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A prospective neurobehavioral investigation of anger experience and its regulation in humans – A prelude to PTSD symptoms

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Dedicated in loving memory of Frida and Josef Gilam, Rachel and Yitzchak Primak and Shelley Primak

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List of Abbreviations

Brain regions: anterior cingulate cortex (ACC); anterior Insula (AI); brainstem (BS); default mode network (DMN); dorsal anterior cingulate cortex (dACC); dorsolateral prefrontal cortex (dlPFC); dorsomedial prefrontal cortex (dmPFC); dorsal posterior Insula (dpI); inferior frontal gyrus (IFG); fusiform gyrus (FFG); lateral prefrontal cortex (lPFC); Locus Coeruleus (LC); medial prefrontal cortex (mPFC); medial Thalamus (mT); periaqueductal grey (PAG); posterior cingulate cortex (PCC); prefrontal cortex (PFC); supplementary motor area (SMA); temporal-parietal junction (TPJ); ventral anterior cingulate cortex (vACC); ventrolateral prefrontal cortex (vlPFC); ventromedial prefrontal cortex (vmPFC);

Statistical and methodological terms: analysis of variance (ANOVA); blood-oxygen-level dependent (BOLD); echo-planar imaging (EPI); electroencephalography (EEG); Emotion Regulation Questionnaire (ERQ); emotional valence index (EVI); false discovery rate (FDR); functional connectivity (FC); functional Magnetic Resonance Imaging (fMRI); General Linear Model (GLM); Geneva Emotion Wheel (GEW); global functional connectivity (gFC); hear-rate (HR); microsiemens (μs); Magnetic Resonance Imaging (MRI); Montreal Neurological Institute (MNI); Neuroticism-Extroversion-Openness – Five Factor Inventory (NEO-FFI); Positron Emission Tomography (PET); Post Traumatic Stress Diagnostic Scale (PDS); Post-Traumatic Stress Disorder Check-List (PCL); psycho-physiological interaction (PPI); reaction time (RT); region of interest (ROI); resting-state (rs); resting-state functional connectivity (rs-FC); spoiled gradient (SPGR); Sensitivity to Reward and Punishment Questionnaire (SPSRQ); skin conductance (SC); skin conductance response (SCR); State-Trait Anger Expression Inventory-2 (STAXI-2); Toronto Alexithymia Scale (TAS); Ultimatum Game (UG);

Other: high-gain / high-gainer (HG); Israel Defense Forces (IDF); Israeli New Shekel (ILS); low-gain / low-gainer (LG); noradrenalin / noradrenergic (NA); Post-Traumatic Stress Symptoms (PTSD);

ABSTRACT

In the animal kingdom, anger is considered an instinctive survival response featuring a bottom-up arousing component. In humans however, anger has evolved into a complex multidimensional emotional construct, highly influenced by socio-cultural contexts on the one hand, and with profound personal and interpersonal ramifications on the other. Indeed in animals and humans alike, anger is a primary precursor for aggression and violence. Human anger is thus inherently subject to and dependant on an individual's ability to assert control and regulation over it. Importantly, while anger tends to escalate quickly, it extinguishes slowly, extending the experience of anger beyond anger provocation. During this period people tend to engage in recurrent negative thought patterns, known as angry rumination, which is considered a maladaptive regulatory response related to the lingering effects of anger and in itself can lead to aggression. Coping with anger is not an easy thing to do and various therapeutic and pedagogical programs have been developed to teach and train people to regulate and mange their anger. Notwithstanding, unbalanced and dysregulated anger is prevalent in a multitude of psychopathological conditions emphasizing the centrality of this emotion in human affairs in health as well as in sickness. Understanding the psycho-biological mechanisms of human anger is not only challenging from an experimental and theoretical perspective, but it also holds promise to inform efforts to mitigate its negative implications on people's lives.

Within this perspective, the current research program set as it far reaching goal to investigate how the human brain processes anger in relation to anger's short and long temporal trajectories and to the development and manifestation of stress symptoms, by conducting a prospective neuroimaging design integrating behavioral, physiological and subjective measures. Participants consisted of combat soldiers from the Paratroopers Brigade of the Israeli Defense Forces (IDF) and civil-service volunteers who were recruited at the beginning and towards the end of a one year period of combat-training and of civil-service, respectively.

It was assumed that no differences in the response to interpersonal anger and in its short-term neural trajectory would exist between these two groups of participants at the first time-point, as indeed was subsequently found in regards to the first two objectives of this research program. However, the differences would emerge at the second time-point in view of the pedagogical and chronic stress inducing experiences endured by combat soldiers as indeed was subsequently found in regards to objectives three and four of this research program.

The first two objectives were to characterize the neurobehavioral substrates of an interpersonal anger experience, presented in chapter four, and to identify the neural traces of such an experience, presented in chapter five. To this end, an anger-infused decision-making task based on the Ultimatum Game (UG) was developed in which participants undergoing fMRI repeatedly received monetary divisions from a putative counter player, whereby if a participant rejected an offer made by that counter player, both players gain nothing. Importantly, the UG has previously been established as an ideal context of interpersonal conflict over monetary rewards in which unfair offers induce anger, rejecting such offers reflects an aggressive retribution, and accepting such offers reflects a capability to control and regulate these angry and aggressive inclinations. To create a naturalistic interaction and to further induce anger beyond the unfairness of offers, spontaneous verbal negotiations were incorporated after each offer. But while participants were led to believe that the putative player was another participant making all his offers in real-time, the sequence of offers was predefined and the putative player was in fact a professional actor who used scripted improvisations to induce more genuine interpersonal anger. Therefore it was assumed that those participants who were able to nevertheless accept unfair monetary offers from an obnoxious and competitive player were able to control and adapt their anger to the contextual demands of the UG.

All participants were predominantly angry and displayed an increase in anger as the anger-infused UG evolved, especially for unfair offers. Results also replicated the classic UG findings showing that participants rejected more of the offers as they became more unequal. Additionally, it was found that participants gaining more money reported less anger and more positive feelings, had

slower decision reaction times, had slower sympathetic response indicative of less sympathetic arousal, had more ventromedial Prefrontal Cortex (vmPFC) and less Locus Coeruleus (LC) activation, and had more connectivity between dorsal-posterior Insula (dpI) and medial Thalamus (mT), and the reverse pattern for those participants gaining less money. It is argued that these two neurobehavioral response patterns reflected a regulated and an unbalanced profile of anger, respectively. Strikingly, vmPFC activation and dpI-mT connectivity contributed to increased gain, possibly by modulating the ongoing subjective emotional experience. This finding provided a model which triangulated neural, subjective and behavioral measures in the representation of anger and as argued here reflects a neural mechanism of anger regulation. This was further supported by the correlation found between vmPFC activation and an independent personality measure of the habitual use of emotion regulation. These results replicated previous findings associating a role of the vmPFC in implicit emotion regulation, of the LC in arousal and stress response in view of threat and of the dpI as the primary cortex of interoceptive representation. Previous findings are extended by providing a direct link between vmPFC, anger and UG behavior, by involving the LC in healthy human individuals' response to anger as well as evidencing a role of the dpI in regulating emotional experiences, all of which are possibly the result of the interactive and genuine nature of the paradigm.

Participants also took part in task-independent resting-state (rs) fMRI scans before and after the anger induction UG, since anger extends beyond provocation and engages maladaptive thought patterns. A data-driven analysis was used to individuate whole brain functional connectivity (FC) modulations in endogenous neural processing in the aftermath of anger. An increase in positive global FC of the amygdala between rs-sessions was found, and specifically between the amygdala and the inferior frontal gyrus (IFG). The amygdala is generally associated with an important role in negative emotional experiences and is often the target for regulatory processes, which may in fact be exerted by the IFG which is generally involved in motor and emotional response inhibition. Previous findings associated increased amygdala-IFG connectivity with efforts to control emotions,

with processes of rumination and specifically angry rumination. Furthermore, and in agreement with previous findings, the magnitude of change in amygdala-IFG connectivity found here, correlated with the habitual tendency to be angry (trait-anger) and with the anatomical volume of the IFG, together supporting the possibility that this increase in amygdala-IFG connectivity reflected an engagement in a process relevant to angry rumination. While the change in connectivity patterns of the amygdala did not relate to the neurobehavioral indices of anger as identified by the anger-infused UG, suggesting different processes engaged during the experience of an emotion compared to its immediate aftermath, amygdala global FC at baseline predicted monetary gain and anger report, pointing at the amygdala's important role in predisposing individual differences in emotional experiences.

The third objective presented in chapter six was to examine the influence of combat-training on neurobehavioral indices of anger. Inspired by anthropological studies, it was assumed that military pedagogy nurtures a Stoic-like attitude that aims to contain and control emotional reactions. Anger regulation is especially promoted in infantry units since soldiers are trained and prepared to face extreme combat situations while maintaining focus in order to carry out their defined missions and anger can be detrimental to this cause. Results seem to indicate that soldiers with an unbalanced anger profile at the begining of combat-training displayed an increase in monetary gain, an increase in reported positive emotions, and an increase in vmPFC activation in response to the anger-infused UG at the end of combat-training, thus supposedly presenting a regulated anger profile. Soldiers with a regulated profile at the begining of combat-training displayed a marginal decrease in monetary gain and an increase in anger, but generally showed no differences compared to their angry colleagues from the first time-point. The civilians control group displayed no changes in any of the anger related measures between time-points. These results point toward the possibility that an intense socio-cultural practice such as becoming a combat-soldier styles one's mind and body, as reflected in these neurobehavioral indices of anger, in a fashion that decreases individual

variability and produces uniform responses to anger. While lacking in statistical power, these findings offer a progressive outlook on the notion of culture and its possible influence on neural processing and emotional responses.

The fourth and final objective presented in chapter seven was to unveil the relation between neurobehavioral indices of anger and combat-training induced stress symptoms. While angry and aggressive outbursts are a clear manifestation of stress related symptoms, especially in post-traumatic stress disorder (PTSD) and in particularly during social interactions, initial evidence suggests that anger may be both a cause as well as a consequence of PTSD. To date however, the relationship between anger and stress symptoms as mediated by the psychobiological mechanisms of anger has been largely overlooked. The intense period of combat-training was assumed to induce chronic stress which would lead to an increase in stress symptoms. While as a group no differences between time-points were found between soldiers and civilians in the neurobehavioral indices of anger, reconfirming the validity of the anger-infused UG, the soldiers displayed an increase in stress symptoms and the civilians as expected did not. Importantly, within the soldiers group, as soldiers gained more money, had more vmPFC activation during anger provocations and less amygdala-IFG connectivity increase in the aftermath of anger at the first time-point pre-exposure to combat-training chronic stress, so they later had less stress symptoms at the second time-point post-exposure to chronic stress. Thus, it is suggested that soldiers better equipped to cope with angering provocations and less susceptible to the lingering effects of anger are more resilient to the development of stress symptoms. Moreover, it was found that as soldiers had a larger increase in LC reactivity to anger provocations between pre and post exposure, so they had more stress symptoms post-exposure, providing the first causal evidence in humans of the involvement of the LC in the acquired manifestation of stress symptoms. Together these findings demonstrate the important link between anger, brain and pathological symptoms, support the important role of emotion regulation in regards to anxiety disorder and provide neural targets for individually tailored treatments for psychopathological manifestations of anger.

In conclusion, defining anger as a single psycho-biological phenomenon has continuously posed considerable theoretical and experimental difficulties. The current research program deconstructed anger into its basic ingredients related to the profound interpersonal and dynamic nature of anger, to the inherent regulatory processes associated with anger management, to the alteration of anger experience following socio-cultural practices that empower emotion regulation, and finally to the conditions in which anger may manifest itself pathologically, namely in PTSD. In parallel, a multi-level approach was administered using various measures, primarily focusing on several indices of brain function (activation and connectivity) and structure, as well as physiological, behavioral, subjective and trait-personality measures to converge results. The prospective investigation on a study group of IDF combat soldiers and a control group of civil-service volunteers, and their response to an interpersonal angering experience, resulted in a reconstructed scaffolding of the "angry brain". This scaffolding delineated several domain-general neural circuits not necessarily specific to anger, and suggests that the interactions within and between brain regions belonging to these networks may mediate the temporal unfolding of anger experience and regulation. The reconstructed "angry brain" provides ample opportunities for hypothesis generation and examination in future studies. Importantly, the naturalistic and interpersonal view on emotional experiences embraced here suggests future studies should aim to embed social interactions in their investigations as this may further push forward the field of affective neuroscience, experimentally as well as theoretically. The findings also support the formulation of stoic pedagogy in military practice as a program that empowers anger regulation by modulating soldiers' neurobehavioral response patterns to an angering experience following combat-training. Finally, the findings consolidate the link between the neurobehavioral substrates of anger and the development and manifestation of stress symptoms following combat-training related chronic stress, providing a platform for the development of intervention and inoculation treatments based on idiosyncratic neural manifestations of anger.

1. GENERAL INTRODUCTION

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"Anybody can become angry, that is easy; but to be angry with the right person, and to the right degree, and at the right time, for the right purpose, and in the right way, that is not within everybody's power and is not easy."

Aristotle (350BCE)

Since the dawn of civilization, myths and legends have emphasized the ubiquity of anger in human affairs (Potegal & Novaco, 2010). Perhaps most notable is the example of the Iliad, Homer's war epic depicting Achilles's rage in relation to the events of the Greek-Trojan war, dated to have been written somewhere between the 8^{th} and 7^{th} century BCE and considered the first poetic contribution to Western literature. Today, anger continues to prevail - people report experiencing anger on a daily basis and consider it as one of the most prototypical exemplars of an emotion (Averill, 1982; Fehr & Baldwin, 1996; Scherer & Tannenbaum, 1986). Indeed, anger is at the core of what it means to be human.

Anger is experienced mostly during social interactions (Averill, 1982; Baumeister, Stillwell, & Wotman, 1990), and is a primary precursor to aggression and violence (Anderson & Bushman, 2002; Siever, 2008), but it may also lead to negative consequences on one's health, well being and social rapport (Johnson, 1990; Phillips, Henry, Hosie, & Milne, 2006; Williams, 2010). Unbalanced levels of anger are also implicated in numerous pathological conditions, such as in *Post-Traumatic*

Stress Disorder (PTSD; Novaco, 2010). The importance of regulating and coping with anger is therefore unequivocal today as it was since history began being recorded (Potegal & Novaco, 2010). Yet defining anger as a single psycho-biological phenomenon has continuously posed considerable theoretical and experimental difficulties. An in-depth consideration of the relevant literature (as summarized below) led to the emergence of four key elements of the anger construct which nicely resonate with Aristotle's anger-quote cited above: (1) a profound interpersonal nature is apparent in most human episodes of anger; (2) anger is inherently a regulated phenomenon; (3) anger is characterized by unique dynamic properties reflected among other by an escalation property and by an endurance in the aftermath of anger provocations; and (4) since coping with anger is difficult, various anger management training frameworks have been developed for normative populations, while in numerous psychopathological conditions unbalanced levels of anger and the dysregulation of anger continues to persist.

The following research program aimed to deconstruct and then reconstruct the anger phenomenon within the framework of these four key elements by integrating neuroimaging, psychophysiology and behavioral measures to investigate the underlying processes that mediate the experience of anger and that may therefore contribute to regulating anger. This was pursued by developing a paradigm that induced anger in a realistic and dynamic interpersonal situation, which was embedded in a unique prospective study on a cohort of Israel Defense Forces (IDF) soldiers undergoing combat-training and active duty and therefore exposed to chronic stress and potentially traumatic events. Combat-training was assumed to modulate anger-coping capabilities and the entire period of military service was expected to induce PTSD symptoms. This further enabled to scrutinize the long-term trajectory of anger and its relation to psychopathology. Taken together, the current work holds promise to advance our basic understanding of the anger construct and to benefit translational efforts to mitigate the negative implications of anger on people's lives. In the following chapter, a psychological and neural deconstruction of anger experience in humans is presented. Subsequently the research objectives are presented and together with the general materials and

methods provide an overview and rational of the entire research program. The next four chapters go into detail of the specific research questions leading to the final chapter that concludes with a detailed integration of the overall research project and considers possible implications and limitations.

