where anger expression and displays of brute force likely helped establish dominance and determine leadership, anger regulation is increasingly important as one needs to moderate displays of anger in order to achieve advantageous outcomes (Averill, 1983; Gilam and Hendler, 2017a; Potegal and Novaco, 2010). However, in the escalation of anger, emotional self-regulation can fail and the display of anger can culminate into aggressive behavior (Coccaro et al., 2009). This reactive aggression can be so swift as if following a '*low road*' of brain activity, such that aggression is perpetrated seemingly without observable escalation or the mediation of cognitive inhibitions (Figure 1).

We dedicate this review to mapping the neuroscience literature to anger feelings and their components, as well as to the linguistic expressions of anger, all as a way of facilitating collaboration and standardizing research efforts. In particular, this work is being undertaken as part of 'The Human Affectome Project', of *Neuroqualia*. Our team was specifically tasked to review the neuroscience research related to anger feelings; to that end we restricted the scope of this review specifically to literature referring to anger and not related feelings/behaviors (e.g., irritability, frustration, aggression). We further consider whether or not anger feelings that people convey in language might inform the way we approach neuroscience research on this topic.

Accordingly, we summarize what is currently known about genetic correlates of state and trait anger and the brain networks activated during the induction of anger feelings, while simultaneously exploring the language that is spoken to convey feelings of anger and metaphors of anger expression. We further discuss whether feelings of anger that people convey in language might be linked to activation of distinct neural circuits and to the anger processes depicted in Figure 1 (see Glossary).

FIGURE 1: ABOUT HERE

2. Components of Anger

2.1 *Arousal*: Autonomic and Stress Reactivity to Provocation

Throughout evolution, anger has had an adaptive role in survival with its fundamental involvement in the fight-or-flight reaction to threat detection (Berkowitz and Harmon-Jones, 2004). As such, physiological responses that share phylogenetically similar mechanisms with other mammals constitute the experience of arousal. Consistent with Selye's (1976) stress model for example, the body increases autonomic arousal in response to a stressor. In this context, stress reactivity is the subjective perception of uncontrollability or unpredictability that is expressed in quality and degree of the response to provoking elements (e.g., perceived threat to physical safety) (Koolhaas et al., 2011). Autonomic arousal, indicated by a raised heart rate and muscle tone, altered posture and facial expression due to adrenaline release, all serve as arousal displays of anger (Stemmler and Wacker, 2010). Not surprisingly, the circumplex model of emotion, which charts feelings on dimensions of *valence* and *arousal*, places anger in the *high arousal* and *negative valence* category of basic emotions (Russell, J.A., 1980). Although *fear* shares feeling components with anger, such as autonomic arousal to threat, the organism is motivated to withdraw and flee under fear (unless escape is not possible). Unlike fear, anger is

characterized by 'approach' motivations, and if confrontation is deemed the best course of action, can help mobilize optimal physiological and cognitive support for action tendencies that promote confronting threat and provocation. Thus, perhaps initial arousal to threat or provocation develops into fear or anger depending on context and personality or trait tendencies.

2.2 *Cognition*: The Role of Anger in Biasing Attention and Cognition

Autonomic arousal during anger feelings is relatively short lived, whereas frequent experiences of anger and thoughts about the provoking situation (i.e., anger rumination) enables the persistence of negative emotions (Potegal, 2010). During a state of anger and perhaps more so during repeated and enduring bouts of anger rumination, attention becomes narrowed and intensely focused toward the source of the provocation (Alia-Klein et al., 2018; Gable et al., 2015a). As such, anger narrows attentional scope (Gable et al., 2015b), often compromising the efficiency of cognitive processing and decision making (Garfinkel et al., 2016). It is suggested that learned bias toward engaging anger in response to stressors can develop as a function of associative network connections across feelings, thoughts, memories and physiological and expressive motor reactions (Berkowitz and Harmon-Jones, 2004). The rapid unfolding of emotional information through this network promotes rapid interpretations and causal cognitive attributions of the provocation, which facilitate enhancement of anger (Maoz et al., 2017). In a recent theory of human anger, the authors expand on the unique cognitive elements of anger (Sell, 2006; Sell, 2011; Sell et al., 2017; Sell et al., 2009). The recalibrational theory holds that anger evolved in humans to bargain for better treatment, as in evolutionary biology and game theory approaches. Since humans rely on language and cognition to bargain, the recalibrational studies and theory rely on the correct assumption that substantial attentional and cognitive resources are diverted toward the source of interpersonal conflict, with such processes mediated

by interactions between prefrontal (PFC) and subcortical brain networks, often with opposing activations (Siever, 2008). Thus, it is interesting to understand the mechanisms behind failure in recalibration, when anger is no longer helpful in negotiation and therefore needs regulation.

2.3 Anger regulation: *low road* from provocation to reactive aggression

Some theories argue that regulatory processes are activated at the initiation of anger experiences, or at later appraisal stages. However, most agree that processes involved in anger regulation occur at different stages of anger escalation, depending on a multitude of factors (LeDoux, 1990), including the degree of emotion regulation capacity (Siever, 2008). The anger regulation strategy of reappraisal depends on one's ability to distance the self from the provocation or to re-evaluation of the provocation as less threatening or frustrating than it is initially perceived. This capacity is sometimes also referred to as *anger control* (Spielberger, 1988) and it can serve to reduce the intensity of anger and prevent escalation to maladaptive behaviors (Szasz et al., 2011).

Because cognitive reappraisal and other higher-level anger management training heavily rely on intact intellectual and executive functioning (Ochsner and Gross, 2008), patients suffering from intellectual disabilities or neurodevelopmental disorders can show frequent loss of control. Even with intact intelligence and despite the availability of cognitive strategies as reappraisal, high levels of arousal and stress reactivity induced during anger can challenge the ability to constrain its expression. In particular, uncontrollable anger situations may trigger a '*low road'* of activation (e.g., with minimal mediation by higher-order cognition), rapidly leading to anger displays and aggression. Some argue that intense *frustration* triggers anger leading to reactive aggression in animals when there is high level of danger and the threat is very close (Blair, 2012). In humans, whether stemming from frustration or from perceived threat,

anger often requires some degree of regulation. However, the inhibiting effects of PFC recruitment during such times of intense and negatively valenced approach emotion may be greatly weakened or circumvented (Alia-Klein et al., 2009). This concept of a *low road* is adapted from fear studies, which have found that a specific fear response reflects an automatic process that does not even require conscious recognition of the feared stimulus (Ohman, 2005; Carr, 2015; Ledoux, 1996). Thus fear reactions (and anger as well) are partly managed by ancient brain systems, primarily the amygdala, that may act relatively independently of the later emerging higher cognitions (LeDoux, 1996; Rosen and Schulkin, 1998). Notably, the use of psychoactive substances such as alcohol can escalate feelings of anger and facilitate the *low road* to rapid aggressive responses (Parrott et al., 2003). Sleep restriction also intensifies anger perhaps by reducing tolerance for provocation (Krizan and Hisler, 2019).

2.4 Physiological and Behavioral *Displays* of Anger

Anger signals are recognized in humans, especially the facial and bodily expressions that exaggerate perceptions of physical strength and fighting ability analogous to animals that bare their fangs (Ekman, 1973). Indeed, facial *displays* of anger often include jaw-clenching, indicating readiness to attack. Face displays of anger are already functional at six months of age and may demonstrate cross-cultural uniformity in its basic elements. As an example, congenitally blind children produce normative anger facial expressions. However, it should be noted that although anger displays are part of a universal species-typical system evolved by natural selection, these are partly calibrated by cultural variation (Clark-Polner et al., 2017; Potegal and Novaco, 2010). Linguistic expressions are also part of the human display of anger. Anger prosody of sound and tone as well as angry language indicating escalation are used as a communication of anger in humans (see section on linguistic expressions). Together, these facial,

bodily, and language displays (raising the voice, pounding on table, shaking a fist, breaking something, physically assaulting) allow for a rapid exchange of information about the ability to inflict costs on the provocateur(s).

3. Disease Correlates of Chronic Anger

The enduring propensity to anger feelings is characterized as high trait anger in the literature (Spielberger, 1988; Gan et al., 2016). Trait anger has been related to chronic disease and negative consequences to one's own health, wellbeing and social support (Johnson, 1990; Phillips et al., 2006; Williams, 2010). In fact, disproportionate and pathological manifestations of anger are a cross-diagnostic feature of many psychiatric disorders, and anger is known as an emotion that exacerbates mental health symptoms and complicates psychiatric recovery (for review see, Novaco, 2010). Intermittent explosive disorder (IED) is perhaps the only disorder in the Diagnostic and Statistical Manual (American Psychiatric Association, 2013) for which repeated manifestations of anger is its core feature (Coccaro, 2000). Lifetime and 12-month prevalence estimates of IED are 7.3% and 3.9%, and most persons diagnosed with the disorder display a mean of 43 lifetime attacks of anger and aggressive behavior (Kessler et al., 2006). Problematic and chronic anger is also a prominent feature in oppositional defiant disorder, bipolar disorder, and borderline personality disorder, to name a few (for review see, Fernandez and Johnson, 2016).