1.1. What is anger?

There is much controversy on the theoretical conceptualization of anger, as on defining emotion in general, and while a survey of the emotion literature breaches the scope of this chapter, two renowned theoretical considerations of anger are briefly noted. According to Berkowitz's Cognitive-Neoassociationistic theory (Berkowitz, 1990, 1993, 2012; Berkowitz & Harmon-Jones, 2004), a primitive form of anger is automatically triggered upon a provocation through an associative network of components including feelings, thoughts, memories and most emphasized, physiological and expressive motor reactions. Only with the temporal yet rapid unfolding of the emotional instance, the affected person makes appraisals, interpretations and causal attributions which enable to construct complex high order thoughts and feelings related to the actual emotion category of anger. Embedded within these later stages is the ability to control and regulate angry feelings and expressions. According to Averill's Social-Constructionist theory (Averill, 1982, 1983), anger is regarded as a social syndrome which cannot be deconstructed into subclasses of physiological, cognitive or any other element. Averill stresses that social rules govern the organization of the various elements of anger, which is considered in itself as a complete response of the person, and because of the great variety in these various elements, influenced by personal and situational circumstances, it is impossible to define a typical angry experience. Anger can thus be understood only within its specific contextual framework.

Though a clear cognitive-physiological vs. social perspectives distinct Berkowitz's and Averill's theories respectively, both agree that there is an intensity element to anger occurrence, from annoyance and irritation to anger and rage. More importantly, Averill and Berkowitz agree

(Berkowitz & Harmon-Jones, 2004) in referring to anger as an *emotional syndrome* because of its multidimensional complexity, and that a temporal unfolding of the emotion is apparent in its construction. They also both point that regulatory processes may intervene along this temporal dynamic. Although theoretical disagreement on the nature and definition of anger remains, the complex and dynamic conceptualization of anger is agreed upon and supported by empirical findings.

1.1.1. Causes of anger

Antecedents and instigators of anger may be sorted into three primary categories which support both Berkowitz and Averill's theoretical frameworks. Various exemplars of these categories reappear in anger inducing paradigms used in the laboratory. These categories are: (1) real or imagined threat such as physical or psychological pain (Bruehl, Burns, Chung, & Chont, 2009; Monteith, Berkowitz, Kruglanski, & Blair, 1990; Trost, Vangronsveld, Linton, Quartana, & Sullivan, 2012), aversive temperature (Anderson, 1989; Berkowitz, Cochran, & Embree, 1981), loud noise (Bushman, 1995; Gehricke et al., 2009) and even polluted air (Zeidner & Shechter, 1988); (2) frustration due to goal obstruction (Carver, 2004; Mauss, Evers, Wilhelm, & Gross, 2006; Pedersen, Gonzales, & Miller, 2000; Stemmler, Heldmann, Pauls, & Scherer, 2001); and (3) perceived personal offense due to unfair treatment (Pillutla & Murnighan, 1996; Srivastava, Espinoza, & Fedorikhin, 2009), violation of social norms (Harmon-Jones, Peterson, & Harris, 2009; Konecni & Doob, 1972; Pedersen et al., 2000; Porath & Erez, 2007; Porath & Erez, 2009; Stemmler, 1997; Wingrove & Bond, 1998), or insults, rejections, criticism and the likes (Bushman, 1995; Gehricke et al., 2009; Harmon-Jones & Sigelman, 2001; Harmon-Jones, Vaughn-Scott, Mohr, Sigelman, & Harmon-Jones, 2004; Memedovic, Grisham, Denson, & Moulds, 2010; Pedersen et al., 2000; Peterson, 1983).

The first category relating to threat reflects the most basic form of anger which is shared across the animal kingdom and is regarded as the instinctive survival response which triggers the fight

feature of the fight or flight reaction (Anderson & Bushman, 2002; Rosell & Siever, 2015; Siever, 2008). Reactive aggression triggered by a threat is perhaps the most typical behavioral expression of anger, and thus anger has been traditionally viewed as interchangeable with aggression. Anger may indeed be pivotal in the generation and propagation of violent acts against the self and others. Nevertheless, aggressive acts may be perpetrated without any trace of anger, and at the same time anger is an emotional construct in its own right, not necessarily a harbinger of aggression. In contrast, a profound interpersonal foundation is apparent in the third category. In accordance, the expressions of anger have evolved from their primitive forms and adapted to socially accepted norms (Averill, 1982; Fehr & Baldwin, 1996). For example, people would probably not shout in the middle of a restaurant at a rude waiter, but rather restrain themselves and choose more accepted forms of rebuttal, such as minimizing the tip. This suggests that in order to realistically capture the multi-faceted concept of anger, experimental designs should incorporate an interpersonal social interaction, and try to dissociate between the experience and the expression of anger.

1.1.2. Defining a social interaction

Social interaction has been defined as a social encounter involving at least two agents who reciprocally influence each other through verbal and/or non-verbal behaviors in a time dependent manner (De Jaegher, Di Paolo, & Gallagher, 2010; Di Paolo & De Jaegher, 2012; Schilbach et al., 2013). In addition, there seems to be a subjective element corresponding to a fluctuating perception or sensation of connectedness, ranging from none at all to possibly reflecting a unique sense of "we", which supposedly enables the agents to better understand each other. A more operationalized definition specifies four criteria for "closing the loop" on social interactions: dynamic interplay, unlimited range of responses, uncontrolled partners and emergent qualities (Przyrembel, Smallwood, Pauen, & Singer, 2012). However, there is an important theoretical debate as to whether the "we-ness" of social interaction indeed reflects an emergent property of the interaction that enables the agents to access additional information about one another or whether it simply

reflects a first-person perspective that captures the self's engagement in social interaction (Gallotti & Frith, 2013). This later approach to social cognition, termed *individualism*, generally suggests that cognitive processing occurs in one's own mind and brain and that this is a precondition for understanding and interacting with others. Thus, the "we-mode" is achieved only when one can represent the others' perspective. The former approach, termed *enactivism*, generally suggests that social interaction is not merely a contextual effect but that it has a constitutive, though not the sole[1], role in generating our capability to understand other people. In this sense, the dynamic co-dependent coupling between two or more agents may "take a life of its own" and in itself may shape the interacting individuals' cognition (De Jaegher et al., 2010; Di Paolo & De Jaegher, 2012). From this perspective, instances of co-presence, the belief of the presence of another, or any other coupling which does not abide by dynamic co-dependency, are social and may have some level of interaction, but cannot be considered fully interactive.

1.1.3. Anger experience

During the actual experience of anger a person is commonly described as having a cluster of physiological, cognitive and behavioral attributes which are directly related to the temporal dynamics of anger. Physiologically, an angry experience is characterized by an increase in respiration, blood pressure, heart-rate, skin and body temperature and skin conductance (Christie & Friedman, 2004; Ekman, Levenson, & Friesen, 1983; Levenson, 1992), indicating the involvement of both sympathetic and parasympathetic systems of the autonomic nervous system. Other bodily changes include specific facial features and a general muscular tightness (Berkowitz & Harmon-Jones, 2004; Scherer & Tannenbaum, 1986). Anger is thus generally considered as a very arousing emotional condition.

A negative cognitive appraisal of circumstances characterizes anger. Recurrent thinking, planning of revenge and retaliation and judgmental and derogative labeling are just some forms of

[1] A stronger version of enactivism called *interactionism* holds that that social interaction has a constitutive and *sole* role in developing our understanding of other people.

angry cognitions (Fehr & Baldwin, 1996). Such intrusive negative provocation-focused thought patterns during anger are termed together as *rumination* (Denson, Pedersen, Ronquillo, & Nandy, 2009; Rusting & Nolen-Hoeksema, 1998; Sukhodolsky, Golub, & Cromwell, 2001) during which people masticate the causes and consequences of the angry event. *Angry rumination* extends beyond the termination of the anger-inducing event and tends to further intensify and prolong the experience of anger and increases aggressive retributions towards the persecutor (Bushman, 2002; Bushman, Bonacci, Pedersen, Vasquez, & Miller, 2005; Rusting & Nolen-Hoeksema, 1998).

Behaviorally, an angry person is in a general nervous attitude with a proneness to some form of physical or verbal aggression (Deffenbacher, Oetting, Lynch, & Morris, 1996; DiGiuseppe, 1999; Fehr & Baldwin, 1996; Siever, 2008; Spielberger, 1999). Arguments with yelling and screaming are also very common during anger episodes (Howard Kassinove, Sukhodolsky, Tsytsarev, & Solovyova, 1997; Scherer & Tannenbaum, 1986). However other expressions may be less confrontational such as using conflict resolution, withdrawing from the situation or implementing relaxation techniques. Studies have generally found a myriad of behavioral expressions of anger which support Averill's (1983) assertion that "given an adequate provocation, nearly any response, and even no response, can count as a manifestation of anger" (there, p.1147).

While physiological responses to anger are generally quite short and last up to several minutes (Levenson, 1988; Stemmler, 2010), the subjective experience of day-to-day anger typically lasts for about half an hour, during which angry-rumination is common (Sukhodolsky et al., 2001), though duration is correlated with intensity (Potegal, 2010). The temporal dynamics of anger experience is also characterized by an escalating property, in which annoyances and irritations accumulate over time, and behavioral responses which begin with mild requests may reach strong angry outbursts (Baumeister et al., 1990; Pruitt, Parker, & Mikolic, 1997). Similar to the folktale of "the straw that broke the camel's back", there seems to be a nonlinear effect in the trajectory of anger in which at the extreme end, a sense of loss of control and irrationality captures the essence of a person's experience and it is more difficult to be soothed or distracted. While anger rises quickly and

declines slowly, it may be terminated by natural decay, quenching or catharsis, all of which may be considered as forms of anger regulation.

1.1.4. Anger regulation

The involvement of processes that control and regulate the experience and expression of anger emerges as a crucial element embedded within this socio-emotional phenomenon. Similar to Aristotle's citation above, Gross (1998) generally defined *emotion regulation* as "the processes by which individuals influence which emotions they have, when they have them, and how they experience and express these emotions" (there, p. 275). Theoretical accounts differ in their view regarding the relation between emotion generation and regulation, as some claim that regulation is an inherent part of the generation process while others separate these two processes (Gross & Barrett, 2011). Nevertheless, it is generally accepted that they are both critical in the construction of the emotional episode as it unfolds over time, and this is apparent in our description of anger thus far. Emotion regulation processes or strategies may be automatic or controlled/aware and implicit or explicit (Etkin, Büchel, & Gross, 2015; Gyurak, Gross, & Etkin, 2011; Phillips, Ladouceur, & Drevets, 2008), and may modulate the emotion at any stage during the evolvement of its experience and expression. There are many different strategies to regulate emotions, yet *cognitive reappraisal*, in which one changes or reinterprets how she thinks about an emotional situation, has been studied the most. There are also large personality differences in the habitual tendency to use various strategies to regulate emotions (i.e. trait emotion regulation; Gross & John, 2003).

Laboratory experimentation on anger down regulation suggest that when facing or recalling an anger provocation, an implicit or primed favorable attitude towards emotion regulation (Mauss, Cook, & Gross, 2007; Mauss et al., 2006), having high compared to low trait cognitive reappraisal (Mauss, Cook, Cheng, & Gross, 2007) and using cognitive reappraisal rather than suppression or rumination (Memedovic et al., 2010; Ray, Wilhelm, & Gross, 2008; Szasz, Szentagotai, & Hofmann, 2011) - all of these lead to a decrease in anger experience and reduce maladaptive

cardiovascular response. Other accounts of anger have shown a large variety in what one may do to cope with anger (Deffenbacher et al., 1996; DiGiuseppe, 1999; Fehr & Baldwin, 1996; Shaver, Schwartz, Kirson, & O'Connor, 1987). For example, some actions may be conciliatory in their nature, such as reciprocal communication and talking it over; while other actions may try to create distance and avoidance from the angering stimuli, such as detachment and time-outs; still another set of actions may focus on the physiological aspect, such as relaxation or drug and alcohol consumption. It is also clear that some of these actions are more adaptive and healthy than others.

1.1.5. Consequences of anger

Anger may have detrimental effects on our lives. It is related to poor quality of life, with people high in trait-anger - that is the tendency and frequency of experiencing anger on a daily basis (Spielberger, Jacobs, Russell, & Crane, 1983)) - having impaired psychological and social well-being (Phillips et al., 2006). Anger is implicated in negative health outcomes, most notably in cardiovascular disease (Siegman & Smith, 1993; Williams, 2010). For example, unrestrained expression or chronic suppression of anger affects essential hypertension and coronary heart disease. Anger irregularity is involved in many psychopathologies, such as psychotic, affective and personality disorders (Kassinove, 1995; Novaco, 2010). Even in anxiety disorders such as PTSD, related primarily to abnormal fear, there is a well documented anger dysregulation which hampers functionality (McHugh, Forbes, Bates, Hopwood, & Creamer, 2012; Olatunji, Ciesielski, & Tolin, 2010). Anger may also have debilitating effects on cognitive processes, such as in task performance and creativity (Porath & Erez, 2007; Porath & Erez, 2009) and judgment and decision making (Lerner & Tiedens, 2006).

Surprisingly, although experiencing anger and being the target of another's anger is primarily negative, many episodes of anger are positively evaluated (Averill, 1983; Baumeister et al., 1990; Kassinove et al., 1997). Indeed, anger has several positive aspects and may potentially be adaptive and functional. Anger has a role in maintaining status-quo and communicating an offensive event,

and may lead to beneficial outcome on personal and social-organizational tiers (Gibson, Schweitzer, Callister, & Gray, 2009; Keltner & Gross, 1999). Importantly, anger is more likely to motivate to take action and approach rather than to withdraw away from a possible or actual confrontation (fight rather than flight; Anderson & Bushman, 2002; Averill, 1983; Berkowitz & Harmon-Jones, 2004; Carver & Harmon-Jones, 2009). This may be instrumental in achieving a wide variety of goals. For example, anger has a pivotal role in negotiations and under certain conditions, expressing anger may lead to beneficial resolutions (Friedman et al., 2004; Hareli et al., 2009; van Dijk, van Kleef, Steinel, & van Beest, 2008). In fact, up-regulating anger may improve performance in a confrontational task (Tamir, Mitchell, & Gross, 2008). Moreover, anger together with disgust underlies *moral outrage*, the emotional reaction to a perceived moral transgression inflicted by others upon others (Salerno & Peter-Hagene, 2013). Anger is thus quite unique as it is regarded as a negative emotion associated with an approach motivational orientation (Carver & Harmon-Jones, 2009).

1.2. The "angry brain"

Disentangling the causes, consequences, experience and expression of anger portrays a contextualized multidimensional construct consisting of physiological, cognitive, subjective and behavioral components. Given the heterogeneous depiction of anger, research on the neural substrates of anger should aim to appreciate not only whether and to what extent anger occurs, but even more so what are the forms and fashions in which anger is induced, experienced, expressed and regulated. For obvious reasons, animal research has been preoccupied with aggression as a behavior rather than the subjective experience of anger. Cannon and Bard's (Bard, 1928; Cannon, 1927) classical studies on decorticated cats showed that the hypothalamus is essential for expressing “sham rage” (i.e. aggressive behavior without anger). Seventy years later, Panksepp (1998), based mostly on studies in rodents, suggested a primitive neural basis for anger shared by all vertebras which in addition to the hypothalamus included the amygdala and periaqueductal grey (PAG).

These brain regions seem to be involved in the rapid identification and response to threat in the environment, thus assumed to have an essential role in the generation of anger and propagation of aggression, which accompany the fight reaction of the fight or flight response (Nelson & Trainor, 2007). Introduction of non-invasive brain mapping methodologies such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) advanced studies in search for the "angry brain" in humans.

1.2.1. Neuroimaging studies of anger

Neuroimaging studies on the neural substrates of human anger can be generally divided into three types as far as how anger was evoked (for a detailed review please refer to Gilam & Hendler, 2015). The first set of studies use images depicting angry faces (Costafreda, Brammer, David, & Fu, 2008; Fusar-Poli et al., 2009). Although the use of faces enables highly standardized stimuli across and within subjects, such static stimuli clearly do not capture the complex nature of anger experience, rather enable to investigate the neural mechanisms mediating the perception and recognition of anger in human faces. The second set of studies used self generation of anger by recollecting and imagining personal autobiographic memories (Damasio et al., 2000; Fabiansson, Denson, Moulds, Grisham, & Schira, 2012) or scripted scenarios (Frewen et al., 2011; Pietrini, 2000) of angry experiences. Autobiographic paradigms enable a more personalized reverberation of anger, though not entirely standardized across subjects. For example in one such study (Kimbrell et al., 1999) some events involved property loss, others involved being wrongly blamed and still others generally involved verbal arguments. Such recollections might also be prone to confounds of memory-biases and limited introspective insight. Scripted scenarios to elicit the imagined anger experience are controlled for these limitations and yet, these are internally generated paradigms of anger induction and thus still lack the fundamental bluntness of actually being provoked. In addition, it has been shown that the generation of emotional experience via internal or external stimuli elicits differential brain networks (Reiman et al., 1997).

Taken together these two sets of studies identified a myriad of brain regions related to anger including prefrontal cortex (PFC) regions, mostly ventro-medial/medial orbital PFC (hereby named vmPFC) regions and the inferior frontal gyrus (IFG) which might be involved in processes associated with the conscious experience of anger and its regulation; limbic and paralimbic regions such as the amygdala, insula, thalamus and hypothalamus, which together with brainstem regions might be involved in processes associated with the generation of anger and a general state of arousal; additional regions included the anterior and posterior cingulate cortex (ACC and PCC respectively) and the adjacent precuneus as well as temporal pole and medial temporal regions and the fusiform gyrus (FFG). This wide distribution may suggest that these studies did not adequately dissect the complexity of the anger construct and did not distinct between different modes of anger manifestation. More importantly, in these types of studies the naturalistic dynamics of anger experience typically rooted in social interactions was completely overlooked (for a detailed review please refer to Gilam & Hendler, 2016).

The third and final set of studies tried to induce anger directly. In the first such study (Denson et al., 2009) participants were requested to solve difficult anagrams and say out loud through a microphone the correct answer or say "no answer" if they did not know the answer. Anger was induced by the experimenter who interrupted participants two times requesting them to speak louder and on a third time stated in a rude and condescending tone of voice "Look, this is the third time I have had to say this! Can't you follow instructions?". The analysis was based on contrasting a baseline period before and after the provocation, during which there was increased activity in the medial and lateral PFC, insula, thalamus, hippocampus, ACC and PCC, of which the dorsal-ACC (dACC) positively correlated with self-reported anger and trait aggression and the insula, hippocampus, rostral-ACC and PCC positively correlated with self-reported angry-rumination. A very similar pattern of activation was apparent in a condition of angry-rumination, during which activity in the medial PFC (mPFC) positively correlated with self-reported angry-rumination. A similar pattern of brain activity, including dorsal regions of the PFC, dACC, insula, thalamus,

amygdala and brainstem, emerged in a subsequent study which asked participants to control their anger in view of such insults (Denson, Ronay, von Hippel, & Schira, 2013). Dorsal-PFC and insula positively correlated with self-reported anger control and negatively correlated with self-reported anger. The brain pattern of anger control was also characterized by a functional coupling between the amygdala and dorso-lateral PFC (dlPFC), dACC and vmPFC which may reflect the efforts of PFC regions to exert control over the angering provocation. However, while this provocation-based anger paradigm incorporates an interpersonal context, participants remain completely passive and while they lay in the MRI scanner they are subjected to the experimenter's criticism but cannot react. In addition, an objective behavioral measure which may reveal their emotional turmoil further than self report was absent. A final key limitation in this paradigm is that anger was not examined during the actual provocation.

1.2.2. The neural basis of emotion regulation

Though neuroimaging studies on emotion regulation tend to focus on general negative aversive states and usually employ down regulation by reappraisal, there has been relatively inconsistent findings (Kalisch, 2009). Several reviews (Gyurak et al., 2011; Ochsner & Gross, 2005; Phillips et al., 2008; Quirk & Beer, 2006) point to widespread frontal activations which vary between studies and at the same time it appears that these same regions are involved in different emotion regulation strategies. Based on methodological considerations, meta-analytic efforts have similarly pointed-out inconsistencies. For example, a first effort to examine reappraisal using an activation likelihood estimation approach revealed dorsomedial PFC (dmPFC) and vmPFC activations (Diekhof, Geier, Falkai, & Gruber, 2011) while a later effort using multilevel kernel density analysis approach revealed no vmPFC activations but did show the involvement of additional regions in lateral PFC, including the IFG, and lateral temporal cortex (Buhle et al., 2014). While it is possible that the differences resulted from the number of studies included in these meta-analyses, about 25 and 50 respectively, other meta-analyses reveal important differences between up and down regulating the

emotional experiences (Frank et al., 2014) and between reappraisal of the stimuli compared to reappraisal via perspective taking (Messina, Bianco, Sambin, & Viviani, 2015) and between reappraisal and other strategies such as suppression (Kohn et al., 2014). This somewhat blurry picture is not entirely surprising since there are functional differences between emotion regulation strategies applied across various emotions and contexts (Gross, 1998). Nevertheless, growing evidence suggests that the main brain regions involved in processes of emotion regulation include large parts of the PFC (dispersed through dorsal and ventral aspects of the lateral and medial PFC), as well as pre-SMA and SMA and regions in the parietal cortex (Etkin et al., 2015; Figure 1.1.), most of which have also been associated with the neural basis of anger. These regulatory sites have been implicated in the moderation of emotion reactivity regions, most notably including PAG, amygdala, insula and dACC.

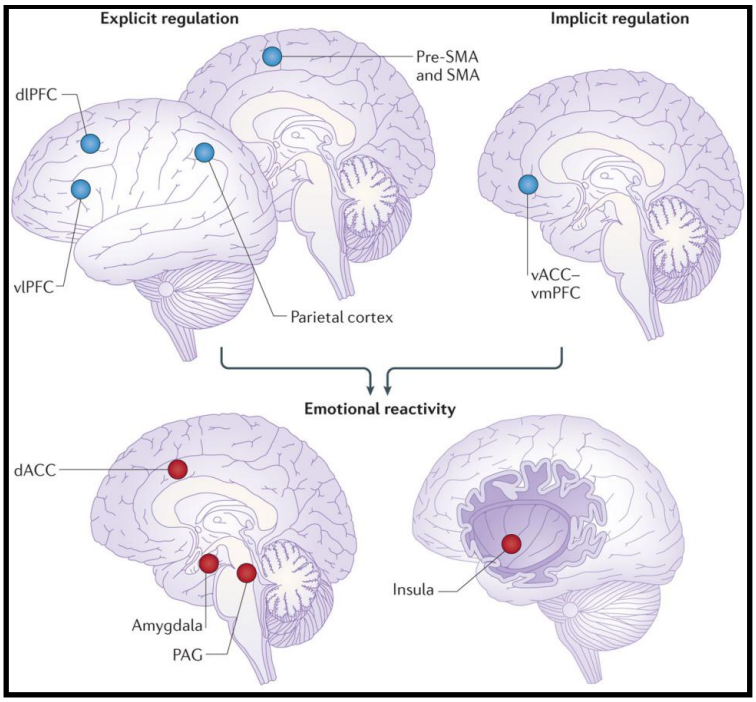

Figure 1.1. Regions implicated in emotion regulation. The dACC, insula, amygdala and PAG (shown in red) have been implicated in emotional reactivity. By contrast, the dlPFC, ventrolateral PFC (vlPFC), SMA, pre-SMA and parietal cortex (shown in blue) have been implicated in 'explicit' emotion regulation, and the ventral ACC (vACC)–vmPFC (also shown in blue) has been implicated in 'implicit' emotion regulation. Image extracted from Etkin and colleagues (2015).

1.2.3. Inducing anger using the Ultimatum Game

An additional experimental approach for the interpersonal induction of anger is the classic social decision-making paradigm - the Ultimatum Game (Güth, Schmittberger, & Schwarze, 1982). In the

Ultimatum Game (UG), two players need to agree on how to split a sum of money between them in order to actually gain the money. One player makes an offer on how to split the sum while the second decides whether to accept or reject the offer. Unequal offers of about 25% and below of the total sum are commonly rejected resulting in monetary loss for both players (Camerer, 2003). Such offers are regarded as unfair offers which violate social norms, elicit anger and thus result in an aggressive retribution at one's own personal cost (Pillutla & Murnighan, 1996; Xiao & Houser, 2005). Indeed, it was shown that anger mediated the relationship between the size of offers and rejection rates such that more anger resulted in increased rejections (Srivastava et al., 2009). Congruently, psycho-physiological findings showed that unfair UG-offers were associated with increased sympathetic arousal as measured by skin conductance response (SCR; van't Wout, Kahn, Sanfey, & Aleman, 2006) and increased emotional orienting response as measured by heart-rate (HR) deceleration (Osumi & Ohira, 2009; though mixed results were shown by Dunn, Evans, Makarova, White, & Clark, 2012). Recent meta-analytic studies on the neural structures involved in processing unfair offers compared to fair offers (Feng, Luo, & Krueger, 2015; Gabay, Radua, Kempton, & Mehta, 2014) found activity in the following regions: ventral, dorsal and lateral regions of the PFC, supplementary motor area (SMA), insula, ACC, PCC, precuneus, parietal lobule, temporal pole, temporal-parietal junction (TPJ) and visual regions including the FFG. As detailed above, most these regions have previously been associated with various anger-related contexts.

Though consistent behavioral, psychophysiological and neural evidence implicated anger with how people cope with unequal offers, it remains true that emotions are not the sole factor in explaining UG behavior (Civai, 2013). Factors such as reward valuation (Tabibnia, Satpute, & Lieberman, 2008) fairness enforcement norms (Baumgartner, Knoch, Hotz, Eisenegger, & Fehr, 2011; Knoch et al., 2006) and self-involvement (Corradi-Dell'Acqua, Civai, Rumiati, & Fink, 2013), amongst others, may influence people's tendency to accept or reject UG-offers. However, for the purpose of inducing anger it does not necessarily make a difference if one is angry because of

the unfairness of an offer or by self-involvement as both are prerequisites for the subjective experience of anger. In addition to portraying an interpersonal situation, an additional benefit of the UG is that one can experimentally separate between the offer phase, which serves as the anger-induction, and the decision-making phase. Thus the behavior – a decision to accept or reject an offer - may serve as an objective measure of the associated emotional experience.

Indeed, additional evidence for the importance of the emotional response in driving behavior in the UG stems also from emotion regulation studies which indicate that regulating anger may be important to the acceptance of unfair offers and that people who are better able to regulate anger associated with such offers are more likely to accept and financially benefit from them (Grecucci & Sanfey, 2013). For example, explicitly instructing to use reappraisal to down regulate emotions associated with unfair offers resulted in increased acceptance rates (van't Wout, Chang, & Sanfey, 2010) which were found to correlate with brain activity in an anterior region of the dlPFC (Grecucci, Giorgetta, Wout, Bonini, & Sanfey, 2013). Furthermore, the insula showed effects of emotion modulation as activation decreased when down-regulating and increased when up-regulating. Additional studies on individual differences regarding the tendency to accept or reject unfair offers point at the involvement of ventral regions of the PFC. One such study revealed that activity in the vmPFC mediated the relationship between pre-UG testosterone levels – a hormonal marker of anger and aggression (Peterson & Harmon-Jones, 2012) – and rejection rates (Mehta & Beer, 2010). Nevertheless, there are several limitations when considering the UG as an anger inducing paradigm. For one, the induction of anger is strictly focused on the amount of money offered. In addition, especially in the neuroimaging literature, the UG is implemented in a "single-shot" mode in which each offer is from a different, most often a virtual proposer, reducing to almost none the dynamic nature of the interaction. Angering situations, especially in bargaining contexts such as the UG tend to spiral and escalate due to personal insults and provocations. The Denson and colleagues set of studies (2009, 2013) similarly lacks this basic feature – subjects are provoked but the naturalistic social-interactive and temporal dynamics of an angry experience is overlooked.

1.2.4. Conceptual notes on the angry brain

Altogether, from a broad perspective, primary regions of interest for the "angry brain" may include limbic, paralimbic and brainstem regions associated with the generation of the emotion, such as amygdala, hypothalamus, insula and PAG, as well as various PFC regions associated with emotion regulation, such as vmPFC, dlPFC and IFG. Nevertheless, there is a lack of evidence regarding the neural substrates of anger experience during dynamic social interactions, hindering the ability to reach a comprehensive understanding of how anger is processed and regulated in the human brain. Moreover, several meta-analyses (Kober et al., 2008; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Murphy, Nimmo-Smith, & Lawrence, 2003; Phan, Wager, Taylor, & Liberzon, 2004, 2002) suggest that neuroimaiging studies to date cannot produce a clear picture regarding the neural mechanisms which process discrete categories of emotions such as anger. These meta-analyses point to the problematic fact that the same categories of emotions have been related to many different brain regions and that the same brain regions have been related to many different categories of emotions and/or regulation processes.

In the last several years the field of cognitive neuroscience has witnessed a shift from a locationist approach, in which complex function is assumed to be consistently and specifically processed in discrete brain regions, to a network-based approach that conceptualizes function as emerging from dynamic interactions of distributed brain regions (Bressler & Menon, 2010). This approach has been advanced by "resting-state" paradigms which reveal intrinsic functional networks such as the "default mode network" (DMN), when there is no external stimulus or task; networks that were also related to the underlying anatomical connectivity (Deco & Corbetta, 2011). The covariance in these resting-state functional networks is also influenced by prior history such as training or acquisition of a new skill (Albert, Robertson, & Miall, 2009; Lewis, Baldassarre, Committeri, Romani, & Corbetta, 2009). Interestingly, recent studies showed changes in resting-state networks in the aftermath of intense negative emotional experiences (Maron-Katz, Vaisvaser, Lin, Hendler, & Shamir, 2016; Vaisvaser et al., 2013; Veer et al., 2011). For example, Veer and

colleagues (2011) revealed that during recovery from a psychosocial stress task there was enhanced amygdala functional connectivity with the mPFC and PCC, two central hubs of the DMN. This supports the notion that exploring non-task induced resting-state functional connectivity (FC) of brain regions in the aftermath of an evoked emotional state may present valuable insight on the dynamics of the emotional episode and on the neural processes that enable to cope with it.

Indeed, the neural-network paradigm shift has also taken place in the field of affective neuroscience (Barrett & Wager, 2006; Kober et al., 2008; Lindquist & Barrett, 2012; Lindquist et al., 2012) in which emotions are reflected by the integration and disintegration of several networks in the brain. Notably, Barrett's (Barrett, 2006a, 2009) *conceptual act model* underlines two processes related to distinct neural circuits in the structure of emotion. *Core affect* refers to a continuous stream of neurophysiological sensations that may be experienced as feelings of pleasure or displeasure with varying degree of arousal. *Conceptualization* refers to the meaningful mental representation of core affect in a given context based on prior experiences, which constructs a subjective feeling of an emotion. The conceptual act model seems to bridge Berkowitz's and Averill's theoretical frameworks of anger because core affect reflects Berkowitz's "low-level" association network and conceptualization reflects Averill's "high-level" context dependant construction of the emotion.

Within this theoretical and methodological framework, meta-analytic efforts have identified several networks of special interest (Kober et al., 2008; Lindquist et al., 2012; Figure 1.2.). Of note, the *core limbic* network, which includes the PAG, hypothalamus, amygdala, hippocampus and areas in the striatum and thalamus, is the closest parallel to findings in animal literature and is related to low-level perception of emotional stimuli. The *lateral paralimbic* network, which includes the ventral striatum, insula, temporal pole and areas in the ventral/orbital PFC, has a role in evaluating bottom-up affective signals and integrating them into motivational states. These two networks are suggested to be associated with emotion generation, and specifically with core affect. Two other networks are suggested to be associated with regulation processes. The *medial PFC* network, which

includes the mPFC and ACC, is involved in monitoring affective state and conflict. The *cognitive/motor* network, which includes lateral PFC regions such as IFG and the pre-SMA, is associated with appraisal of emotional information and control over emotional reactions, possibly by utilizing semantic and executive processing. The medial PFC network and an additional *medial Posterior* network are similar in structure to the DMN and are suggested to represent the process of conceptualization. From this meta-analytic perspective, human anger is generally hypothesized to be the result of interactions between brain regions that belong to different functional networks that mediate emotion generation/expression and regulation and these networks seem to functionally couple (or uncouple) during the dynamic unfolding of the emotional episode.