Importantly, these detrimental manifestations of anger do not only express themselves in psychiatric symptoms but also may result in chronic diseases of the heart and digestive and immune systems, due at least in part to the chronic arousal and hypervigilance associated with anger experiences, combined with the high cognitive and physiological resources needed to downregulate such chronic anger (Johnson, 1990). Several pathways linking anger to chronic

disease states have been explored in studies. First, anger may influence health status and disease processes through its effects on inflammation. Anger has been associated with increased circulating inflammatory and coagulation markers, such as interleukin-6 (IL-6), a pro-inflammatory cytokine, and fibrinogen (Carroll et al., 2011). Specifically, both trait anger and outward displays of anger (e.g., yelling, slamming doors) have been associated with higher IL-6 and fibrinogen, whereas better anger control (and reappraisal) predicts lower IL-6, at least among women (Boylan and Ryff, 2013). Socioeconomic status, a broad concept including educational attainment, socio-cultural variables, and ethnicity (Boylan et al., 2015), has also been shown to moderate the relationship between anger and inflammation.

Second, chronic and acute episodes of anger can be detrimental to the cardiovascular system and is considered the most robust personality-related predictor of cardiovascular disease (Russell et al., 2016). The risk of cardiovascular events following outbursts of anger has been examined in a meta-analysis (Mostofsky et al., 2014): based on the totality of the evidence, in the 2 h following episodes of anger there is a significant risk of myocardial infarction, acute coronary syndrome, ischaemic and haemorrhagic stroke, and arrhythmia among individuals at risk of a cardiovascular event. However, the impact of anger outbursts may be modified by trait anger, since individuals with an angry temperament, showing chronically high levels of physiological arousal and stress reactivity, and persons with traits characterized by anger (i.e., Type A personality) are considered coronary-prone. Experiences of competitiveness and angry, hostile and distrusting dispositions require higher levels of vigilance, resulting in prolonged neurohormonal activation conducive to atherosclerosis and coronary disease (Pollock et al., 2017). It has been shown that sympathetic effects and increased cardiac output prevail in the context of harassment or personalized recall of anger events. Thus, the persistent and pervasive

action of physiological arousal sustained by the emotion of anger can well explain the consistent relationship between anger, cardiovascular disease (Cox et al., 2017; Siegman, 1993) and hypertension (Harburg et al., 1991). Indeed, several studies have shown that high levels of both expressed and suppressed anger predict risk for hypertension and stroke across cultures (Kitayama et al., 2015), as well as increase the risk of recurrent cardiac events and earlier mortality among patients with previous coronary heart disease (Russell et al., 2016).

Third, anger has been associated with motility, functional gastrointestinal disorders, and to visceral and pain hypersensitivity, as shown for other negative emotions. For example, anger control and suppression, consisting of cognitive and behavioral efforts to restrain angry feelings, are associated with prolonged gastric emptying, and a delayed gut transit (Bennett et al., 2000; Evans et al., 1996; Zoccali et al., 2006). These effects, likely mediated by the corticotropin-releasing factor, which is involved in the central stress response, are probably a way to prevent digestion during a stressful period when energy is better spent on defense. In contrast, gastric hyperemia and increased secretion have been reported during states of acute anger and aggressive behavior (Drossman, 1998). For example, patients with irritable bowel syndrome have been shown to display increased anger, as well as colonic motor activity and decreased antral motor activity, during experimental anger-provoking conditions compared to healthy controls (Welgan et al., 2000). When classified according to the predominant bowel habit alteration as constipation or diarrhea predominant, different profiles of irritable bowel syndrome have been extracted which differ along the dimensions of anger, depression and anxiety (Muscatello et al., 2016, 2010, 2014).

4 The Neuroscience of Anger

4.1 Measurement of the Phenotype in Humans

Although anger and aggression are substantially related and may be part of a particular affective-behavioral complex, researchers differentiate between *anger*, the self-reported emotion and *aggression*, the behavior (Blair, 2012). The lack of ability to ask non-humans about their feeling state or emotion greatly limits the study of anger in animals and thus limits translation. In human studies, self-report is the predominant way in which anger is operationalized, although autonomic response, electrophysiological brain changes and facial coding have also been used in the context of experimental provocations or mood inductions (Parrott et al., 2003; Waldstein et al., 2000)—see section on brain activation in response to laboratory-induced anger. On self-report assessments, individuals are simply asked to endorse the degree to which they feel angry or endorse other statements or phrases that commonly describe the feeling (e.g., "*I feel like a keg ready to explode*"). In this, we see the first indication that operationalizations of anger are dependent on language and phrases that have been validated through psychometric studies. The State-Trait Anger Expression Inventory (STAXI) (Spielberger, 1988) is probably the most widely-used questionnaire of state and trait anger; it has been used in genetic, neuroimaging, cardiovascular, and behavioral studies for decades and has been translated in several languages. The STAXI assesses seven facets of anger. The facets are: State Anger ("how do you feel right now") and Trait Anger ("how do you usually feel"); Anger-in (expressed inwardly: "I boil inside but do not show it"), Anger-out (expressed outwardly: "I do things like slam doors"), Angry Temperament ("I have a fiery temper"), Angry Reaction ("I get angry when I'm slowed down"), and Anger Control ("I keep my cool").

4.2 Genetic Components of Anger

Twin studies have ascertained that the variance among individuals in anger and anger-related personality traits can be explained by both genetic and environmental factors (Wang et al., 2005). For example, genetically-informed studies have found that the heritability rates for State Anger and Anger-out are moderate, and higher heritability has been reported for Anger Control (Clifford et al., 2015; Deater-Deckard et al., 2007; Gagne and Goldsmith, 2011). Here we review studies linking anger to specific genotypes or polymorphisms, carefully limiting our discussion to studies using self-report anger inventories, and not aggression inventories. The literature review began by a PubMed search for (anger[Title/Abstract] AND (polymorphisms[Title/Abstract] or anger[Title/Abstract] AND gene[Title/Abstract]), yielding 48 and 121 manuscripts, respectively, which were all reviewed. Studies were included only if they had used an anger questionnaire or subscale (i.e., anger subscale of the Buss-Perry Aggression Questionnaire; Buss and Perry, 1992) in association with one or more genetic variants, and only if the participants did not have any intellectual disabilities or neurodevelopmental disorders. This selective search resulted in 21 manuscripts; the 18 which showed statistically significant results are included in Table 1. Data summarized in Table 1 show that the candidate gene approach, versus whole genome approach, has been the preferred method to investigate the genetic bases of anger. As a consequence, only a few candidate genes belonging to the monoamine pathways have been studied and many others still remain to be investigated.

The studies have involved mostly healthy subjects and individuals with a history of suicide attempts. Both in healthy controls and suicide attempters, variations in the nucleotide sequence of specific genes belonging to serotonergic and catecholaminergic

pathways, known to play a key role in impulse control disorders and aggressive behaviors, have been implicated in individuals differences in anger and anger related traits (Iofrida et al., 2014; Gagne and Goldsmith, 2011; Palumbo et al., 2018; Verona et al., 2006; Wang et al., 2005). Most of the discussed studies used the STAXI to operationalize anger (Antypa et al., 2013; Baud et al., 2007, 2009; Giegling et al., 2006, 2007, 2008; Gietl et al., 2007; Hasler et al., 2012, 2015; Perlis et al., 2007; Perroud et al., 2010; Rujescu et al., 2002, 2003; Serretti et al., 2007;Vermeersch et al., 2013; Yang et al., 2010, 2007; Yoon et al., 2012). However, a few studies used the Buss-Perry Aggression Questionnaire (Buss and Perry, 1992) (anger subscale) (Banlaki et al., 2015; Butovskaya et al., 2013), and one study (Reuter et al., 2009) used the Affective Neuroscience Personality Scale developed by Davis et al. (2003) (see Table 1). Of note, several correlational results are conflicting, suggesting that larger samples as well as correcting for confounding factors including ancestry, age, gender and the influence of the environment are needed to confirm results (Fernàndez-Castillo et al., 2017; Merjonen et al., 2011; Mick et al., 2014, 2011; Springer et al., 2007; Wang et al., 2005). Indeed, there has been considerable critique of candidate gene studies, as they have generally suffered poor replicability, likely reflecting a publication bias (Duncan and Keller, 2011; Ficks and Waldman, 2014).

Openly available data secured from the database of Genotypes and Phenotypes were analyzed for genome-wide associations of proneness to anger using the STAXI-II. They observed only one, nominally significant finding ($p = 2.9E-08$, $\lambda = 1.027$ - corrected pgc = 2.2E-07, $\lambda = 1.0015$) on chromosome 6q21 in the gene coding for the non-receptor protein-tyrosine kinase. *Fyn* signaling pathways regulating intracellular calcium

homeostasis, which are relevant to memory, learning, and neuronal survival, may in part underlie the expression of Angry Temperament (Mick et al., 2014). Nonetheless, the mostly non-significant findings of this genome-wide association study with very large sample size further calls into question the candidate gene findings referred above and listed in Table 1.

Epigenetics may be a better and more dynamic approach at identifying genetic links to anger. However, very little data exist on the epigenetic mechanisms underlying anger and anger-related personality traits. Only one study reported an association between anger and higher levels of methylation within the promoter region of the oxytocin receptor gene, which has been associated with increased activity of the amygdala in response to angry faces (Puglia et al., 2015).

4.3 Gene-Brain-Anger Relationships

The advent of neuroimaging techniques advanced the search for the neural substrates of human anger. Functional MRI (fMRI) allows for the collection of brain activity data, which as compared to positron emission tomography, has adequate temporal and high spatial resolution, facilitating the study of dynamic processes and network activations. A small set of genetic studies tested associations of trait anger and genes with brain activation using fMRI. For instance, male carriers of the monoamine oxidase A low activity risk allele (*MAOA*-L), compared to carriers of the *MAOA*-H (high activity alleles), show altered brain activity in lateral PFC and anterior cingulate cortex (ACC) during social and emotional tasks (Meyer-Lindenberg et al., 2006), including left lateralized amygdala and thalamic response to negative word presentations (Alia-Klein et al., 2009). Denson et al. (2012), found a functional connectivity between the amygdala and dorsal ACC when participants were asked to control their angry

feelings in response to an insult. In a follow-up study, insult by a rude experimenter increased ACC and amygdala activation (Denson, 2014), and this heightened activation mediated the relationship between MAOA-L genotype and self-reported effort at controlling their angry feelings. Other studies show an involvement of *MAOA-L* in resting-state default mode brain networks (Clemens et al., 2015; Klasen et al., 2018; Ma et al., 2018).

Genetic variation in human tryptophan hydroxylase 2 (TPH2, G/G allele) has also been associated with anger expression and anger control. In one study, participants with the G/G genotype had significantly higher anger control scores and significantly lower gray matter in the ventral orbitofrontal cortex (OFC), compared to the T allele carriers (G/T and T/T genotype) (Yoon et al., 2012). Likewise, outward anger expression and trait anger scores were negatively correlated with gray matter concentration in the ventral OFC and hippocampus, suggesting that reduced gray matter concentration in ventral OFC is related generally to anger scales (whether anger control or anger expression). The dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32), which has been linked to anger in a large cohort, is also related to left amygdala volume (Reuter et al., 2009). Finally, a polymorphism near the cyclic adenosine monophosphate response element binding protein gene (CREB1) has recently been associated with greater self-reported effort at anger control, with risk for antidepressant treatment-emergent suicidality in men, and with insula activation to behavioral avoidance of angry faces (Perlis et al., 2008). These few candidate gene, brain, and anger studies are quite consistent in implicating the same brain networks that are mapped during anger induction, as reviewed below.

Table 1 about here

4.4 Literature Review Criteria

There are several noteworthy studies and reviews of fMRI processing of angry faces and brain activity during anger induction conditions, as well as brain activation during reactive aggression paradigms (e.g., Gan et al., 2016; Gilam and Hendler, 2017a,b; Kose et al., 2015; Krämer et al., 2007; Lotze et al., 2007). In this review however, we summarize studies on the neural underpinnings of a feeling state of anger rather than a behavior that might be assumed to follow anger (i.e., aggression). Thus, we conducted a search of the literature exclusively for fMRI studies that utilized anger induction procedures in both healthy and patient populations. The literature review began by a PubMed search for (anger[Title/Abstract] AND (fMRI[Title/Abstract] OR functional Magnetic Resonance Imaging[Title/Abstract])), yielding 175 manuscripts, which were all reviewed. Studies were included only if they had a clear anger induction (i.e., a condition that was associated with an increase in state anger) during fMRI. Studies were excluded if individuals with neurodevelopmental or intellectual disabilities were included or if they only reported a correlation with anger traits, measured retaliative behavior but not anger specifically, or showed passive viewing of angry faces, for example. This selective search resulted in only 13 manuscripts as described below and in Table 2 and Figure 2. (Positron emission tomography imaging studies were not included in this review. see especially, Dougherty et al., 2004; Dougherty et al., 1999)

FIGURE 2 ABOUT HERE

4.5 Brain Networks of Laboratory Induced Anger Feelings

The *salience network* (see Table 2) consists of the dorsal ACC and anterior insular cortex, as well as subcortical areas including parts of the thalamus, the amygdala, and the brain stem dedicated to detecting behaviorally-relevant salient changes in internal states and any threatening external stimuli (Menon, 2015; Seeley et al., 2007). In the studies reviewed, anger induction was

linked to activation of the anterior insula, the thalamus, and the amygdala (Denson et al., 2012, 2014; Fabiansson et al., 2012; Gilam et al., 2018, 2015, 2017b; Herpertz et al., 2017; Jacob et al., 2013; Krauch et al., 2018; Pawliczek et al., 2013; Radke et al., 2018). In concert, these brain regions facilitate autonomic arousal, interoception and activation of the stress response, upon recognition of threat or provocation. It should be noted that several studies in Table 2 focused on anger in borderline personality disorder, due to the high prevalence of anger and aggression in borderline patients. Compared to the activation in healthy controls asked to take the perspective of a protagonist that is treated disrespectfully, borderline patients in the same induction reported increased anger and showed stronger activation of the amygdala. Another study used a script-driven imagery approach involving interpersonal rejection and physical aggression, and found stronger amygdala reactivity in men with borderline personality disorder compared to both women with the same disorder and healthy control men (Herpertz et al., 2017). Interestingly, the only study not showing *salience network* activation involved a small sample of violent offenders (Tonnaer et al., 2017).

Another dominant network in anger induction is the default mode network that is also called the *mentalizing network*. Mentalizing activates midline-parietal and frontal areas including the precuneus, posterior cingulate cortex (PCC), and the dorsal medial PFC, as well as lateral temporo-parietal areas (Adolphs, 2009; Van Overwalle, 2009). These mid-line areas of the so-called default mode network are active during rest and have been associated with self-referential processing (Fox et al., 2005; Greicius et al., 2003; Raichle et al., 2001). In several of the reviewed studies, anger experiences activated primarily the PCC and the precuneus of the *mentalizing network* (Krauch et al., 2018; Tonnaer et al., 2017), suggesting engagement of self-referential mental imagery (Cavanna and Trimble, 2006) and social cognition (Laird et al.,

2011). Interestingly, there was a significant difference in precuneus activation in adolescent borderline vs. control groups (Krauch et al., 2018). Only two studies failed to show activation of the mentalizing network during anger, which could be a result of their use of region-specific analyses (vs. whole brain analyses) (Gilam et al., 2017b; Jacob et al., 2018).

The *self-regulation network* known as the executive network consists of medial and lateral PFC areas including the ventromedial PFC, the subgenual/rostral ACC, the inferior frontal gyrus, and the dorsolateral PFC. Anger feelings induced by mental imagery and autobiographical recall activated the ventromedial PFC, the inferior frontal, and the dorsolateral PFC (Fabiansson et al., 2012; Herpertz et al., 2017; Jacob et al., 2018; Laird et al., 2011; Tonnaer et al., 2017) involved in response selection and behavioral control. Interestingly, violent offenders experienced more pronounced anger feelings while showing higher activity in the self-regulation network and lower activity in the mentalizing network during anger engagement relative to healthy controls (Tonnaer et al., 2017). Similarly, individuals with better anger regulation had greater activity in the ventromedial PFC, and less activity in the brainstem's locus coeruleus area, as well as greater medial thalamus-dorsal posterior insula functional connectivity (Gilam et al., 2015).