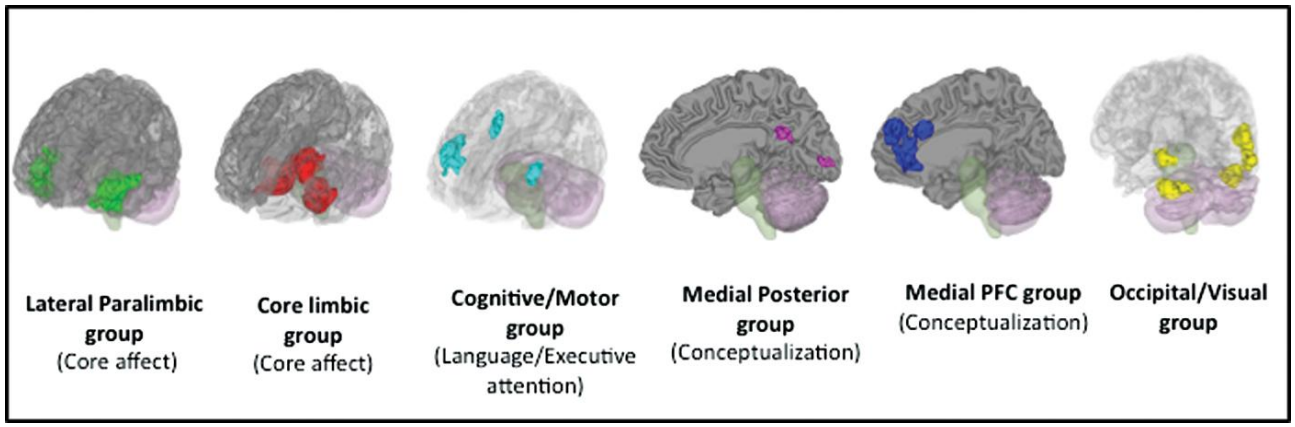

Figure 1.2 Meta-analytic emotional networks. Six functional networks were revealed by a multivariate meta-analysis of emotion studies and depicted in 3D rendering (Kober et al., 2008). The two core affect networks are suggested to be associated with the generation of emotion while the medial PFC and cognitive/motor networks are suggested to have roles in emotion regulation. Image extracted from Lindquist and colleagues, 2012.

1.3. Anger, military training and PTSD

1.3.1. Stoicism, military training and anger regulation

In its root, the Stoic philosophical school (Baltzly, 2010; Sherman, 2007) popular during the Helenistic era (323-146 BC), taught the development of self-control and fortitude as the means by which to overcome and reject the destructive nature of emotions. Interpersonal emotions were particularly underlined, specifically anger which was claimed to be most difficult to moderate. The formulation of Stoicism states that by practicing self-discipline one may take

command of his or her physiological, cognitive and behavioral responses and reactions to all events as they occur.

In her book "Stoic Warriors" (Sherman, 2007), Nancy Sherman argues that military pedagogy nurtures a Stoic-like attitude focused on emotional regulation, and specifically on the containment of anger. The goal of such pedagogy is forming combatants that will continue to operate even under life-threatening situations, focused and dedicated to carry out their defined missions. Sherman reveals a synergy between Stoicism and contemporary military thinking in which both regard anger as a sign of vulnerability because it reveals a hostile but defensive posture. Anger regulation is thus considered critical for combatants in the battlefield and therefore becomes a common and important objective in basic military pedagogy.

From boot-camp to the officers' academy, training a combat soldier involves disciplined physical and psychological manipulations intended to maintain strength and endurance, and desensitize uncontrolled spontaneous reactions (Darash, 2005; Lieblich, 1989; Sherman, 2007). Trainees are subject to verbal and physical treatments that in other contexts may be considered as abuse and are permanently on the verge of aggressive reactions. At the same time, as part of their professional practice, they are encouraged to abstain from emotional storms and are punished for inappropriate manifestations and uncontrolled outbursts. Such pedagogy can be thought of as an effective technique which trains soldiers to stay in control even under extreme conditions.

Military service has a central status within the Israeli society (Kimmerling, 1993) and because this service is mandatory to Israeli boys and girls 18 years of age, its profound impact on a personal level is far reaching. Indeed, the military service represents an intensive meeting point between the collective and the individual (Lomsky-Feder & Ben-Ari, 1999). Regardless of its moral end, military training, where Stoic-like pedagogy promotes anger regulation, offers a paradigmatic, and in Israel, an institutionalized case study for examining response to provocations and internalization of emotion regulation strategies.

1.3.2. PTSD and anger

Epidemiological findings suggest that almost every person will be exposed at least once during their lives to a potentially traumatic event, but only one in ten will continue to develop PTSD (Atwoli, Stein, Koenen, & McLaughlin, 2015; Breslau, 2012). This indicates that some individuals are predisposed and vulnerable to the disorder while others seem to be resilient. Notwithstanding, almost all individuals exposed will experience the symptomatology of PTSD, even without developing the full blown disorder. Sometime these symptoms will dissipate after a few weeks and this is referred to as Acute Stress Disorder. In other occasions the traumatic event is not a single point in time but a continuum of overlapping events thus inducing symptoms via chronic stress. PTSD symptoms are organized into three main clusters (American Psychiatric Association, 2013): (1) Re-experiencing - which involves flashbacks, nightmares and recurrent thoughts about the traumatic event, all of which may cause problems in a person's everyday routine; (2) Avoidance - which basically reflects evading anything that can somehow prompt the traumatic event, thus causing a change in day-to-day personal routine and losing interest in activities that were enjoyable in the past; and (3) Hyper-arousal – which includes various symptoms such as being tense and on the edge, thus easily startled and over vigilant to stimuli, having trouble falling asleep, irritated even by very mild provocations and thus with a tendency to angry and aggressive outbursts.

While, anger is pronounced in most anxiety disorders, it is specifically emphasized in PTSD, with variations across anger domains (Olatunji et al., 2010). For example, angry-rumination has an effect on PTSD and seems to be linked to re-experiencing (Orth, Cahill, Foa, & Maercker, 2008; Orth & Wieland, 2006). In addition, because deficits in anger amongst PTSD patients are apparent in physiological, cognitive and behavioral aspects (Chemtob, Novaco, Hamada, & Gross, 1997), it seems a general dysregulation of anger characterizes PTSD. Although anger has been reported in various PTSD populations such as survivors of transport accidents and assault victims, it is mostly associated with military and emergency services personnel and veterans (McHugh et al., 2012). In such cases, anger and hostility have been

found to account for over 40% of the variance of PTSD symptoms (Heinrichs et al., 2005; Novaco & Chemtob, 2002). Moreover, in these populations, anger dysregulation is especially emphasized during social interactions, and in many cases ends-up with aggression and violence (Beckham, Moore, & Reynolds, 2000; Lenhardt, Howard, Taft, Kaloupek, & Keane, 2012; MacManus et al., 2015). However, it is not quite clear whether difficulties in coping with anger are a cause or consequence of PTSD. Initial evidence suggests that it might be both. For example, a prospective study conducted by Meffert and colleagues (2008) on police recruits showed that trait-anger measured during training predicted elevated PTSD symptoms one year into active duty, and that greater PTSD symptoms at one year into active duty correlated with an increase in reported state-anger - that is the level of anger experienced in the current moment (Spielberger et al., 1983). Additional important evidence suggests that anger generally restricts and impedes treatment efficacy of PTSD (Andrews, Brewin, Rose, & Kirk, 2000; Forbes et al., 2008), underlining anger treatment as high priority for PTSD. Taken together, there seems to be a unique involvement of anger in PTSD which may reflect an individual tendency thus representing a risk or resilience factor for trauma and stress related psychopathology.

2. RESEARCH OBJECTIVES

The far reaching goal of the proposed study was to shed light on the complexity of human anger. Recognizing the multi-dimensionality of the anger construct, a multi-modal approach was opted using neural (structural and functional MRI), physiological (skin conductance), behavioral (monetary gains in a game and response times), subjective (self report) and trait personality measures (questionnaires). Together these measurements enabled to provide converging evidence on the individual experience of anger and possibly reflect differential regulation capabilities. In particular, efforts were made to capture the dynamic experience of anger, in both short and long term trajectories, and evaluate how its variable neural and behavioral expressions may relate to each other, how they may alter following combat-training, and what is their causal link to the development and manifestation of PTSD symptoms. Therefore a prospective research program was utilized. These goals were pursued by four objectives as follows.

2.1. Objective 1: Characterizing the neurobehavioral substrates of an interpersonal anger experience

To fulfill this objective an interpersonal anger provocation paradigm was developed based on a modified version of the UG (hereby termed as the anger-infused UG) during fMRI scanning. Unfair UG-offers have been repeatedly and convincingly associated with angry experience (Andrade & Ariely, 2009; Pillutla & Murnighan, 1996; Rotemberg, 2008; Srivastava et al., 2009; van't Wout et al., 2006) and greater acceptance rates of these offers was similarly shown to relate to enhanced emotion regulation capabilities (Dunn et al., 2012; Grecucci et al., 2013; Halali, Bereby-Meyer, & Ockenfels, 2013; Kirk, Downar, & Montague, 2011; Koenigs & Tranel, 2007; van't Wout et al., 2010). Our modification of the UG incorporated on-line verbal negotiations after each offer with a putative player which was in fact a professional actor trained with scripted improvisations to further infuse anger to the interaction. The realistic paradigm was to be validated by skin conductance measures which were recorded simultaneously with fMRI, and by subjects' retrospective report of

their emotional experience during the game, which was further used to characterize the anger experience.

It was assumed that differentiating individuals according to their total monetary gain accumulated throughout the game (i.e. *low-gain* vs. *high-gain*) will converge with behavioral, subjective, physiological and neural measures and reflect different anger-coping capabilities. In other words it was expected that unfair offers in concert with scripted provocations within the UG context will evoke anger, reflected by individual differences in total gain, and that this would manifest in a unique neural pattern of activation and connectivity. Accordingly the following hypotheses were specifically tested on data collected at the first time-point:

(1A) Participants will accept more fair compared to unfair offers.

(1B) Participants will report more negative than positive emotions, specifically anger, and anger will increase as the game evolves, especially for unfair offers. Similarly, sympathetic arousal reactivity will be apparent more for unfair compared to fair offers.

(1C) Low- and high- gain participants will display a differential emotional report and sympathetic arousal reactivity, the former reporting more intense anger and stronger sympathetic reactivity compared to the later.

(1D) Low-gain participants will display increased brain activations in regions associated with core affect such as amygdala, PAG and/or insula, while high-gain participants will display increased brain activations in regions associated with emotion regulation such as the vmPFC and/or dlPFC.

2.2. Objective 2: Identifying the neural traces of anger experience

To fulfill this objective, endogenous neural signals were recorded during task-independent resting-state (rs) fMRI before and after the anger-infused UG. Anger persistence beyond the presence of the provoking stimulus is a well known phenomenon and commonly relates to angry rumination (Bushman et al., 2005; Deffenbacher, Petrilli, Lynch, Oetting, & Swaim, 2003; Denson

et al., 2009; Pedersen et al., 2011; Rusting & Nolen-Hoeksema, 1998; Snyder, Crowson, Houston, Kurylo, & Poirier, 1997; Sukhodolsky et al., 2001). Therefore, a data-driven approach was used to examine FC modulations comparing the rs-fMRI session in the aftermath of anger to the rs-session at baseline, assuming that the identified neural changes between these resting periods will reflect neurological traces of the induced anger experience. This analysis was expected to reveal rs-FC modulations involving brain regions previously associated with angry rumination as well as in the aftermath of intense emotional experiences such as the amygdala and/or IFG (Denson et al., 2009; Fabiansson et al., 2012; Maron-Katz et al., 2016; Veer et al., 2011), that are associated with core affect and emotion regulation processes respectively. These modulations over time were expected to further relate to the neurobehavioral indices characterizing anger experience as detailed in objective 1, thus probing individual differences and relating anger experience and regulation to the lingering effect of anger. It was further questioned whether the identified rs-FC modulations would relate to trait-like measures associated with anger, namely individual differences in trait-anger and in grey matter volume. Accordingly the following hypotheses were specifically tested on data collected at the first time-point:

(2A) Identified rs-FC modulations will correlate with total gain, self-reported anger, sympathetic arousal, and with brain regions characterizing anger experience as identified in objective 1.

(2B) Identified rs-FC modulations will correlate with trait-anger and with grey matter volume in the same brain regions in which anger related rs-FC modulations will be identified.

2.3. Objective 3: Examining the influence of combat-training on neurobehavioral indices of anger

To fulfill this objective a prospective neuroimaging design was pursued, prior to and following intensive infantry training of combat soldiers. Regulation empowerment was assumed as an outcome of such training, following the stoic formulation of military indoctrination (Darash,

2005; Sherman, 2007). The study group therefore consisted of combat soldiers recruited from a Special Forces unit (*Duvdevan*) in the Paratroopers Brigade of the IDF, in which soldiers are specifically trained to internalize emotional regulation strategies, especially for anger, in order to cope with face-to-face life-threatening situations during a one-year period of combat-training. A two time-points prospective experimental design enabled to examine the effects of such training with regards to the experience of anger. A control group was recruited, consisting of age matched volunteers who took part in one-year pre-army civil-service national programs. Thus, while it was expected that no differences would be found between the study and control groups before training (first time-point), after the training period (second time-point) different patterns of anger experience would emerge such that the control group will exhibit no changes between time-points. However, low-gain soldiers reflecting an unbalanced anger profile will tend to exhibit a neurobehavioral pattern of anger associated with high-gain as identified in objective 1 and 2, while no changes would be detected for the high-gain soldiers who would be considered as having anger regulation capabilities a-priori. Accordingly, the following hypotheses were specifically tested:

(3A) Considering the anger-infused UG as described in objectives 1, low-gain soldiers of the study group from the first time-point will display an increase in total gain and associated neurobehavioral indices of anger in response to anger induction in the second time-point, while no changes will occur neither for high-gain soldiers nor for the civilians control group.

(3B) Considering the identified rs-FC modulations as pertinent to objective 2, a similar pattern of results as described in hypothesis (3A) will also be displayed. In other words, low-gain soldiers of the study group will display a change in rs-FC modulations that will be similar to the one displayed by high-gain participants at the first time-point, while no changes will occur neither for high-gain soldiers nor for the civilians control group.

2.4. Objective 4: Unveiling the relation between neurobehavioral indices of anger and combat-training stress symptoms

To fulfill this objective, PTSD related stress symptoms were assessed in the study and control groups at two time-points - before and after combat-training and civil-service respectively. An additional third time-point of symptom-assessment was added for the study group two-years into active combat duty and before completing the mandatory three-years of military service in the IDF. Elevated PTSD symptoms were expected to develop as a result of combat-training chronic stress (Bernton, Hoover, Galloway, & Popp, 1995; Day & Livingstone, 2001; Lin et al., 2015; Taylor et al., 2007), and furthermore as a result of exposure to life-threatening potentially traumatic event during active combat duty. The dependency of PTSD symptoms development on exposure to an acute or chronic stressful experience provides an exclusive opportunity to disentangle predisposing (pre-exposure) risk-factors from acquired (post-exposure) abnormalities by utilizing a prospective approach that examines individuals at high risk of exposure (emergency service personnel such as soldiers) before and after exposure (Admon, Milad, & Hendler, 2013). Since only a small subset of exposed individuals will ultimately develop PTSD, the current study will investigate inter-individual variability in the magnitude of exhibited psychopathological symptoms. It was assumed that a participant displaying neurobehavioral indices of anger as pertinent to a high-gain profile in the first time-point, reflected an emotionally regulated individual. Therefore, such an individual would be more apt to cope with stress and trauma and hence it was expected that such an individual from the soldiers study group will exhibit lower levels of symptoms. Notwithstanding, it was generally expected to replicate findings from the first time-point indicating that all participants accepted less unfair offers than fair offers, reported on angry feelings as the predominant emotional experience throughout the anger-infused UG, especially for unfair offers, and that there was a negative relationship between self-reported anger and total-gain. Accordingly the following hypotheses were specifically tested:

(4A) Soldiers but not civilians will display an increase in stress symptoms at the second time-point (post-exposure to combat-training chronic stress) and more so at the third time-point (following active duty).

(4B) Soldiers who gained more money throughout the game as described in the first time-point (objectives 1), will have fewer stress symptoms at later time-points.

(4C) Within the study group, neurobehavioral indices of anger revealed in the first time-point (objectives 1 and 2) and the change in these measures between time-points will correlate with symptoms level measured at later time-points.

3. GENERAL MATERIALS AND METHODS

The following chapter describes the general design, materials and methods that were applied in most phases of the research program. Specific aspects related to these issues are described in subsequent chapters.