A recent cross-over, sham-controlled, double-blind simultaneous fMRI and brain stimulation study supports a potential causal role of the ventromedial PFC in anger regulation (Gilam et al., 2018). Results indicated that brain stimulation led to increased ventromedial PFC activity during the processing of unfair anger-inducing offers, resulting in behavioral improvement. Additional support for the ventromedial PFC's role was demonstrated in analysis of network connectivity during emotion regulation (Jacob et al., 2018). There also seems to be cross-talk between the *salience* and *regulation* networks, as increased functional connectivity has been observed between the amygdala and the inferior frontal gyrus after anger induction in healthy individuals

(Gilam et al., 2017b), as well as in women with borderline personality disorder while imagining angry situations (Herpertz et al., 2017). This finding is also supported by increased functional connectivity between the amygdala and the dorsolateral PFC, the dorsal ACC, and the OFC following provocation with insults (Denson et al., 2012). Although it is expected that the vast majority of anger studies should show prefrontal involvement during attempts to constrain anger, several of the studies listed in Table 2 did not in fact show activations in the self-regulation network associated with anger control (Denson, 2014; Gilam et al., 2015; Jacob et al., 2018; Krauch et al., 2018). Regardless, the increased ventromedial PFC activity combined with thalamus-insula connectivity presumably indicates participants' efforts to attenuate their angry feelings (for example, to accept unfair offers) in order to increase their monetary gain in a task (Gilam et al., 2015). In support of this, participants with high anger traits who had been provoked still chose to button-press for money as opposed to button-press for retaliation (Gan et al., 2016). This would suggest, and remains to be explored, that reward alternatives can help attenuate anger expression or aggression.

Traditionally, the appetitive approach system is assumed to be evoked by positively valenced stimuli and generally associated with positive affective experiences (Elliot, 2006). However, approach motivation can be also activated by negative stimuli and the instigation of approach motives can constitute a negative affective experience (Carver, 2004; Elliot et al., 2013). The potential involvement of the reward network, or what we term here, the *habit network*, is present in only two studies that induced script-driven anger imagery and recall of anger-inducing autobiographical memories, showing activation of the putamen, the caudate and the globus pallidus (Fabiansson et al., 2012; Krauch et al., 2018). Interestingly, the *habit network* seems to be specifically linked to personal and internally induced anger experiences.

4.6 Internally versus Externally Induced Anger

From the review of the literature, we note that experimental paradigms using anger inductions are either *internally* or *externally* generated. Internal anger induction procedures rely on each individual's mental imagery and recall of autobiographical memories, and are associated with activation of the insular and limbic-subcortical parts of the *salience network*, in particular, but also in the parietal parts of the *mentalizing network*, the ventromedial and ventrolateral PFC of the *self-regulation network*, as well as the striatal *habit network* (Denson et al., 2012, 2009; Fabiansson et al., 2012; Herpertz et al., 2017). External induction procedures induce anger by provocation from outside, for example with unfair monetary offers (Gilam et al., 2015), social exclusion (Radke et al., 2018), frustrating unsolvable tasks and insults (Denson et al., 2012). Notably, both anger induction approaches activate similar networks but external induction shows a more widespread activation, tending to activate dorsal ACC, possibly due to conflict between wanting to perform well in the task at hand and distraction by the social provocation. Across induction types whether internally or externally induced, the pattern of activation relevant to the *self-regulation network*, including the ventromedial PFC, the inferior frontal gyrus, and the dorsolateral PFC, was common to all inductions, in line with recently proposed domain general scaffolding for how the human brain constructs an experience of anger (Gilam and Hendler, 2017a).

TABLE 2 ABOUT HERE

4.7 Imaging Studies of High Trait Anger and IED

Since disproportionate bouts of anger and reactive aggression in response to provocation are core symptoms of IED, imaging studies on this population can give insight into the function and structure of neural networks of high trait anger. Functional MRI studies documented

disproportionate reactivity to emotional stimuli with impaired PFC response by individuals with IED. In two studies there was exaggerated amygdala reactivity and diminished OFC activation and poor amygdala-OFC coupling in response to a social threat signal (Coccaro et al., 2007; McCloskey et al., 2016). Another study found that to high-arousal unpleasant images increased activation in the left-lateralized ventral fronto-parietal attention network in individuals with high trait anger as compared to controls (Alia-Klein et al., 2018). During a color-word Stroop task that provides challenge to inhibitory control, error-related activity was especially high in IED in the dorsolateral PFC that correlated with trait anger expression (Moeller et al., 2014). In one study, men with threshold diagnosis and subclinical symptoms of IED, showed higher resting state connectivity efficiency in left lateralized regions of the habenula, thalamus, dorsolateral PFC, right temporal pole, as well as a trend for decreased connectivity clustering in mentalizing network nodes (Gan et al., 2018).

There is some evidence that cortical to subcortical connectivity is structurally impaired in individuals with high trait anger. As compared to psychiatric controls, individuals with IED had lower white matter integrity in long-range connections between the frontal and temporo-parietal regions (Lee et al., 2016). Gray matter volume was found to be significantly lower also in the OFC, ventromedial PFC, ACC, amygdala, insula, and uncus (Coccaro et al., 2016). A study examined the volume and shape of the amygdala-hippocampal complex, using morphometric analysis of structural 3-Tesla MR scans, and found morphometric deformation suggestive of cell loss in amygdala and hippocampal structures bilaterally in IED participants (Coccaro et el., 2015). A later study found trait anger has been associated with gray matter volume in the right amygdala, as well as in the lateral occipital cortex and middle frontal gyrus (Wang et al., 2017).

4.8 Summary of neurobiology of anger: common and unique elements of feelings

Genetically-informed studies have found that the heritability rates for state or trait anger are moderate, and higher heritability has been reported for anger control. Nevertheless review of the polymorphisms or whole-genome associated with anger (Table 1) are limited by small sample sizes and candidate genes; therefore nothing much can be summarized except for noting that more studies should ascertain genetic correlates of anger.

It is difficult to separate anger from its common consequence (aggression) and to separate anger from other negative feeling states (fear, for example, which is also induced by perceived threat) to understand unique dynamics and the neurobiology of anger. Other negative feelings cause an individual to withdraw: fear, sadness and disgust propel individuals away from the provocation, and often show right-lateralized EEG (Mathersul et al., 2008). Looking at Table 2 and Figure 2, the fMRI review produced clear left lateralization particularly in the *mentalizing* and the *self-regulation networks* but also in *salience network* involving left-lateralized insula activation. This is reminiscent of anger's general motivational orientation towards approach behavior (Carver and Harmon-Jones, 2009) with left-lateralized asymmetry during anger (for a review, see Harmon-Jones and Gable, 2017). Researchers have found increased activation in left anterior cortical areas during the actual experience of anger (Harmon-Jones and Sigelman, 2001), and correlations of this lateralized activation with trait anger (Harmon-Jones, 2004; Harmon-Jones and Allen, 1998) and provocation-induced aggressive behavior (Verona et al., 2009). Results from neuro-imaging studies corroborate these findings (see the meta-analysis by Murphy et al., 2003). This left lateralization is quite unique to anger, reflecting a readiness to confront the source of provocation (Harmon-Jones and Sigelman, 2001).

Whether discrete emotions correspond to distinct brain regions (Izard, 2010) or to generalized brain networks (Lindquist et al., 2012), it is apparent that the experience of anger and

correlations with trait anger involve multiple brain regions that form networks that may be linked back to elements of anger (e.g., the salience network with autonomic arousal). Most studies documented enhancement of limbic and other regions of the salience network with concomitant impairment in the self-regulation and mentalizing networks, with some morphometric studies showing structural impairments in some of these networks. The emergent pattern validates theories on reactive aggression (Siever, 2008). Yet this pattern is also common in addiction and other externalizing behavior disorders. Possibly the self-regulation impairment is overlapping externalizing disorders while disproportionate emotional response involve different subcortical regions in different phenotypes (e.g., amygdala involvement in IED, striatal involvement in addiction). Nevertheless there are not enough studies to substantiate a region-specific uniqueness to anger. The network activations in Figure 2 are reminiscent of feeling states during appetitive or rewarding cues, when wanting is stronger than liking as in addiction to substances (Berridge and Robinson, 2016). Indeed, the conflict between desire to retaliate and self-regulation induced by feelings of anger suggest that these feelings have reinforcing properties and that in order to stop escalation toward unwanted behaviors, PFC brain networks are actively recruited to regulate choices and behaviors associated with anger feelings. In the section below on the linguistic framework of anger, the conflict between intensity of feeling and self-regulation is reflected in language that describes anger.

5. A Linguistic Framework for Feelings of Anger

With the current state of neurobiology research of anger as a backdrop, our team was specifically tasked to review the language that people use to express anger-related feelings and components. The Human Affectome Project taskforce agreed that any attempt to create a

linguistic inventory of articulated feelings would need to first define feelings in a manner that can help us understand the full range of terms. The resulting definition is as follows:

> *A "feeling" is a fundamental construct in the behavioral and neurobiological sciences encompassing a wide range of mental processes and individual experiences, many of which relate to homeostatic aspects of survival and life regulation (Buck, 1985; Damasio and Carvalho, 2013; LeDoux, 2012; Panksepp, 2010; Strigo and Craig, 2016). A broad definition for feeling is a perception/appraisal or mental representation that emerges from physiological/bodily states (Damasio and Carvalho, 2013; LeDoux, 2012; Nummenmaa et al., 2014), processes inside (e.g., psychological processes) and outside the central nervous system, and/or environmental circumstances. However, the full range of feelings is diverse as they can emerge from emotions (Buck, 1985; Damasio and Carvalho, 2013; Panksepp, 2010), levels of arousal, actions (Bernroider and Panksepp, 2011; Gardiner, 2015), hedonics (pleasure and pain) (Buck, 1985; Damasio and Carvalho, 2013; LeDoux, 2012; Panksepp, 2010), drives (Alcaro and Panksepp, 2011), and cognitions (including perceptions/appraisals of self (Ellemers, 2012; Frewen et al., 2013; Northoff et al., 2009), motives (Higgins and Pittman, 2008), social interactions (Damasio and Carvalho, 2013; Gilam and Hendler, 2016; LeDoux, 2012; Panksepp, 2010), and both reflective (Holland and Kensinger, 2010) and anticipatory perspectives (Buck, 1985; Miloyan and Suddendorf, 2015).*
>
> *They are often represented in language (Kircanski et al., 2012) (although they can sometimes be difficult to recognize and verbalize) and some feelings can be*

influenced/shaped by culture (Immordino-Yang et al., 2014). Feelings that are adaptive in nature (Izard, 2007; Strigo and Craig, 2016) serve as a response to help an individual interpret, detect changes in, and make sense of their circumstances at any given point in time. This includes homeostatic feelings that influence other physiological/body states, other mental states, emotions, motives, actions and behaviors in support of adaptation and well-being (Damasio and Carvalho, 2013; Strigo and Craig, 2016). However, some feelings can be maladaptive in nature and may actually compete and/or interfere with goal-directed behavior.

5.1 Linguistic Themes of Feeling Angry

Using the definition of feelings as a starting point, the linguistics team of the Human Affectome Project undertook a formal linguistic analysis and ultimately proposed nine broad categories of feeling states (Siddharthan et al., 2018). We reviewed the expressions extracted for the Anger category and found that anger words could generally be grouped along a continuum that refers to: the *degree of arousal*, the *speed of escalation*, outward *displays*, and sources of *provocation*.

The degree of arousal is a very important component of anger feelings, as reviewed above; not surprisingly, it is reflected in language with terms reflecting the degree: mild anger (e.g., annoyed) at one extreme and intense anger (e.g., feelings of fury) at the most extreme, with moderate levels of anger conveyed by a word like "*angry*". The linguistic expressions of arousal tended to operate within a temperature metaphor, such as in heat escalation ("boiling up"). The speed in which anger escalates and is expressed, which reflects the components of display and regulation of anger, is another notable observation that came from our analysis of anger words. A

gradual escalation of anger is expressed as a building of pressure or bringing the internal state to a boiling point. Also notable were word senses that referred to anger-related displays (e.g., rancorous) and behavioral outbursts (e.g., rage). Lastly, some words were related to different sources of provocation that reflected attributions about the social provocations, such as experiences of social threats (e.g., alienation) or unfair treatment (e.g., indignation) and the resulting feelings of anger directed at the sources of those threats (e.g., animosity, misanthropy) (Supplemental Materials: anger spreadsheet). These metaphors involving heat, escalation and building-pressure are also found in self-report questionnaires (e.g., STAXI, Buss-Perry Aggression Questionnaire), which are primary operationalizations of the phenotype and themselves constitute a corpus of linguistic phrases related to anger surveyed among populations of individuals (Buss and Perry, 1992; Spielberger, 1988).

5.2 Motivators of anger: Need for safety and need for dominance and reward

It is argued that anger has had an adaptive role in improving conditions for optimum life fitness and survival. As with fear, anger can be motivated by a *need for safety*. There is a functional logic underlying anger and the motivation to use anger depending on perceived formidability of the target or threat (e.g., the extent of body size and apparent body strength or power through authority). Thus, anger is displayed to compel a target to bargain, so as to avoid the threat posed by anger and to incentivize the target to withdraw. For example, the recalibrational theory of anger is described as an attempt to reverse engineer anger (Sell, 2006; Sell et al., 2009). In essence, the theory posits that anger is a response designed to bargain for better treatment. At the same time, anger can be an effective instrument of threat for the purpose of intimidation and *domination of others*. The superordinate goal of this action tendency is to obtain control, and the "primary actions" employed to achieve this goal are "attacking,

intimidating, hurting, biting, scratching, reactance" (Frijda and Parrott, 2011). Indeed, anger that is elicited by a provoking situation is predicted by higher behavioral activation but not by behavioral inhibition scores and comprises the pursuit of appetitive goals, responsiveness to reward, and a tendency to seek out new reinforcers and act quickly (Carver and White, 1994). Interestingly, children who tended to react exuberantly to emotionally positive situations at age five were also more anger-prone in negative situations and positive emotions–exuberance significantly predicted externalizing problems two and three years later (Rydell et al., 2003).

5.3 Cultural variation in anger feelings and displays

The recalibrational theory describes anger as a social bargaining tool (Sell, 2006; Sell et al., 2009, 2017). Displaying anger is purportedly designed to gather the target's attention, and the most common response to anger is a rapid information exchange. The theory also holds that apologies typically extinguish anger. From this perspective, anger responses coordinate facial expressions, vocal changes, verbal arguments, the withholding of benefits, the deployment of aggression, and a suite of other cognitive and physiological variables in the service of leveraging bargaining position into better outcomes. Sell et al (2017) recently conducted twenty-three experiments to test the theory's predictions about anger using participants from the US, Australia, Turkey, Romania, India, and Ecuador. Using vignettes describing anger-inducing scenarios, the team found that subjects across all six cultures similarly judged that anger would intensify when: (i) the cost was large, (ii) the benefit the offender received from imposing the cost was small, or (iii) the offender imposed the cost despite knowing that the angered individual was the person to be harmed. So, this theoretical framework for anger appears to have a degree of validity across different cultures.

Although the anger is evident across most cultures, anger responses are highly contextualized and therefore subject to variation across cultures (Alonso-Arbiol et al., 2011; Bender et al., 2012; Boiger et al., 2013). Distinct cultural variations in anger have been shown in research. For example, Kirchner et al. recently compared anger response differences between American and Japanese respondents, in a study designed to explore the transformation of high-intensity shame into anger (a phenomenon known as "humiliated fury") (Kirchner et al., 2018). The research team conducted two studies and compared the occurrence of shame-related anger in North American cultural contexts (where shame is devalued and anger is valued) to its occurrence in Japanese culture (where shame is valued and anger is devalued). In both studies, shame predicted anger for American respondents but not Japanese participants. Japanese respondents only reported shame-related anger when presented with North American cultural contexts, suggesting that shame-related anger is a culture-specific phenomenon.

In fMRI study, de Greck et al (2012) scanned Chinese and German healthy subjects to determine whether or not these cultural differences would foster distinct brain activity Analyses revealed several brain regions that showed comparable hemodynamic responses across groups. However, their results confirmed some cross-cultural differences, specifically enhanced emotion regulation mediated by the left dorsolateral PFC during empathy to anger faces among participants from the interdependent culture vs. individualized culture. The tolerance of anger in the individualized culture was associated with increased activity of the right inferior and superior temporal gyrus and the left middle insula (de Greck et al., 2012). Together these results support features of anger experience common across cultures and other elements of distinctions in the processing of anger across cultures with different world views.

6. Conclusions

In this review of the neuroscience of anger we introduced the components of anger feelings (see Figure 1). We also find in the literature that chronic anger that is a ubiquitous experience in some individuals is associated with the development and worsening of major disease states (Mostofsky et al., 2014). In terms of psychiatric symptoms, high trait anger is associated with treatment resistance and frequent relapse of psychiatric symptoms, relative to low trait anger (Fernandez and Johnson, 2016). Although anger is common in numerous disorders, only one psychiatric disorder features bouts of anger as a core symptom. That is, IED is quite prevalent in the general population and almost equal in prevalence across men and women (Kessler et al., 2006). In sum, regulating and coping with anger is crucial for the brain (reducing psychiatric problems) and for other organs in the body, making a strong case for appropriate anger regulation generally being more advantageous to optimal living than chronic anger expression.

Our first literature search on common genetic markers of anger traits (Table 1) captured mostly monoamine candidate gene studies, limiting our knowledge of genome-wide association that might open the door for other unknown genes or the interaction across hundreds or thousands of genes. One genome wide study found a link with Fyn signaling pathways (Mick et al., 2014), although the effect size was quite small, as is typical in such studies relating genome to behavioral phenotypes. We conclude that more genetic and epigenetic studies are needed that are genome-wide using larger samples and varied populations to ascertain the full picture. Reviewing brain-candidate gene studies of anger, we found that these documented network impairments analogous to impairments found in individuals with high anger and aggression.