3.1. General procedure

Upon arrival to the laboratory of the Tel Aviv Center for Brain Function at Tel-Aviv Sourasky Medical Center, participants received a through explanation of the planned prospective study and experimental procedures (Figure 3.1.). After signing an informed consent and completing various personality questionnaires, participants were given specific task-related instructions, then assembled with skin conductance (SC) electrodes and then entered the MRI scanner. The first scans were anatomical, lasting about 15 minutes. Subsequently participants performed various tasks unrelated to the work presented here, lasting about 30 minutes. They next performed a 6-minute rs-fMRI scan, followed by the anger-induction UG task which lasted for about 11 minutes, and then performed another 6-minute rs-fMRI scan. Upon exiting the MRI participants completed a retrospective emotional rating and continued to perform behavioral tasks unrelated to the work presented here. The exact same procedure was conducted in the first two-time points for both study and control groups. For the study group an additional third time-point included measuring the same personality questionnaires, with an emphasis on PTSD symptoms assessment, and various behavioral tasks unrelated to the work presented here. Debriefing was conducted for all participants at the end of the last time-point, as relevant per the study and control groups.

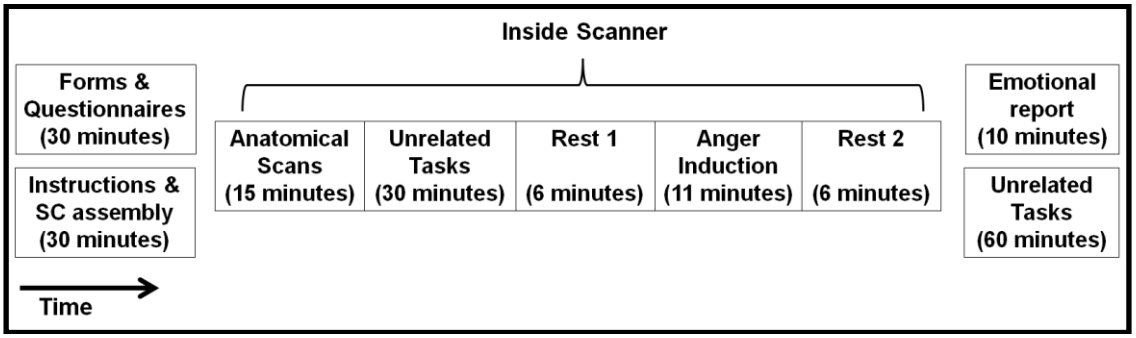

Figure 3.1. An overview of the experimental procedure.

3.2. Participants

3.2.1. Study group

The study group consisted of male IDF soldiers that volunteered and subsequently selected to serve in the Paratroopers Brigade. Recruited soldiers were only those selected as candidates for the Special Forces unit Duvdevan, noted for conducting face-to-face urban warfare and counter-terrorist undercover operations behind enemy lines. Each soldier serves a mandatory three years in the IDF, the first year dedicated to training and the two subsequent years in active duty. The time line of Duvdevan training (Figure 3.2.) begins with about 3.5 months of basic infantry training (boot camp) conducted in the Paratroopers Brigade base-camp, and followed by nine months of special training at the Duvdevan unit base. These months are segmented into three periods: (1) advanced infantry training that lasts about 2 months; (2) Special Forces combat-training that lasts about 6 months; and (3) personal specialized courses that last up to 1 month. After completing their training, Duvdevan soldiers are posted in combat duty and were thus expected to be exposed to potentially traumatic events.

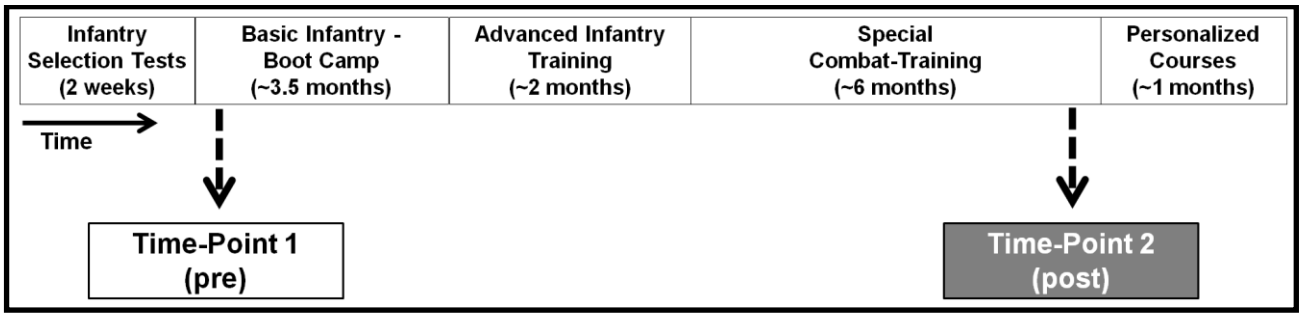

Figure 3.2. An overview of soldiers' combat-training time-course. The timing of the first two time-points of the prospective study is also illustrated as relevant to the training time-course.

Several important issues are note worthy regarding the 13-month training period. First, this period is very intensive and stressful, yet it does not involve a threat to life and thus is not considered a potential traumatic event. Second, though much of the basic training is focused on teaching basic warfare capabilities to each soldier, team spirit and being part of a squad that works together is very much emphasized. As a result, soldiers are constantly spending time together as a group. Finally, the counter-terror combat course Lotar, notoriously known as the

most physically difficult and disciplined part of Duvdevan training takes place during the Special Forces combat-training period. The Lotar course is considered as the "diploma" of Duvdevan training focusing on *Krav Maga* training, a noncompetitive self-defense technique with a key principle to counter attack and neutralize the opponent as quickly as possible. A landmark Krav Maga exercise in Lotar course demands soldiers to avoid any reaction while they are subject to physical and verbal violence. This specific training of Duvdevan soldiers makes them especially apt to exert physical, cognitive and emotional control (Darash, 2005).

The study group was therefore tested at three time points: (1) At the beginning of infantry-training, immediately after being selected as a candidate for Duvdevan (time-point 1); (2) One year into combat-training, before the personalized courses and subsequent deployment (time-point 2); and (3) two years into combat duty, before completing their mandatory military service (time-point 3).

3.2.2. Control group

The control group consisted of males who volunteered to take part in one of several one-year pre-army national civil-service programs which entail living in small sized communes around the country and involved assisting disadvantaged communities, youth at risk, and various other civic projects. It was assumed that such individuals that are willing to dedicate themselves to national concerns would share similar socio-educational background as combat-soldiers who are willing to risk their lives behind enemy lines. Moreover, conscription rates among graduates of pre-army national civil-service programs are almost 100% and many continue to infantry units. Importantly, civil-service volunteers do not live in a stressful and disciplined environment such as in the army. They may undergo specific courses related to the educational oriented program, such as to connect with children with needs or how to teach them basic skills, but there is no training which may lead to specific proneness to emotional regulation.

Participants of the control group were tested at two time points: (1) at the first two weeks of their civil-service program; and (2) about one year into their civil-service program, before being recruited themselves to military service in the IDF. These two time-points thus provided adequate control for the first two time-points of the study group.

3.2.3. Recruitment

In accordance with the IDF's and national civil-service programs' approval for conducting the research, participation was based solely on a voluntary basis with no material payoffs. Therefore, recruitment was based only on individuals willing to volunteer to take part in the prospective nature of this project. The study group was recruited at the Paratroopers Brigade base-camp in a meeting room in which the study's goals and general design were presented, including an overview on fMRI safety issues and matters of confidentiality. To avoid any compliance effects by ranking officials, the meeting was conducted behind closed doors from any commander. A form with the research description was given to the soldiers for additional consideration and consultation with their parents. The control group was recruited in various civil-service activity centers, at which the study's goals and general design were similarly presented. The same form with the research description was given for additional consideration and consultation with their parents.

At the first time-point, 50 male soldiers (age 18.89±0.92, mean±sd) and 23 male civilians (age 18.17±0.38) volunteered to participate. All participants were Israeli citizens of Jewish religious orientation, had completed secondary education, had no reported history of psychiatric or neurological disorders, no current use of psychoactive drugs, no previous exposure to abuse during childhood and/or potentially traumatic events before entering the study, and normal or corrected-to-normal vision. All participants provided written informed consent and the study was approved by the Institutional Ethics Committee of the Tel-Aviv Sourasky Medical Center and by the Medical Corps Ethics Committee of the IDF. Only those soldiers from the first time-point who did not

drop-out from the training period, and after re-presenting the study's goals and general design agreed to continue as participants, were recruited to participate in the second time-point. The same procedure was repeated when recruiting for the third time-point as for when recruiting civilians for their second time-point. The number of participants per group per time-point is summarized in Table 3.1.

Table 3.1. Number of participants per group per time-point

	Time-Point 1	**Time-Point 2**	**Time-Point 3**
Study group	50	36	32
Control group	23	17	-

It is important to note at this point that the two-year period of active duty for soldiers turned out to be void of exposure to potentially traumatic events, probably due to the region's political status-quo, and was in fact characterized by a descriptive decrease in symptoms compared to at the end of combat-training (for the 32 soldiers participating in both these time points: symptoms-time2=26.13±8.37; symptoms-time3=24.91±9.01; $t_{df=31}$=0.60, p=0.60; *Cohen's d*=0.14). Therefore, the third time-point was discarded from further investigations presented in this manuscript. Subsequently, the results presented below (chapter 7) focused on exposing possible vulnerability and/or resilience factors of chronic stress related symptoms developed following combat-training and their relation to anger.

3.3. Psychological Questionnaires

3.3.1. State-Trait Anger Expression Inventory-2 (STAXI-2)

The STAXI-2 (Spielberger, 1999) is a 57-item gold-standard questionnaire used to comprehensively assess anger using several scales: State-anger – the intensity of anger as an emotional state at a specific time (includes 3 sub-scales); Trait-anger – the frequency of angry feelings experienced over time (includes 2 sub-scales); and four more relatively independent anger-related traits: anger expression-in – holding in or suppressing angry feelings; anger expression-out – expressing angry feelings toward other people and/or objects; anger control-

in – controlling angry feelings by preventing expression-out; and anger control-out – controlling suppressed angry feelings by cooling off. The psychometric properties of these scales are well established (Spielberger & Sydeman, 1994; Spielberger, Sydeman, Owen, & Marsh, 1999). Items are rated on a 4-point frequency scale from 1 (not at all) to 4 (very much). Trait-anger was the main focus of the current investigation.

3.3.2. Emotion Regulation Questionnaire (ERQ)

The ERQ (Gross & John, 2003) is well established 10-item questionnaire used to assess individual differences in the use of two emotion regulation strategies: reappraisal and suppression. Items are rated on a 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree).

3.3.3. Neuroticism-Extroversion-Openness – Five Factor Inventory (NEO-FFI)

The NEO-FFI (Costa & McCrae, 1992; McCrae & Costa, 2008) is an extensively used gold-standard questionnaire which includes 60 items assessing the "big five" personality traits: neuroticism, extraversion, openness, agreeableness and conscientiousness. These personality traits are regarded as the default model of personality structure, a meeting point for disparate human personalities, and have been associated with various physiological and psychiatric features. Items are rated on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree).

3.3.4. Sensitivity to Reward and Punishment Questionnaire (SPSRQ)

The SPSRQ (Torrubia, Avila, Moltó, & Caseras, 2001) is a 24 yes/no item questionnaire intended to asses individual differences in two scales: (1) Sensitivity to reward is used to measure behavioral activation in response to reward cues or approach appetitive situations (Smillie & Jackson, 2005); (2) Sensitivity to punishment is used to measure behavioral inhibition in response to punishment or to avoidance of aversive situations (Caseras, Avila, & Torrubia, 2003).

3.3.5. Toronto Alexithymia Scale (TAS)

The TAS (Bagby, Parker, & Taylor, 1994) is a 20-item questionnaire widely used to assess alexithymia. Three sub-scales measure difficulty in describing feelings, difficulty in identifying feelings and externally-oriented thinking (minimizing emotional experience). Items are rated on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree).

3.3.6. Post Traumatic Stress Diagnostic Scale (PDS)

The PDS (Foa, 1995; Foa, Cashman, Jaycox, & Perry, 1997; McCarthy, 2008) is an instrument which assesses the presence and severity of PTSD using a total of 49 items in four sections. The first section has a checklist to identify potentially acute traumatic events experienced by the respondents. In the second section, respondents indicate which event has troubled them the most in the past month and describe it in more details to determine if it meets the DSM's stressor criteria. In the third section, respondents rate 17 items representing PTSD symptoms experienced in the past month on a four-point frequency scale from 1 (not at all) to 4 (almost always). In the fourth and final section, respondents indicate whether these symptoms impair their day-to-day lives.

3.3.7. Post-Traumatic Stress Disorder Check-List (PCL) - military version

The PCL (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996; Forbes, Creamer, & Biddle, 2001; Weathers et al., 1993) is a 17-item questionnaire representing PTSD symptoms, widely used to assess PTSD based on the DSM's stressor criteria. Respondents rate each item on a 5-point frequency scale from 1 (not at all) to 5 (extremely), indicating the extent to which they have experienced a specific symptom during the past month. The PCL military version used here assess PTSD-symptoms experienced specifically in relation to stressful military experiences. This questionnaire was applied only to soldiers and only in time-points two and three.

3.4. fMRI

fMRI is the most commonly used noninvasive neuroimaging technique which provides the blood-oxygen-level dependent (BOLD) signal. This signal has been shown to reflect hemodynamic responses coupled with neuronal activity, and thus it comprises an indirect measure of such local activity (Heeger & Ress, 2002). While neuronal activity influences blood volume and blood oxygenation (Belliveau et al., 1991; Fox, Raichle, Mintun, & Dence, 1988), it is mainly the coupled increase in blood flow that enhances the BOLD signal. Following glutamate release during neural activation, neurons and astrocytes send molecular messengers inducing nitric oxide, prostaglandins and epoxyeicosatrienoic acid to smooth muscles of the adjacent blood vessels. These messengers cause the dilation of the vessels and thus increase the blood flow (Attwell et al., 2010). The enhanced flow locally increases the ratio between red blood cells containing oxidized hemoglobin and those that have a deactivated form of hemoglobin. Deoxidized hemoglobin has stronger magnetic influence on its surrounding compared with oxidized hemoglobin and thus this ratio leads to measurable inhomogeneity in a magnetic field manifested as an increase in BOLD signal. This increase in the BOLD signal is known to take place between two to six seconds after the actual neuronal activity, and thus the temporal resolution of fMRI is quite low. However, fMRI does provide high spatial resolution (up to 1mm) and allows for brain mapping of specific regional activity as well as large scale networks. Finally, it should be noted that comparative studies of fMRI and intracranial recording indicate that BOLD reflects mainly local field potential, which is influenced by synaptic input to the local neurons (post-synaptic activity) and internal neural processing rather the by regional output (Heeger & Ress, 2002).

3.4.1. Data acquisition

All brain imaging scans included in this research program were performed in 3 Tesla, General Electric scanner, Signa Excite echo speed scanner with an 8-channel head coil located at the Wohl Institute for Advanced Imaging at the Tel-Aviv Sourasky Medical Center. Functional whole-brain

scans were performed with a gradient echo-planar imaging (EPI) sequence of functional T2*-weighted images (TR / TE=3000 / 35 ms; flip angle=90°; FOV=200 × 200mm; slice thickness=3 mm; no gap; 39 interleaved top-to-bottom axial slices per volume). Structural T1-weighted 3D axial spoiled gradient (SPGR) echo sequences (TR/TE = 7.92/2.98 ms; flip angle=15°; FOV=256 × 256mm; slice thickness=1 mm) were acquired to provide high-resolution grey matter anatomical images.

3.4.2. MRI Audio equipment

OptoAcoustics™ adaptive and automatic noise canceling FOMRI-III™ optical microphone and matching insulated headphones with built-in loudspeakers were used to minimize interferences during verbal interactions within the scanner.

3.5. General note on statistical analysis

Statistical analysis throughout this work was carried out using Statistica 10 (StatSoft) and SPSS 20 IBM). Parametric and non-parametric analyses were used in context and accordance with standard procedures, including Student t-tests, various models of analysis of variance (ANOVA), Wilcoxon signed-rank test. Pearson's r and Spearman's ρ were used to examine correlations. Tukey's HSD correction was applied when testing post-hoc simple effects and p-values were always two-sided unless mentioned otherwise.