In our second literature review (Table 2, Figure 2) we summarized fMRI studies of human brain networks activated specifically during experimentally induced anger feelings. These

networks correspond nicely to components of anger that were introduced in the beginning of the manuscript: the *salience network* amygdala and insula involvement captured components of autonomic arousal and stress reactivity, the *mentalizing network* captured cognitive components and self-referential anger experiences, and interactions between salience and self-regulation and mentalizing networks through connectivity of the ventromedial PFC with thalamus and insula. It was found, as in many reviews and experiments on anger, that there is a strong left lateralization in active and suppressed brain networks, possibly as a result of the strong approach tendency in anger feelings (Carver and Harmon-Jones, 2009). Notably, anger feelings appear to trigger opposing processes between PFC top-down control and subcortical limbic pressure. Particularly compelling, a recent study demonstrates that modulating activity in ventromedial PFC with transcranial direct-current stimulation led to decreased aggression retribution, and mitigated the increase in self-reported anger following provocation (Gilam et al., 2018).

Just as anger triggers specific body and brain responses, anger is expressed through specific language in humans (Supplemental Materials: anger spreadsheet). It was observed that anger words could generally be grouped along a continuum that refers to the *degree of arousal*, the *speed to escalation*, types of anger *display*, and *source of provocation*. Linguistic expressions capture arousal and pressure terms, and loss of regulation. The language also reflects the different possible sources of provocation and attributions about social situations that may lead to anger, such as being ignored or alienated. Despite these interpretations of the literature, research is not available that explicitly tests associations between language displays and particular patterns of neural activation or arousal. These types of studies would advance knowledge of the ways in which language reflects the psychobiological experiences of humans. The language analysis further suggests that anger is motivated by both a need for safety and a need for

dominance, depending on individual personality traits and on the situation at hand. Thus, anger is expressed to manage fear (reduce threats to safety), or to increase a sense of reward from the act of dominating others. We note that self-report questionnaires that characterize state or trait anger are a linguistic corpus in themselves, as they use language to describe the feeling and have individuals endorse the feeling and the degree to which it describes them. Thus, research on the gene and brain correlates of individual differences in self-report anger are themselves a guide to mapping language to neuroscience. The main problem is that studies of anger are few and disparate, relative to research on the behavioral output of anger (e.g., aggression). There is clearly a need for an integrated model of affect that encompasses anger, and, as such, more studies are needed on the experience and the regulation of anger feelings.

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Glossary

ACC	anterior cingulate cortex
Anger	A negative, high arousal feeling and basic emotion that includes specific facial expressions and specific cognitions attributed; and approach motivation toward the target of anger.
Feeling	perception/appraisal or mental representation reflective and anticipatory perspective that emerges from physiological/bodily states, from emotions drives and cognitions.
fMRI	Functional magnetic resonance imaging. Used to image the brain during experience of anger as compared to other states in humans.
FYN	non-receptor protein-tyrosine kinase. Signaling pathways regulating intracellular calcium homeostasis, associated with anger traits in one genome-wide association study.
Habit Network	The appetitive approach system generally associated with positive feelings. It was active during two internally induced autobiographical anger induction showing activation of the putamen, caudate and globus pallidus.
Human Affectome Project	Organized in 2016 by a non-profit organization, Neuroqualia. The project produced a series of overarching reviews focused on the development of a comprehensive and integrated model of affect.
IED	Intermittent explosive disorder in DSM-5: repeated manifestations of anger are its core feature. Higher prevalence in the community as compared to antisocial personality disorder.
IL-6	Interleukin 6 a pro-inflammatory cytokine and fibrinogen. Positive correlation with anger expression.
MAOA	Monoamine oxidase A MAOA polymorphism associated with anger and with aggression in interaction with severe maltreatment.
Mentalizing network	Default-mode, active during rest and has been associated with self-referential processing. Anger induction activated primarily the PCC and the precuneus of this network.
OFC	Orbitofrontal cortex
PCC	Posterior cingulate cortex Part of the mentalizing network
PFC	Prefrontal cortex. All aspects (lateral, medial, ventral, dorsal) participate in anger and anger control
Prosody	The patterns of rhythm and sound or intonation used in anger are quite unique and have a high rate of accurate indentification.
Reappraisal	A cognitive strategy that is used to reduce emotional intensity by either *distancing* oneself from the provocation or *re-evaluating* it as less threatening or provoking than initially thought.
Rumination	A cognitive aspect of anger; rumination or recurrent thoughts about the provoking situation give rise to persistent negative emotions.
Salience network	Detects behaviorally-relevant salient changes in internal states and any threatening external stimuli. Anger induction was linked to activation of the anterior insula, the thalamus, and the amygdala of this network.
Self-Regulation Network	Executive network, involved in response selection and behavioral control. Anger feelings induced by autobiographical recall or by provoking task conditions activated several regions of the PFC.
STAXI-II	State-Trait Anger Expression Inventory – second edition widely-

	used questionnaire of state and trait anger.
Valence	The direction of any stimuli as positive or negative in quality. Anger cues are negative valence but they are involved in high arousal versus sadness, that is also negatively valenced but it involves low arousal.

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Fig. 1. The dynamics of the threat perception-anger arousal feedback loop pointing upward toward the escalation of anger and expression of aggression. *Low road* refers to the pathway where provocation can lead to aggression, often bypassing the anger arousal loop. Bottom panel: facial, bodily and threat displays.

Fig. 2. Brain regions activated during anger induction in the reviewed literature, were organized into four major networks, color coded as follows: Mentalizing Network (orange), PCC: posterior cingulate cortex, vmPFC: ventromedial prefrontal cortex, SFG: superior frontal gyrus, MTG: middle temporal gyrus, STG: superior temporal gyrus. Salience/threat detection Network (blue), dACC: dorsal anterior cingulate cortex. Habit Network (purple). Self-Regulation Network (red), dlPFC: dorsolateral prefrontal cortex, IFG: inferior frontal gyrus, vmPFC: ventromedial prefrontal cortex. rACC: rostral anterior cingulate cortex, sgACC: sub-genu anterior cingulate cortex. Table 2 results are overlaid on templates MNI coordinates x= -7 (sagittal), y=-4 (coronal) and z= -1 (axial).

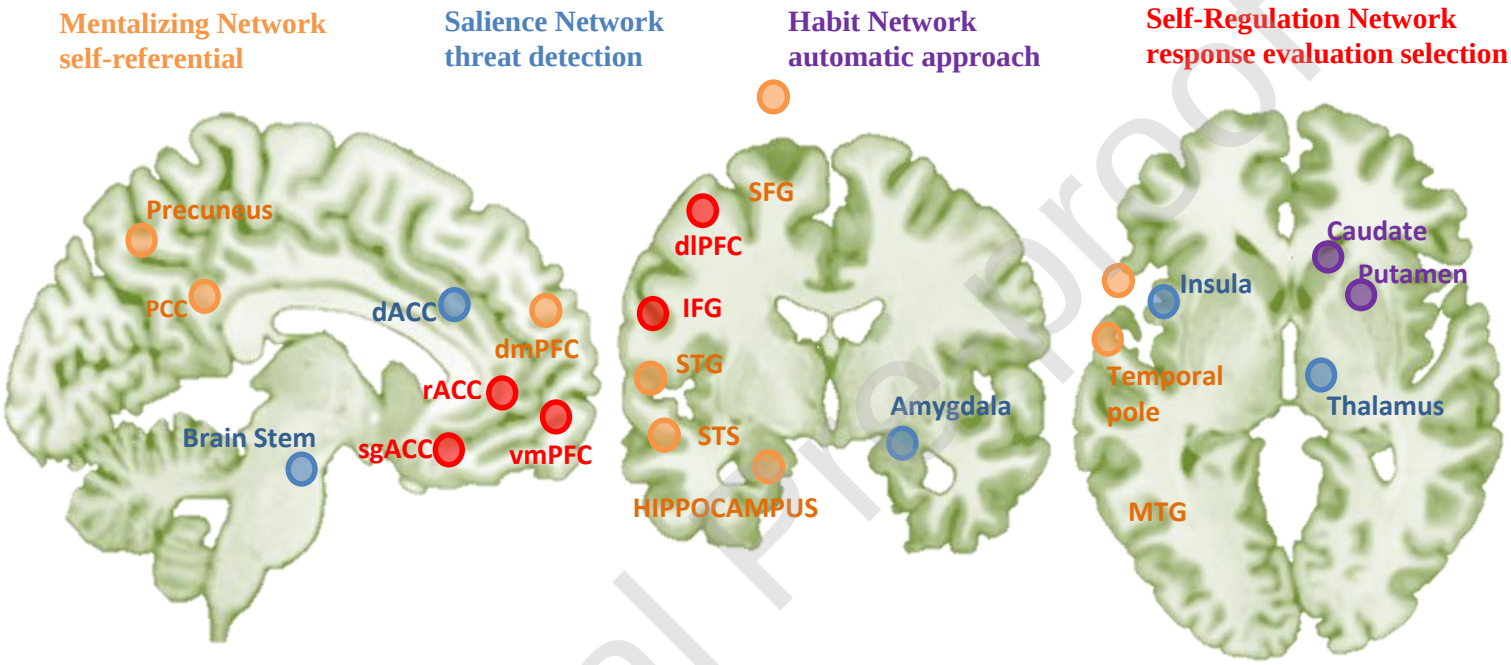

Table 1. Gene associations with anger questionnaires scores. "+"= positive association, "-"= negative association, n.a= not associated, n.t.= not tested