4. OBJETIVE 1: Characterizing the neurobehavioral substrates of an interpersonal anger experience

**** Excerpts from the current chapter were published in:**

Gilam G., Lin, T., Raz, G., Azrielant, S., Fruchter, E., Ariely, D. & Hendler T. (2015). Neural substrates underlaying the tendency to accept anger-infused ultimatum offers during dynamic social interactions. *Neuroimage, 120,* 400-411.

4.1. Introduction

In human relationships, interpersonal conflicts are almost inevitable, occurring whenever two or more interdependent individuals disagree or have opposing goals, and often result in a surge of aggression and violence (De Dreu, Beersma, Steinel, & Van Kleef, 2007; Forgas, Kruglanski, & Williams, 2011; Van Kleef, 2010). The dynamics of interpersonal conflict evoke strong emotions, most typically anger, which tends to progressively escalate and further fuels the conflict. While anger and aggression are considered as inherent survival responses in animals, humans are endowed with the capability to regulate such negative emotions and thus adapt to different social situations (Davidson, Putnam, & Larson, 2000; Ekman & Davidson, 1994; Gross & Thompson, 2007). Consequently, in managing our way through interpersonal conflict, anger regulation may play a crucial role in avoiding violent repercussions and in promoting cooperation. A common framework that enables studying interpersonal conflict is the UG. While focusing on monetary resources, the decision to accept or reject an offer in the UG provides an objective measure for the beneficial (i.e. both players gain money) compared to detrimental (i.e. both players lose money) outcome of conflict, respectively.

As illustrated above (section 1.2.3.) and resonating with the now common knowledge that emotions impact decision-making (Lerner, Li, Valdesolo, & Kassam, 2015), unequal UG-offers are considered unfair offers that elicit primarily anger, and the rejection of such an offer is regarded as reflecting an aggressive retribution at one's own personal cost (Ma et al., 2012; Pillutla &

Murnighan, 1996; Xiao & Houser, 2005; Yamagishi et al., 2009). Interestingly, a recent example for individual differences in the emotional response to UG-offers was shown in a study in which greater resting HR-variability, a marker of trait emotion regulation capability which was measured before playing the UG, predicted subsequent increased acceptance rates (Dunn et al., 2012). Further support for the role of emotion regulation in one's response to UG-offers stems from findings such that depleting cognitive control resources resulted in decreased acceptance rates (Halali et al., 2013), while explicitly instructing to regulate emotions resulted in increased acceptance rates (van't Wout et al., 2010). Therefore it seems that regulating anger may be important to the acceptance of unfair offers and that people who are better able to regulate anger associated with such offers are more likely to accept and financially benefit from them (Grecucci & Sanfey, 2013). The focus of the current study was on the neural substrates that underlay the response to UG-offers using fMRI. The goal was to characterize individual differences in the tendency to accept these offers and therefore gain more money, assuming this would reveal neural processes related to the associated emotional experience.

Several neural processes have been shown to be involved in social decision making, including reward processing, perspective taking, social-norm enforcement and emotion regulation amongst others (Rilling & Sanfey, 2011). These processes have been largely associated with neural activity in the PFC and have been specifically implicated in the neural response to being made an offer in the UG, i.e. before the actual decision to accept or reject. The first fMRI study to investigate ultimatum decision-making found that accepting unfair offers was associated with stronger dlPFC activation compared to the anterior-Insula during the offer period, and the reverse pattern was associated with rejection of unfair offers (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). It was suggested that this might reflect a self-control process exerted by the dlPFC. Indeed, the dlPFC has been associated with domain-general cognitive-control processes (Miller & Cohen, 2001), and specifically with emotion regulation via cognitive reappraisal (Buhle et al., 2014). Congruently, a recent study instructed participants to reappraise their negative emotional response to unfair offers

and found that increased activity in a region of the dorsal-PFC positively correlated with acceptance rates (Grecucci et al., 2013). Nevertheless, other studies have suggested that both dlPFC (Baumgartner et al., 2011; Knoch et al., 2006) and anterior Insula (AI; Corradi-Dell'Acqua et al., 2013) may have a role in fairness enforcement norms, rather than the emotional response per-se. Specifically, dlPFC's involvement in self-control processing of UG-offers might reflect the need to abide to social-norms of what is considered fair.

Interestingly, it has been shown that fair and rewarding offers have been associated with neural activity in a region of the vmPFC, and accepting unfair offers of equal absolute value was associated with increased activity in a more lateral region of the ventral-PFC (Tabibnia et al., 2008). Though unfair offers are regularly rejected, accepting such offers might be related to one's valuation of the monetary outcome rather than the perceived fairness of the offer. The vmPFC has been associated with reward valuation, but also with other roles in social and emotional processing (Adolphs, 2009; Bechara, Damasio, & Damasio, 2000; Mitchell, 2009; Rolls, 2004), and has also been ascribed a specific role in emotion regulation, for example during extinction (Davidson et al., 2000; Diekhof et al., 2011; Quirk & Beer, 2006). In fact, it has been suggested that while the dlPFC is mainly related to voluntary-explicit emotion regulation, the vmPFC is related to automatic-implicit emotion regulation (Etkin et al., 2015; Gyurak et al., 2011; Phillips et al., 2008). These multiple functionalities have posed difficulty in interpreting the role of the vmPFC during ultimatum decision-making. For example, patients with vmPFC-lesions and an acquired deficit in emotion regulation that played the UG had increased rejection rates compared to controls, suggestive of vmPFC's role in regulating the emotional response to unfair-offers (Koenigs & Tranel, 2007). In contrast, it was suggested that reward sensitivity rather than emotion-regulation per-se was the domain of deficit, since if payment of rewards was in cash immediately after the game, vmPFC-lesion patients did not differ from controls (Moretti, Dragone, & di Pellegrino, 2009). Albeit an additional vmPFC-lesion study suggested that vmPFC's role in accepting unfair offers was related to perspective-taking capabilities (Shamay-Tsoory, Suleiman, Aharon-Peretz,

Gohary, & Hirschberger, 2012). Importantly, an fMRI study revealed that individual differences in the tendency to accept unfair offers was related to increased vmPFC activity during unfair offers, which also mediated the relationship between pre-UG testosterone levels and acceptance rates (Mehta & Beer, 2010). While pointing at the role of the PFC in UG behavior, imaging studies have yet to provide a clear indication of the neural substrates involved in the idiosyncratic emotional experience associated with the decision to accept or reject offers in the UG.

Taken together, the UG provides a promising platform for studying individual differences in anger experience and its' regulation within a social decision-making context, representing interpersonal conflict over monetary resources. However, the interaction between players in the UG lacks fundamental characteristics of the naturalistic social dynamics of such an interaction. A true engagement in social interaction occurs when people can communicate with other people in their environment, conveying their feelings, thoughts and intended actions, and adapting themselves in a response-contingent manner (Przyrembel et al., 2012; Schilbach et al., 2013). Yet the vast majority of findings on the neurobiological underpinnings of complex human affective phenomena are based on "offline" paradigms during which participants' brains are studied in isolation from other agents in the environment (Gilam & Hendler, 2016). This seems at odds with the notion that emotional episodes occur and emerge mostly via our social interactions (Fischer & van Kleef, 2010). Indeed, during interpersonal conflict these interactions take the form of negotiations which may spiral to personal insults and provocations and are thus an additional source for anger induction. Nevertheless, in most UG studies communication is based on restricted information of offers and decisions. Moreover, most UG studies implement a "single-shot" paradigm in which each offer is from a different, most often a virtual proposer, reducing to almost none the dynamic nature of the interaction. In addition, the induction of anger has been based solely on the magnitude of offers and not on the type of emotional experience which evolves during the interaction. To account for these gaps a modified repeated version of the UG was implemented (Slembeck, 1999), in which participants needed to decide whether to accept or reject offers from the same putative proposer. In

addition on-line verbal negotiations between the players were incorporated after each round. During these verbal negotiations participants were confronted with an obnoxious hard-playing confederate proposer, which was in fact a professional actor who improvised with scripted provocations in order to infuse more genuine and interpersonal anger to the conflict.

Participants in the scanner played 10 UG-rounds with the same proposer who was outside the scanner, and were generally informed they could utilize negotiations to improve their subsequent offers. Unbeknownst to them, the provocations during negotiations were in concert with a sequence of predefined offers allotted from a pot of 20 Israeli New Shekel (ILS) per offer. Therefore, participants were led to believe that their verbal negotiations had an influence on subsequent offers from the proposer, but in fact the purpose of these negotiations was to emphasize the anger probing nature of the game in a realistic and interpersonal fashion. In addition to BOLD brain activity measured with fMRI, simultaneously SCR was obtained to estimate sympathetic arousal. Following scanning, and to characterize the emotional experience unfolded during the anger-infused UG, participants were asked to report their feelings on a round-by-round basis, based on the Geneva Emotion Wheel (GEW; Scherer, 2005). The game was divided into two seamless fMRI scans to reduce head-movement artifacts. The generated dynamic experience was assessed by comparing both emotional ratings and brain activity between the two halves of the game, and also by FC analysis. Overall, it was hypothesized that participants would report more anger compared to other negative emotions and compared to positive emotions, and it was expected that anger would increase in the second half of the game compared to the first. While the relevance of factors such as reward sensitivity in accepting UG-offers were not precluded, it was assumed that gaining money throughout the game would reflect at least in part a trait-like capability to regulate these angry emotions within the entire interpersonal conflict scenario. Participants were thus characterized based on the median split of the total monetary gain accumulated throughout the game (hereby termed high- or low- gainers). It was hypothesized that high-gainers would report less anger, and exhibit less sympathetic arousal compared to low-gainers. In view of vmPFC's association with

individual differences in UG behavior and its suggested role in implicit emotion regulation, it was also hypothesized that increased activity in this region would relate both to high-gain and to reduced anger. This also corresponds to the fact that participants were not explicitly informed about the expected emotional experience during the game, and were not instructed to regulate it. Importantly, while regulatory processes may occur at any time-point during the game, analyses focused on the offer period because that is the "moment of truth" in which one needed to confront the actual monetary-offer and prepare for making the decision which will influence both himself and the proposer, and would be a basis for subsequent negotiations. Finally, since unfair offers induce more anger, it was expected the behavioral and neural effects would be more accentuated during such offers compared to fair offers.

4.2. Materials and methods

4.2.1. Participants

Sixty male participants (age 18.62±0.88) were recruited on a voluntary basis. Twenty–two civilians (age 18.18±0.39) civilians were from Israeli civil-service programs and 38 soldiers (age 18.87±0.99) were newly enlisted to military service in the IDF and designated to a combat-unit. All participants provided written informed consent and the study was approved by the Institutional Ethics Committee of the Tel-Aviv Sourasky Medical Center and of the IDF. Thirteen additional participants were discarded from the final analysis: four soldiers and one civilian since they expressed suspicion of the manipulation, seven soldiers did not partake in the anger induction manipulation and one soldier decided to abort entering the MRI scanner. Since there were no differences between civilians and soldiers in all measures they were considered as one single group (see Table 4.3.).

4.2.2. Anger-infused ultimatum game

A previously used fMRI UG protocol (Sanfey et al., 2003) was modified by incorporating 30second verbal negotiations between the participant and a putative proposer following each UG-round (Figure 4.1.). The proposer was in fact one of three professional actors (counterbalanced between participants) trained with scripted improvisations (see below) to further evoke anger and intensify conflict. The negotiations gave participants the possibility to express themselves spontaneously in reaction to the terminated UG-round and solicit the putative proposer regarding the next round. Similar modifications have previously been used but not with on-line verbal communication, rather computer-based messaging (Kravitz & Gunto, 1992; Xiao & Houser, 2005). Participants were led to believe that negotiations enabled them to bargain with the proposer to maximize monetary gain but no indications were made regarding the emotional experience which might be associated with these negotiations. Participants were also explained that to avoid any pre-game agreements between the two players they would never meet. Each participant was photographed and told the photo would be used as a cue for starting negotiation. During scanning the participants saw a photo of the proposer and their own photos were only used in pre-scan simulation practices. Participants played the responder and were led to believe that their decisions to accept or reject (via a button press) were made vis-à-vis offers by a proposer who supposedly split 20ILS in real-time. In reality, four pre-determined sequences of both fair (10:10, 11:9, 12:8) and unfair (2×15:5, 16:4, 17:3, 18:2, 2×19:1) offers were counterbalanced between participants (Table 4.1.). Since there were no differences between these sequences in all measures they were collapsed across all analyses (see Table 4.3.). In addition, expecting verbal negotiations to entail increased head-movements, the game was divided into two seamless 5-round fMRI scans to reduce movement effects on the BOLD signal.

Before starting the game, a quick introduction was conducted between the two players via the shared audio system. Participants were described as civilians or soldiers and the putative proposers as volunteering students. Subsequently, the experimenter exposed a bogus high-score table to increase competitiveness and motivation. In accordance with the Institutional Ethics Committee

demands, there were no actual material payoffs of any kind. Portraying the UG as a game in which one should aim for a high total-gain of money (even if fictive) and reach the high-score table was assumed as an adequate context to motivate participation, especially in view of the prospective nature of our study. This also goes hand-in-hand with the division into high-gain and low-gain participants. Previous findings showed no difference in acceptance rates of fair and unfair offers among healthy subjects when comparing abstract to cash rewards while interacting with a supposedly human proposer (Moretti et al., 2009). To ensure interest and motivation in playing the game participants were asked to rate their desire to gain money upon completion of the task (on a 0 to 10 scale) and found high ratings across all subjects (6.47±2.71), with no influence of recruitment group (soldier/civilian), gain-group (low/high) nor the interaction between them (p-values>0.40).

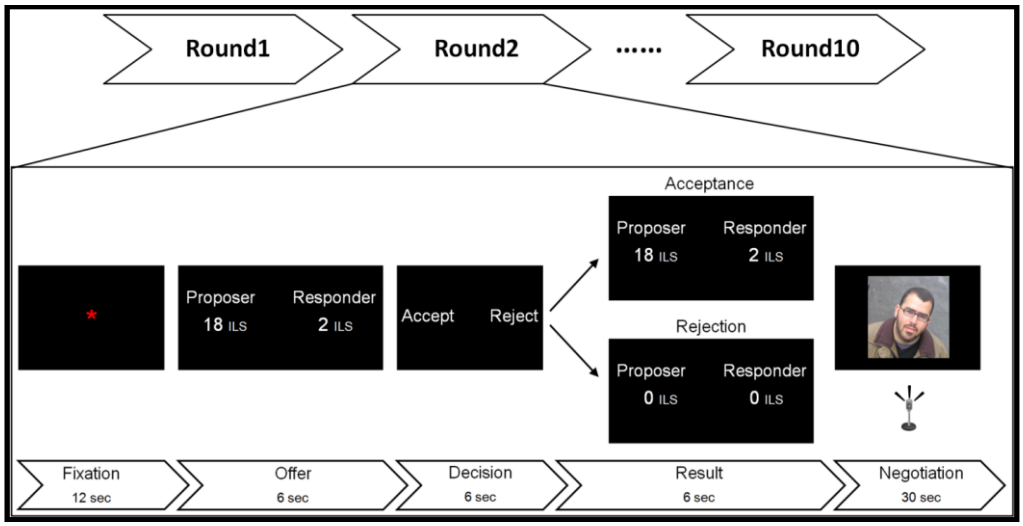

Figure 4.1. Anger-infused UG design. Each round began with a fixation period, supposedly the time in which the proposer decided how to split the sum of 20 ILS. Participants then saw the offer, decided whether to accept or reject and then viewed the result of their decision. Verbal negotiations followed and began when a fictitious picture appeared, supposedly belonging to the other player. This sequence was repeated 10 times in total.

Table 4.1. The four sequences of offers used in the anger-infused UG

	1st fMRI scan					2nd fMRI scan				
	1st offer	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
1st sequence	10:10	12:8	15:5	16:4	18:2	17:3	15:5	11:9	19:1	19:1
2nd	17:3	15:5	11:9	19:1	19:1	10:10	12:8	15:5	16:4	18:2
3rd	10:10	18:2	12:8	15:5	16:4	19:1	17:3	15:5	11:9	19:1
4th	19:1	17:3	15:5	11:9	19:1	10:10	18:2	12:8	15:5	16:4

Table 4.1. The four pre-determined sequences of offers used in the modified UG included the exact same 10 offers, allotted from a pot of 20 ILS. In order to minimize artifacts of head-movement, the sequences were divided into two seamless fMRI scans. The 1st and 2nd fMRI scans of the 1st sequence were switched in order in the 2nd sequence, while the 1st and 2nd fMRI scans of the 3rd sequence were switched in order in the 4th sequence.