Gene symbol / Gene name	**Polymorphism / risk allele**	**State trait anger expression inventory STAXI**							**Buss-Perry Aggression Questionnaire**	**Affective Neuroscience Personality Scale**	**Sample**
		State anger	**Trait anger**	**Anger-In**	**Anger-Out**	**Anger Temperament**	**Anger Reaction**	**Anger Control**	**Anger subscale**	**Anger subscale**	**Sample PMID Author, year**
ABCG1 ATP binding cassette subfamily G member 1	rs225374 G-allele	+	n.a.	n.a.	+	n.a.	n.a.	n.a.	n.t.	n.t.	167 German suicide attempters (109 women) and 312 (174 women) German healthy subjects 17187964 Gietl et al., 2007
TPH1 tryptophan hydroxylase 1	A218C (rs1800532) C-allele	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	+	n.t.	n.t.	875 (619 women) European suicide attempters 20002200 Perroud et al., 2010
		+	+	+	n.a.	+	+	n.a.	n.t.	n.t.	86 (56 women) German suicide attempters 12399958 Rujescu et al., 2002
	A779C (rs1799913) C-allele	+	+	+	n.a.	+	+	n.a.	n.t.	n.t.	
	A218C (rs1800532) C-allele	n.a.	n.a.	n.a.	n.a.	n.t.	n.t.	+	n.t.	n.t.	
		n.a.	n.a.	n.a.	n.a.	n.t.	n.t.	+	n.t.	n.t.	544 (378 women) French suicide attempters 19220488 Baud et al., 2009
THP2 tryptophan hydroxylase 2	G703T (rs4570625) G/G	n.a.	n.a.	n.a.	+	n.t.	n.t.	n.a.	n.t.	n.t.	228 healthy Korean women 20628266 Yang et al., 2010
		n.t.	n.a.	n.a.	n.a.	n.t.	n.t.	+	n.t.	n.t.	63 healthy Korean women 22649797 Yoon et al., 2012

HTR2A serotonin receptor 2A	C1.439T (rs6311) C/C	n.a.	+	n.a.	-	n.a.	+	n.a.	n.t.	n.t.	203 (135 women) German suicide attempters 16814396 Giegling et al., 2006
	rs7322347 T/T	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	+	n.t.	877 (481 women) healthy Hungarian 25658328 Banlaki et al., 2015
MAOA monoamine oxidase A	MAOA uVNTR 4R-4R	n.t.	n.a.	n.a.	+	n.t.	n.t.	n.a.	n.t.	n.t.	211 healthy Korean women 17943028 Yang et al., 2007
		+	n.a.	n.a.	n.a.	n.t.	n.t.	n.a.	n.t.	n.t.	Perroud et al., 2010
	rs6323 C-allele females	n.a.	n.a.	n.a.	+	n.a.	n.a.	n.a.	n.t.	n.t.	171 (111 women) German suicide attempters 23111930 Antypa et al., 2013
COMT catechol-o-amine-oxidase	Val158Met (rs4680) Val/Val in females	n.a.	+	n.a.	n.a.	n.t.	n.t.	-	n.t.	n.t.	427 (302 women) French and Swiss suicide attempters 17510945 Baud et al 2007
	Val/Val	+	n.a.	+	-	n.a.	n.a.	n.a.	n.t.	n.t.	149 German male suicide attempters 12842306 Rujescu et al., 2003
	Val-allele	n.a.	+	n.a.	+	n.t.	n.t.	n.a.	n.t.	n.t.	Perroud et al., 2010
	Val-allele with history of child abuse	n.a.	+	n.a.	n.a	n.t.	n.t.	n.a.	n.t.	n.t.	
	Val/Val	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.a. + in interaction with DAT1-10 repeat	n.t.	138 Datoga men 24193094 Butovskaya et al., 2013
SLC6A3 solute carrier family 6 A3	DAT1 40bp-VNTR 10 repeat	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.a. + in interaction with	n.t.	

	9.5 repeat								rs4680-Val/Val		
		n.a.	-	n.a.	n.a.	n.a.	n.a.	n.a.	n.t.	n.t.	77 (22 girls) ADHD subjects 25555995 Hasler et al., 2015
DARPP-32 dopamine-cAMP-regulated neuronal phosphoprotein	rs907094 T-allele	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	+	838 (511 women) healthy Germans 19463699 Reuter et al., 2009
CREB1 CAMP responsive element binding protein 1	rs4675690 C/C	n.a.	n.a.	n.a.	+	n.t.	n.t.	n.a.	n.t.	n.t.	265 European male suicide attempters 22574704 Hasler et al., 2012
		+ with STAXI expression index score that provides a summary measure of the experience of angry feelings							n.t.	n.t.	94 Caucasians (52 women) with major depressive disorder 17300755 Perlis et al., 2007
DRD2 dopamine receptor 2	Taq1A (rs1800497) A2-allele	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	+	n.t.	Butovskaya et al., 2013
ESR1 estrogen receptor α	PvuII P-allele in females	n.t.	n.a.	+	-	n.t.	n.t.	n.t.	n.t.	n.t.	599 healthy Caucasian adolescents (298 girls) 23206990 Vermeersch et al., 2013
	XbaI X-allele in females	n.t.	n.a.	+	-	n.t.	n.t.	n.t.	n.t.	n.t.	
AR androgen receptor	CAG repeats	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	-	n.t.	Butovskaya et al., 2013

Table 2. Summary table of our literature search through the PubMed database, probing for articles on anger in human populations as studied by functional magnetic resonance imaging (fMRI) technology. The review excluded all search results that did not show a clear behaviorally validated anger-induction procedure (i.e., passive film viewing tasks). All abbreviations are indicated at the end of the table.

First author	Study Population	♂:♀ Ratio	Anger Induction	Task	Condition decrease/ increase	Main Brain region/s	Network/s	Gender Comparison	Study Site
Gilam 2018	Healthy participants (n=25)	10:15	Unfair monetary offers and written provocations	Anger-infused Ultimatum Game	Increase in anger between before and after the task Contrast of interest: Active vs. sham stimulation during unfair offer phase and activity during fair vs. unfair offers	Active vs. sham during unfair offers: ↑ R vmPFC (10), ↓ L ACC (32), ↓ L INS (anterior, middle and posterior; 13), Unfair vs. Fair offers: ↑ dmPFC (9/10), ↑ Bi anterior insula/IFG (13/47), ↑ L Thalamus, ↑ Bi TPJ (38), ↑ L Temporal Pole (38), ↓ Medial and bilateral PFC, ↓ L MCC (23), ↓ L PCC (31), ↓ L posterior INS (13) L INS/IFG (13/47) positively correlated with trait anger and post-aiUG anger	mentalizing; self-regulation; Salience	Not mentioned	Israel
Radke 2018	Student Volunteers (N=80)	40:40	Social exclusion as anger induction	Cyberball	Cortisol and Testosterone ↓, Anger and Distress ↑ Contrast of Interest: Social vs. Technical exclusion	L anterior INS (13) ↑, R vmPFC (11) ↑, R dlPFC (46) ↑, R MFG ↑, R Paracentral Lobule ↑, R Rolandic Operculum ↑ (48), R SMA (medial BA 6) ↑, R IFG (45) ↑, Bi Precuneus (medial BA 7) ↑	mentalizing; self-regulation; Salience	♀ rated the technical exclusion condition more highly, ♀ ↓ cortisol levels more quickly	Austria