4.2.3. Actor training

Three actors playing as proposers received a thorough explanation regarding the UG and the modifications performed in its' current version, and were instructed to be generally antagonistic and uncooperative while incorporating scripted provocations in a realistic fashion during verbal negotiations, in congruence with the pre-programmed sequence of offers. Actor training included simulations on bogus subjects in a mock scanner. Actors' scripted provocations were generally divided into three categories aimed to induce anger by aversive interpersonal communication (Kowalski, 2001): (1) insulting the related self-image of the participant, for example: "you have only muscle and no brains" (for soldiers) or "this is not summer camp" (for civil service volunteers); (2) violating appropriateness of conduct and interaction, such as interrupting the participants and raising the tone of voice; and (3) direct confrontation regarding the game, for example: "I owe you nothing!" or "take it or leave it!". Actors were instructed to incorporate provocations from all three categories and to pursue what seemed to induce most anger, while keeping content credible and concomitant with the sequence of both fair and unfair offers. In this regards, they were also instructed to try and provoke responders even after accepted offers by saying for example, "I didn't believe you'd go so low" or sarcastically "your making my life a piece of cake". Additionally, actors were generally instructed to be emotional and irritated in response to participants' rejections and possible counter provocations to portray a realistic engagement in the game and possibly influence participants' emotional state via emotional contagion (Hatfield, Cacioppo, & Rapson, 1993). Furthermore, previous findings have implied that repeated bargaining in the UG in which responders play with the same proposer is influenced by reputation and strategic reasoning and that players are generally more competitive than in single-shot UGs (Slembeck, 1999). While increasing competitiveness is an important and relevant feature for the current paradigm, it was expected that strategic reputation-thresholds would be a possible demand by participants during negotiations. In other words, it was expected that some participants would demand better offers for them to accept. Therefore, the improvisation-training included specific

options for response, such as insisting that the participant himself would be the one to concede and accept an unfair offer, which would supposedly be reciprocated by an improved offer, or stating that they (the proposers) would "not be intimidated by threats". The possibility that reputation would actually determine behavior in these circumstances was thus diminished, especially since all offers were predetermined. Importantly, since there were no differences between the three actors in all measures they were collapsed across all analyses (see Table 4.3.).

4.2.4. Emotional rating

An iterated version of the GEW (Scherer, 2005) scheme was used to obtain post-scan subjective reports of the emotional experience during the anger-infused UG, on a round-by-round basis and in accordance with participants' actual decisions. The retrospective nature of the report aimed to avoid affect labeling as well as interference with the spontaneous interaction between participants and actors. Similar post-scan dynamic ratings of emotional experiences have previously been performed with strong reliability and validity (Raz et al., 2012), as in other UG experiments (Dunn et al., 2012; Osumi & Ohira, 2009). The GEW comprises 16 emotions arranged in a circular pattern based on two axes, valence (positive/negative) and potency (high/low): pride, elation, happiness, satisfaction, relief, hope, interest, surprise, anxiety, sadness, boredom, shame/guilt, disgust, contempt, hostility and anger (Figure 4.2.). In the current implementation of the GEW, participants received a print-out of 30 screen-shots that portrayed each offer, result and negotiation periods in the exact sequence of UG-rounds as played in the scanner. Adjacent to each print-screen was a GEW and participants were instructed to rate each emotion on a 7-point intensity scale from 0 (none) to 6 (very high), in relation to how they felt in that exact period during the actual game in the scanner. Specifically for the negotiation screen-shots, which featured the photo of the putative-proposer, participants were generally instructed to try and replicate the content of interaction and rate the emotional experience accordingly.

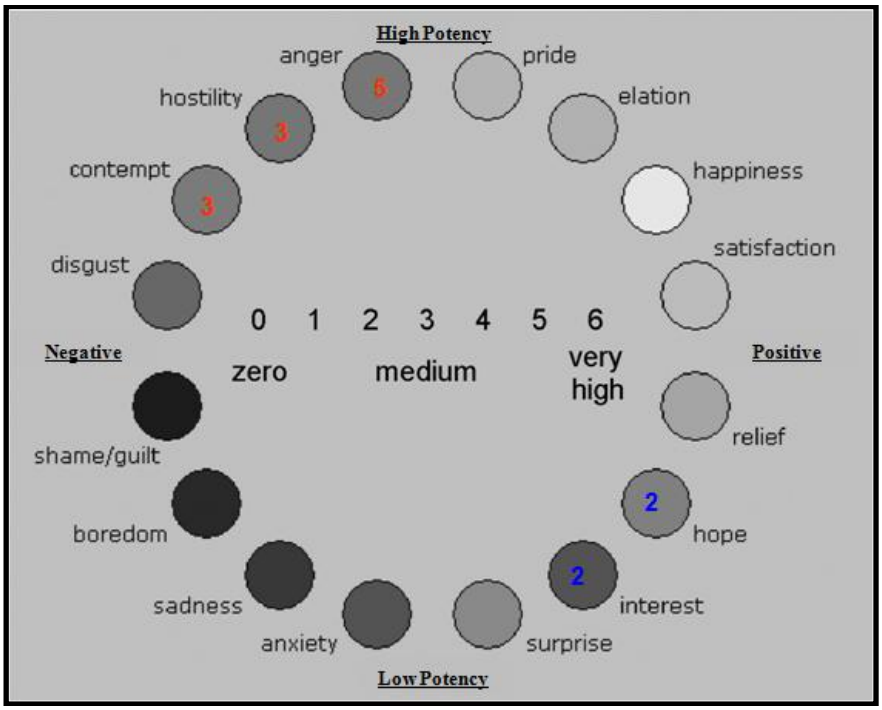

Figure 4.2. Emotional rating based on the GEW. The GEW is organized in a circular pattern according to two axes: valence (positive/negative, to the right and left respectively) and potency (high/low, on top and bottom respectively). As illustrated, participants were instructed to mark the intensity of each emotion in the empty circle next to that emotion, or to leave it empty if they did not feel that emotion.

4.2.5. Questionnaires

The prospective study included various personality questionnaires of which general details are provided in section 3.3 and in Table 4.2.

Table 4.2. Reliability, gain-groups differences and correlations with vmPFC for the questionnaires

Questionnaire	Subscale	N[#]	Reliability (Cronbach's α)	Gain-groups difference	vmPFC correlation
ERQ	Suppression	60	0.69	t_{58}=-0.96, p=0.34, *Cohen's d*=-0.25	**r=0.32, p=0.02**
	Reappraisal	60	0.82	t_{58}=0.15, p=0.88, *Cohen's d*=0.04	r=0.19, p=0.17
NEO-FFI	Neuroticism	60	0.77	t_{58}=-0.11, p=0.91, *Cohen's d*=-0.03	r=-0.07, p=0.63
	Extraversion	60	0.55^	t_{58}=-0.05, p=0.96, *Cohen's d*=-0.01	r=-0.08, p=0.59
	Openness	60	0.63	t_{58}=-0.82, p=0.42, *Cohen's d*=-0.22	r=0.07, p=0.63
	Agreeableness	60	0.65^	**t_{58}=-2.17, p=0.03, *Cohen's d*=-0.57**	r=0.09, p=0.54

	Conscientiousness	60	0.82	t_{58}=-1.35, p=0.18, *Cohen's d*=-0.35	r=0.00, p=0.99
SPSRQ	Reward Sensitivity	59	0.63	t_{57}=1.54, p=0.13, *Cohen's d*=0.41	r=-0.17, p=0.24
	Punishment Sensitivity	59	0.79	t_{57}=-1.22, p=0.23, *Cohen's d*=-0.32	r=0.19, p=0.18
STAXI-2	Trait-Anger	60	0.74	t_{58}=-0.25, p=0.80, *Cohen's d*=-0.06	r=0.07, p=0.63
TAS		55	0.78	$t_{39.53}$=1.26,p=0.22, *Cohen's d*=0.35	r=0.06, p=0.67
Post-scan desire to gain money		60	-	t_{58}=-0.06, p=0.96, *Cohen's d*=0.02	r=0.01, p=0.97

Table 4.2. General details on the questionnaires is provided, including number of participants who completed the questionnaire (denoted by #), reliability, comparison between gain-groups, and correlation with vmPFC activity during the offer period. ^ denotes that one item was removed because it impacted reliability and *denotes a significant result. For Agreeableness, LGs (29.04±3.87) had a lower average score compared to HGs (31.55±4.89). The last measure refers to a post-scan self-report of participants' desire to gain money in the game.

4.2.6. Skin conductance data acquisition and analysis

SC was simultaneously recorded during fMRI scans using the GSR-MR BrainAmp-MR ExG system (Brain Products). Raw data was sampled at 5 kHz and recorded using the BrainVision Recorder software (Brain Products). SC was recorded via two Ag/AgCl electrodes filled with isotonic NaCL unibase electrolyte attached to the volar surface of the second phalanx of the second and third fingers of the non-dominant hand. Pre-processing the data consisted of gradient artifacts removal using a FASTR algorithm and then down-sampling the signal to 250Hz. Technical malfunctions led to the availability of only 37 participants (low-gainers=18, high-gainers=19). Analysis utilized EEGLAB 6.01 software package (Schwartz Center for Computational Neuroscience, University of California, San Diego) for cardio-ballistic artifacts removal. Ledalab software (http://www.ledalab.de/) was used to differentiate between the tonic and phasic components of SC signal, changing it into discrete events which enabled to analyze SC in response to specific periods (Benedek & Kaernbach, 2010a, 2010b). While there are different approaches for the analysis of SC, it has recently been shown that Ledalab is comparable to other such approaches (Green, Kragel, Fecteau, & LaBar, 2014). The data was framed within a response time-window of

between 1-5 seconds after the stimuli appeared. SCR during the offer periods was inspected. Minimal threshold was set at 0.02 microsiemens (μs) and a log transformation was incorporated to normalize the data. Two SC parameters were analyzed: (1) SCR-intensity – the average SCR within the response time-window and (2) SCR-latency – the onset in seconds of the first SCR in the response time-window. SCR-latency was shown to reflect sympathetic arousal similarly to SCR-intensity (Witvliet & Vrana, 1995). The first offer had stronger SCR-intensity compared to all other offers ($p<0.05$ compared to almost all other offers). There was no difference between gain-groups in this first offer (intensity: Student's $t_{35}=-0.06$, $p=0.95$, *Cohen's d*=-0.02; latency: $t_{33}=-0.01$, $p=0.99$, *Cohen's d*=0.00), thus data of the first offer was discarded from all subsequent analyses, assuming it reflected a novelty effect.

4.2.7. fMRI data preprocessing and analysis

Preprocessing and statistical analyses were conducted using BrainVoyager QX version 2.4 (Brain Innovation). Each fMRI scan began with 10 volumes (30 seconds) of blank screen which were removed to allow for signal equilibrium. Subsequently, slice scan time correction was performed using cubic-spline interpolation. Head motions were corrected by rigid body transformations, using 3 translation and 3 rotation parameters and the first image served as a reference volume. Trilinear interpolation was applied to detect head motions and sinc interpolation was used to correct them. The temporal smoothing process included linear trend removal and usage of high pass filter of 1/128 Hz. Functional maps were manually coregistered to corresponding structural maps and together they were incorporated into 3D data sets through trilinear interpolation. The complete data set was transformed into Talairach space and spatially smoothed with an isotropic 6mm FWHM Gaussian kernel. Applying a criterion for exclusion based on excessive head-movements at 1 voxel (3mm/3˚) left only 40 participants which had both fMRI scans of the game. Increasing the criterion by an additional 1mm/1˚ increased the number of participants to 54 (low-gainers=26, high-gainers=28). Since there were no differences in results between these two criterions (Figure 4.3.),

the results are presented for the larger sample. To note, no differences were found between the two gain-groups' average peak head-movements (across both fMRI runs) in both translation (t_{52}=1.62, p=0.11, *Cohen's d*=0.44) and rotation (t_{52}=1.65, p=0.10, *Cohen's d*=0.45) parameters. Four additional subjects had excessive head-movements on one or both fMRI scans and were discarded from analysis, and two more participants were discarded due to scanner technical malfunctions during acquisition.

A single whole-brain random effects General Linear Model (GLM) was computed which included eight regressors, two for each period of the game (offer, decision, result, negotiation) to represent the two fMRI scans. Regressors were convolved with a canonical hemodynamic response function. Additional nuisance regressors included the head-movement realignment parameters and the time course of averaged activity in cortical white-matter. The fixation period of both scans was used as baseline. A grey matter mask and a correction for temporal autocorrelations using a second-order autoregressive model were also used. The BOLD brain activity during the offer period was then submitted to a 2 (gain-groups: Low/High) × 2 (fairness of offer: fair/unfair) × 2 (game-half: $1^{st}/2^{nd}$) mixed-model ANOVA. The gain-group effects were the focus of analysis since they could specify brain regions related to the tendency to accept or reject offers during the game. Correction of brain activation maps for multiple comparisons was performed by setting a voxel-level threshold at p<0.005 (uncorrected) with a minimal cluster-size of 10 contiguous functional voxels (where each voxel corresponds to a functional volume of 3*3*3mm) thus producing a desired balance between Types I and II error rates (Lieberman & Cunningham, 2009). To further decrease the likelihood of Type I errors, mean parameter estimates (beta values) were extracted for further analyses only for those regions of interest (ROIs) whose peek voxel had a false discovery rate (FDR) of α = 5% (Benjamini & Hochberg, 1995; Benjamini & Yekutieli, 2001). Beta values were averaged across the entire ROI voxels and for each experimental condition separately.

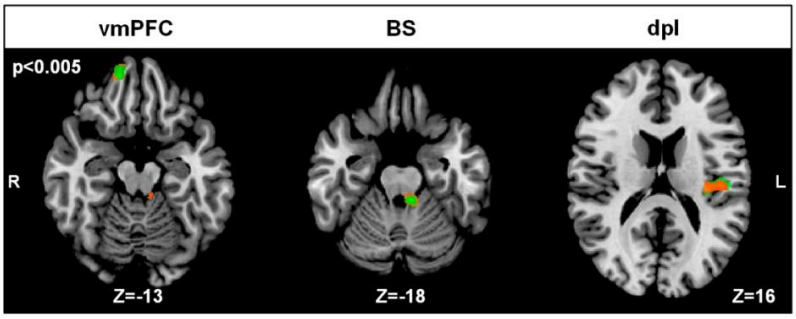

Figure 4.3. Overlap of ROIs in two separate GLMs. An overlay of the main brain regions subsequently discussed from two separate GLMs (both illustrated at p<0.005, k ($3mm^3$) >10). The regions found in the GLM which included 54 participants at a 4mm/4˚ head-movement threshold are depicted in orange. The regions found in the GLM which included 40 participants at a 3mm/3˚ (1 voxel) head-movement threshold are depicted in green. On the left and middle panels are the clusters in the brainstem and vmPFC respectively, found in the [gain-groups] main effect, and on the right panel is the dorsal posterior Insula found in the [gain-groups*fairness] interaction effect. The orange and green blots clearly show the overlap.

4.2.8. Functional connectivity analysis

A whole-brain generalized psycho-physiological interaction (PPI; Cisler, Bush, & Steele, 2014; Friston et al., 1997; O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012) random effects GLM analysis was conducted to test for task-dependant FC of the functionally identified ROIs. Regressors included: (1) the psychological variable – the original regressor of the specific experimental condition (2) the physiological variable - the time course activity in the seed ROI and (3) the interaction variable – an element-by-element product of the psychological and physiological variables. The psychological and physiological variables were included as confounds of no-interest (in addition to the nuisance regressors mentioned above). Correction for multiple comparisons and ROI analysis followed the same steps as detailed in the previous section.

4.2.9. Mediation analysis

Mediation analysis enables to statistically test whether the indirect path between an independent and a dependant variable passes fully or partially through a third mediating variable (Preacher & Hayes, 2004, 2008; Shrout & Bolger, 2002). An indirect path may reveal an otherwise inexistent direct relation between two variables. Using bootstrap procedures to test significance of indirect paths is especially important for small to medium sized samples because the estimate of the indirect effect cannot be assumed to distribute normally and because otherwise such samples lack power.