Krauch 2018	BPD Youth (N=40) Adults (N=66)	0:106	Rejection based script/narrative	Script-driven imagery	BPD patients emotional reactivity ↑, Level of social pain ↑ Contrast of Interest: During the anger induction phase	Youth-BPD vs. Youth-HC: L dorsal posterior INS ↑ (13), L Putamen ↑, L Claustrum ↑ Youth-BPD relative to Youth-HC, Adult-BPD and Adult-HC: L Post-central gyrus ↑, L Precuneus ↑	mentalizing; salience , habit	n/a	Germany
Jacob 2018	Healthy participants (n=74)	74:0	Anger-inducing movie	Anger Inducing Film Excerpt	Anger ↑ along the movie generate low vs high anger epochs	↑ vmPFC in high vs. low anger epochs	mentalizing	n/a	Israel
Gilam 2017a	Soldiers (N=29) and Civil-service volunteers (N=15)	44:0	Unfair monetary offers and verbal provocations	Anger-infused Ultimatum Game	Self-reported ↑ in anger (as in Gilam et al, 2015) Contrast of Interest: Functional connectivity before and after anger induction (rest1 and rest2)	R AMYG and R IFG (47) FC ↑ Global R AMYG connectivity at baseline positively associated with self-reported angry feelings	Salience; self-regulation	n/a	Israel
Tonnaer 2017	Violent offenders (N=16) and Non-offender controls (N=18)	34:0	Anger engagement story condition	Anger-Association Test (Anger-STIAT) → Anger Engagement and Distraction Task	Offenders vs. Controls ↑ anger during anger-engagement condition, all groups showed ↑ anger vs. neutral condition Contrast of Interest: Anger	Offenders during anger engagement vs. neutral compared to controls: L Cerebellum (18) ↓, L IFG (45) ↑, R PCC/Precuneus (31/7) ↓	Mentalizing; self-regulation	n/a	The Netherlands

					engagement vs. neutral engagement				
Herpertz 2017	BPD (N=56) and HC (N=56)	49:63	Interpersonal rejection narrative	Script-driven imagery task	mBPD and fBPD reported a trend in more vivid imagination and sustained anger Contrast of Interest: During anger induction phase	mBPD vs. fBPD: L AMYG ↑ (36) mBPD vs. mHC: L AMYG ↑	Mentalizing; self-regulation; salience; habit	L AMYG - posterior MCC and L AMYG -IFG ↑ FC in fBPD, L AMYG -R dlPFC is positively modulated by trait anger in fBPDs, L AMYG -R vlPFC, LOFC and R dlPFC is negatively modulated by trait anger in mBPDs	Germany
Gilam 2015b	Soldiers (N=38) and Civil-service volunteers (N=22); LGs=27 and HGs =33.	60:0	Unfair monetary offers and verbal provocations	Anger-infused Ultimatum Game	Measured by GEW: Anger cluster of feelings (anger, hostility, contempt and disgust) ↑ during unfair offer and negotiatio	Gain-groups main effect: HGs: L LC/BS ↓, R vmPFC (11) ↑, LGs: L LC/BS ↑, R vmPFC (11) ↓ HGs during unfair offers: L dpl (13) ↑, dpl-mTFC ↑ during gain increase	Mentalizing; salience	n/a	Israel

					n periods. LGs and HGs reported similar anger levels. Contrast of Interest: Unfair vs. fair offers				
Denson 2014	MAOA-L (n=16) and MAOA-H (n=22	38:0	Insults during an anagram task	Provocation procedure	Self-reported increase in anger (measured with the PANAS-X) and effort toward anger control Contrast of Interest: Post-insult vs. baseline	MAOA main effect: MAOA-L: L dACC (32) ↑, Bi AMYG ↑; ↑ AMYG-dACC connectivity following provocation Mediation: dACC and AMYG activation mediated effect of MAOA genotype on effort toward anger control	salience	n/a	Australia
Pawliczek 2013	High Trait Aggression (N=21) and Low Trait Aggression(N=18) Student volunteers	39:0	Unsolvable anagrams and loss of compensation	Functional frustration task	13 of HA and 4 of LA group showed ↑ negative affect and anger ratings (HA > LA) Contrast of Interest: Solvable vs. unsolvable conditions	LA relative to HA: R vlPFC (44) ↑, R dlPFC (46) ↑ HA during the unsolvable condition relative to LA: L dACC (24) ↓, L AMYG ↓, R vlPFC (44) ↓ During solvable condition for both groups: L AMYG ↑	Mentalizing; self-regulation; salience	n/a	Germany
Denson 2013	Healthy volunteers (N=19)	19:0	Insults during an anagram task	Provocation procedure	Self-reported increase in anger and effort toward anger control	Response to induced anger control (provocation vs. baseline): L dACC (32) ↑, L dmPFC/dACC	Mentalizing; self-regulation; salience	n/a	Australia

					(measured with the PANAS-X) Contrast of Interest: Provocation vs. baseline	(6/24) ↑, L AMYG ↑, R INS (13) ↑, Bi BS ↑, Bi Thalamus ↑, Bi SFG (stronger in left) (9,10) ↑, L dmPFC/dACC and R Anterior INS correlated with ↑ self-reported anger control, AMYG- L dlPFC/dACC/ OFC FC ↑ following provocation Hormone analyses: ↑ vmPFC-AMYG FC exhibited in subjects at baseline with high testosterone and low cortisol, ↑ dlPFC and Thalamus activity correlated with testosterone only when cortisol levels were low (following anger control)			
Jacob 2013	BPD (N=17) and HC (N=18)	0:35	Anger-inducing short story	Emotion induction and subsequent go/no-go task	Self-reported increase in anger Contrast of Interest: Anger vs. neutral mood	BPD: R AMYG ↑	Self-regulation; salience	n/a	Germany
Fabian s-son 2012	College student volunteers (N=21)	11:11	Internally generated autbiographical memory	Recall of an anger-inducing memory followed by anger regulation strategies (reappraisal,	Participants reported feeling the most anger during angry rumination	R vmPFC/vlPFC (11/47) ↑, R anterior INS (13), R AMYG ↑, R Putamen ↑, R Caudate head ↑, R Lateral globus pallidus ↑, R	Mentalizing; self-regulation; salience	Not mentioned	Australia

				analytical rumination and angry rumination)	Contrast of Interest: Activation during all three regulation conditions relative to baseline	Precentral gyrus (44), R Medial, anterior and posterior orbital gyrus (11/47) R Thalamus (medial dorsal, ventral lateral and lateral posterior nuclei) ↑, R Lingual gyrus (18) ↑			
Denson 2009	College student volunteers (N=20)	8:12	Insults during an anagram task	Provocation-focused rumination	Self-reported increase in anger during provocation and of provocation-focused rumination Contrast of Interest: Provocation vs. Baseline fixation	Provocation relative to baseline: R rACC ↑ (24,32), Bi aPFC ↑ (10), Bi dACC ↑ (32), L Thalamus ↑, Bi INS ↑ (13), Bi PCC (23) ↑, Bi MFG ↑ (9/10), Bi Lateral MFG (10), B-Hippocampus ↑ (37) During provocation-focused rumination: L Anterior Precuneus ↑ (medial BA 7), L Thalamus, Bi dACC ↑ (24), Bi dmPFC ↑ (9), Bi INS (13), Bi MFG ↑ (10), Bi PCC (23), Bi rACC ↑ (32), Bi vlPFC ↑ (45) Hippocampus, R INS, rACC and PCC activity (+) correlated with self-reported rumination following provocation, Aggression (+) correlated with dACC activity	Mentalizing; self-regulation; salience	Not mentioned	Australia

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aiUG: Anger-infused Ultimatum Game, GEW: Geneva Emotion Wheel, HC: Healthy Control group, HA: High Trait Aggression, HGs: High-gainers, LA: Low Trait Aggression, LGs: Low-gainers, BPD: Borderline Personality Disorder, mBPD: ♂ BPD participants, fBPD: ♀ BPD participants, ↑: increased, ↓: decreased, L: Left, R: Right, Bi: Bilateral. AMYG: amygdala, BS: brainstem, dACC: dorsal anterior cingulate cortex, dlPFC: dorsolateral prefrontal cortex, dpl-mT: dorsal-posterior Insula-medial thalmus pathway, FC: functional connectivity, HC: hippocampus, IFC: inferior frontal cortex, IFG: inferior frontal gyrus, INS: insula, MCC: middle cingulate cortex, MOG: middle occipital gyrus, MTG: middle temporal gyrus, OFC: orbitofrontal cortex, PCC: posterior cingulate cortex, PFC: prefrontal cortex, pMFC: posterior-medial frontal cortex, SFG: superior frontal gyrus, sgACC: subgenual anterior cingulate cortex, STS: Superior Temporal Sulcus, STG: superior temporal gyrus, vlPFC: ventrolateral prefrontal cortex, vmPFC: ventromedial prefrontal cortex. n/a: not applicable