Statistical significance is based on a confidence interval. The range of the bootstrapped distribution (here based on 10000 iterations) of the confidence interval provides for the statistical significance as long as it does not contain zero, since the null hypothesis is that the indirect effect is non-existent, i.e. equal to zero.

4.3. Results

4.3.1. Acceptance rates and total-gain

Acceptance were averaged (in percentage) for the two fairness categories (fair/unfair) and submitted to a 2 (recruitment-group: soldiers/civilians) × 4 (sequence of offers: 1/2/3/4) × 3 (actor: 1/2/3) mixed-model ANOVA. In line with standard UG results, a main effect of fairness was revealed ($F_{1,36}$=144.83, p<0.001, η_p^2=0.79) such that fair offers (75.00±26.49) were accepted more than unfair offers (25.24±21.91). None of the between-subject factors influenced this result (or any of the below detailed results; see Table 4.3.) and therefore were collapsed across all subsequent analyses. In accordance with the assumption and independently from the fairness of offers, participants were classified as high-gainers (HGs; n=33) or low-gainers (LGs; n=27) based on the median of total-gain (27.00ILS out of maximum 48.00ILS; 26.55±10.29), reflecting an objective measure of the final outcome of the anger-infused UG. Though total-gain and overall acceptance rates highly correlated (r=0.91, p<0.001), total-gain is a more accurate measure for individual differences (e.g. one who only accepts a 10:10 and 4:16 offers would have a different gain but equal acceptance rate to one who accepted a 9:11 and 8:12 offers). Confirming the LG/HG division, the average total-gain of LGs (17.15±6.40) was lower than HGs (34.24±5.15; t_{58}=131.67, p<0.001, *Cohen's d*=2.95). To test the difference in the pattern of acceptance rates per magnitude of offer between the two groups, a repeated-measures ANOVA per offer-size (10:10, 11:9, 12:8, 15:5, 16:4, 17:3, 18:2, 19:1) with gain-groups (LGs/HGs) as between-subject factor was performed. This revealed a main effect of offer-size ($F_{7,406}$=32.63, p<0.001, η_p^2=0.36), a main effect of gain-group ($F_{1,58}$=87.77, p<0.001, η_p^2=0.60) and an interaction effect ($F_{7,406}$=2.12, p=0.04, η_p^2=0.04; Figure

4.4.A) which indicated that although acceptance rates decreased with offer size, HGs exhibited higher acceptance rates than LGs for each offer-size (uncorrected $p<0.05$, except for 19:1 for which there was no difference).

Table 4.3. Statistical results for recruitment-group (civilians/soldiers), sequence of offers (1/2/3/4) and actors (1/2/3) factors

	Main Effect	Interaction with Fairness (fair/unfair)	Interaction with gain-groups (LGs/HGs)
A. Acceptance Rates (LGs=27, HGs=33)			
Recruitment Group	$F_{1,36}=1.51$, $p=0.22$, $\eta_p^2=0.04$	$F_{1,36}=0.55$, $p=0.46$, $\eta_p^2=0.01$	$F_{1,56}=0.60$, $p=0.44$, $\eta_p^2=0.01$
Sequence	$F_{3,36}=0.88$, $p=0.46$, $\eta_p^2=0.07$	$F_{3,36}=1.44$, $p=0.25$, $\eta_p^2=0.11$	$F_{3,52}=1.43$, $p=0.24$, $\eta_p^2=0.08$
Actor	$F_{2,36}=1.08$, $p=0.34$, $\eta_p^2=0.06$	$F_{2,36}=0.57$, $p=0.57$, $\eta_p^2=0.03$	$F_{2,54}=1.14$, $p=0.33$, $\eta_p^2=0.04$
B. Reaction Times (LGs=27, HGs=31)			
Recruitment Group	$F_{1,34}=0.70$, $p=0.41$, $\eta_p^2=0.02$	$F_{1,34}=0.27$, $p=0.61$, $\eta_p^2=0.01$	$F_{1,54}=1.04$, $p=0.31$, $\eta_p^2=0.02$
Sequence	$F_{3,34}=0.33$, $p=0.80$, $\eta_p^2=0.03$	$F_{3,34}=1.36$, $p=0.27$, $\eta_p^2=0.11$	$F_{3,50}=1.99$, $p=0.13$, $\eta_p^2=0.11$
Actor	$F_{2,34}=0.80$, $p=0.46$, $\eta_p^2=0.04$	$F_{2,34}=0.01$, $p=0.99$, $\eta_p^2=0.00$	$F_{2,52}=2.05$, $p=0.14$, $\eta_p^2=0.07$
C. Emotional Ratings (LGs=27, HGs=33)			
Recruitment Group	$F_{1,56}=0.26$, $p=0.61$, $\eta_p^2=0.00$	$F_{1,56}=1.55$, $p=0.22$, $\eta_p^2=0.03$	$F_{1,56}=0.26$, $p=0.61$, $\eta_p^2=0.00$
Sequence	$F_{3,52}=1.55$, $p=0.21$, $\eta_p^2=0.08$	$F_{3,52}=1.96$, $p=0.13$, $\eta_p^2=0.10$	$F_{3,52}=0.70$, $p=0.55$, $\eta_p^2=0.04$
Actor	$F_{2,54}=0.37$, $p=0.69$, $\eta_p^2=0.01$	$F_{2,54}=2.33$, $p=0.11$, $\eta_p^2=0.08$	$F_{2,54}=0.38$, $p=0.69$, $\eta_p^2=0.01$
D. SCR-intensity (LGs=18, HGs=19)			
Recruitment Group	$F_{1,33}=0.00$, $p=0.95$, $\eta_p^2=0.00$	$F_{1,33}=2.5$, $p=0.12$, $\eta_p^2=0.07$	$F_{1,33}=0.00$, $p=0.96$, $\eta_p^2=0.00$
Sequence	$F_{3,29}=0.72$, $p=0.56$, $\eta_p^2=0.07$	$F_{3,29}=0.55$, $p=0.65$, $\eta_p^2=0.05$	$F_{3,29}=1.41$, $p=0.26$, $\eta_p^2=0.13$
Actor	$F_{2,31}=1.96$, $p=0.16$, $\eta_p^2=0.11$	$F_{2,31}=0.43$, $p=0.66$, $\eta_p^2=0.03$	$F_{2,31}=0.36$, $p=0.56$, $\eta_p^2=0.01$
E. SCR-latency (LGs=18, HGs=19)			
Recruitment Group	$F_{1,33}=0.31$, $p=0.58$, $\eta_p^2=0.01$	$F_{1,33}=1.07$, $p=0.31$, $\eta_p^2=0.03$	$F_{1,33}=2.33$, $p=0.14$, $\eta_p^2=0.07$
Sequence	$F_{3,29}=0.47$, $p=0.71$, $\eta_p^2=0.05$	$F_{3,29}=0.39$, $p=0.76$, $\eta_p^2=0.04$	$F_{3,29}=2.00$, $p=0.17$, $\eta_p^2=0.06$
Actor	$F_{2,31}=0.78$, $p=0.47$, $\eta_p^2=0.05$	$F_{2,31}=0.48$, $p=0.62$, $\eta_p^2=0.03$	$F_{2,31}=1.01$, $p=0.30$, $\eta_p^2=0.03$

Table 4.3. ANOVA results showing that the recruitment-group (civilians/soldiers), sequence of offers (1/2/3/4) and actors (1/2/3) did not have an influence on (A) acceptance rates, (B) reaction times, (C) emotional ratings – here specific tests were carried out to examine whether these factors influenced the interaction found between potency (low/high) and valence (positive/negative); and (D-E) skin conductance response (SCR) measures.

4.3.2 Reaction times

Decision reaction times (RT) were measured in milliseconds from the onset of decision period and were log-transformed to normalize the data. Due to technical malfunctions, RTs of two participants (both from high-gain group) were not recorded. RT of the first offer was discarded from subsequent analyses due to what was assumed as a novelty effect – the first offer had a slower RT compared to all other offers (p-values<0.05). There was no difference between gain-groups in the average RT of this first offer (t_{55}=0.96, p=0.34, *Cohen's d*=0.26). Average RT was thus submitted to a 2 (fairness: fair/unfair) × 2 (gain-groups: LGs/HGs) ANOVA and there was no significant fairness ($F_{1,56}$=0.07, p=0.79, η_p^2=0.00) or interaction ($F_{1,56}$=0.26, p=0.61, η_p^2=0.00) effects but there was a gain-groups effect ($F_{1,56}$=4.20, p<0.05, η_p^2=0.07) such that HGs had slower RT (1402.87±538.87ms) compared to LGs (1150.81±399.29ms). In fact, there was a positive relation between total-gain and average RT (r=0.35, p=0.008), indicating that slower decisions related to increased gain in the game. This may suggest that HGs, which tended to accept more offers compared to LGs, exerted some form of deliberation in their decisions (Rubinstein, 2007), while LGs were more impetuous. There was no difference in the average standard deviation of decision RTs between HGs (836.89±504.69) and LGs (704.55±446.46; t_{56}=0.37, p=0.71, *Cohen's d*=0.10), suggesting that the results found based on the average RT were not a mere difference in individuals' tendency to respond faster or slower.

4.3.3. Emotional rating

The average reported emotions were examined for all periods and all rounds of the retrospective emotional rating based on the two GEW-axes of potency (high/low) and valence (positive/negative) and a significant interaction was found ($F_{1,36}$=29.65, p<0.001, η_p^2=0.45) which indicated, as expected, that the negative high potency cluster which included anger, hostility, contempt and disgust (hereby named anger-cluster) was the dominant category of emotions, compared to all other categories (1.57±1.34; p<0.001). At the same time, both positive clusters did not differ from each other (low=0.95±0.76; high=0.85±0.82; p=0.85) and the negative low potency cluster was the least

reported of all emotion clusters (0.49±0.60, $p<0.05$). Subsequent analyses were focused on the relation between the anger-cluster compared to an all-positive-emotions cluster. To further validate these clusters of emotions a k-means clustering for two, three and four clusters was conducted. In all these cases the anger-cluster was separated from all other emotions and all positive emotions were clustered together. To note, the average emotional rating for each of the 16 different emotions of the GEW for all periods and all rounds of the game were submitted to a repeated-measures ANOVA and a significant effect was found ($F_{15,885}=15.25$, $p<0.001$, $\eta_p^2=0.21$), indicating that Anger (1.86±1.38) was the most highly reported emotion ($p<0.05$), though just qualitatively higher in comparison to hostility (1.59±1.48) and contempt (1.55±1.55).

To assess the impact of the anger-infusion manipulation it was tested whether there was a difference in emotional rating in the two emotion-clusters (positive/anger) between the different periods of the game (offer, result, negotiation). A significant interaction was found ($F_{1,118}=19.94$, $p<0.001$, $\eta_p^2=0.25$) which revealed that the result period was generally less angering (1.26±1.39) than both the offer (1.70±1.30; $p<0.001$) and the negotiation periods (1.74±1.49; $p<0.001$). However, there was no difference in emotional rating between the offer and negotiation periods for both the anger ($p=0.99$) and the positive (offer=0.94±0.71; negotiation=0.79±0.79; $p=0.36$) emotion-clusters. In addition, there was a strong correlation between emotional ratings of the offer and negotiation periods for both anger ($r=0.91$; $p<0.001$) and positive ($r=0.91$; $p<0.001$) clusters of emotion. Results thus far generally indicated that the anger-infused UG indeed induced anger, which at least as subjectively reported, was comparable between the offer and negotiation periods. Since analysis of the physiological and neural measures was focused on the offer period, subsequent analyses used the emotional rating specifically during the offer period.

Next, the ratings in the two emotion clusters (positive/anger) for the two halves of the game ($1^{st}/2^{nd}$) were averaged and submitted to a 2 (fairness: fair/unfair) × 2 (gain-groups: LGs/HGs) mixed model ANOVA. As expected, a significant interaction was found between emotion clusters,

fairness of offers and the two halves of the game ($F_{1,58}$=9.53, p=0.003, η_p^2=0.14; Figure 4.4.B), indicated that unfair offers were associated with more anger and less positive emotions compared to fair offers, and more so in the second half of the game. Interestingly, even fair offers seemed to have become more irritating in the second half of the game, pointing at the effect of the anger-infused social dynamics between participants and the putative proposers. In addition, a significant interaction was found between emotion clusters and gain-groups ($F_{1,58}$=5.72, p=0.02, η_p^2=0.09) suggesting that LGs reported enhanced anger (1.54±1.11) compared to positive emotions (0.96±0.67; p=0.08), while HGs did not differ between these emotion clusters (anger=1.26±1.14; positive=1.45±0.94; p=0.82). There were no differences between LGs and HGs in each of these emotion clusters (p_{anger}=0.71; $p_{positive}$=0.25). This indicated that while LGs are primarily angry, HGs seem to balance anger and positive emotions. To further examine this finding both anger and positive clusters were incorporated in a regression model and it was found that incorporating both emotional clusters explained significantly more than each of them alone (R^2_{anger}=0.07, p=0.04; $R^2_{positive}$=0.09, p=0.02; R^2_{both}=0.21, p=0.001, R^2_{change}=0.14, p=0.003). Therefore, a standardized emotional valence index (EVI) was calculated that incorporated both emotion clusters: (positive cluster - anger cluster) / (positive cluster + anger cluster). A positive EVI indicated that more positive and less anger emotions were reported while a negative EVI indicated the reverse. As expected, a more positive EVI was related to greater total gain (r=0.44, p<0.001; Figure 4.4.C). In line with the hypothesis, these results suggested that as subjects gained more money they reported less anger, but also more positive emotions.

4.3.4. Skin conductance

Averaged SCR intensity and latency, for the two fairness categories (fair/unfair) were submitted separately to an ANOVA with gain-groups (LGs/HGs) as between-subject factor. In line with the hypothesis, a gain-groups main effect in SCR-latency was found ($F_{1,35}$=6.40, p=0.02, η_p^2=0.15), such that HGs had slower SCR (2401.52±373.54ms) compared to LGs (2834.08±425.55ms). In

fact, there was a positive correlation between total-gain and SCR-latency (r=0.54, p=0.001; Figure 4.4.D), indicating that slower SCR onsets related to increased gain in the game. No other significant results were found for SC measures (Table 4.4.).

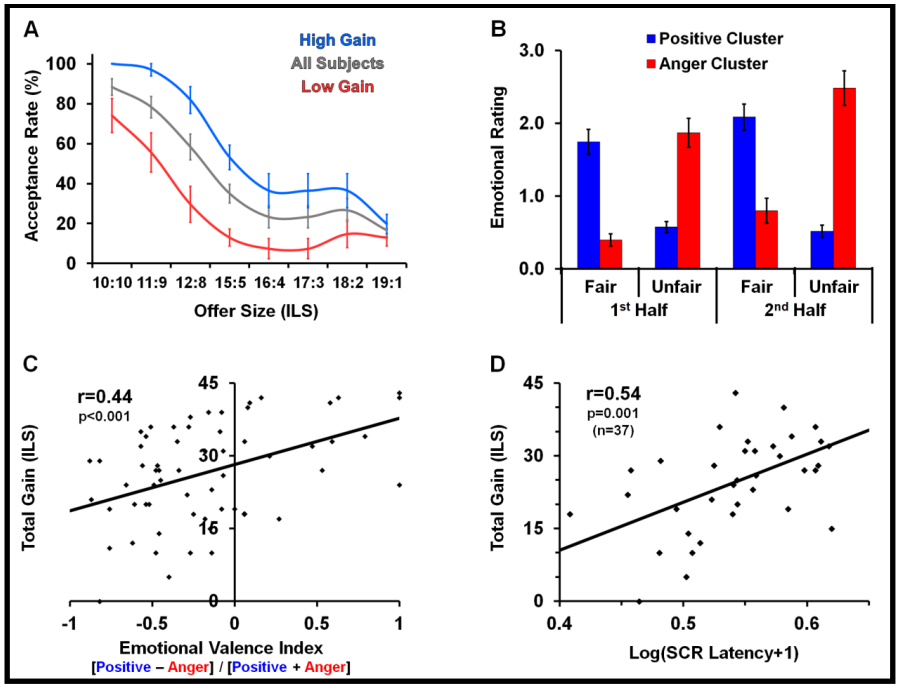

Figure 4.4. Behavioral and physiological results. (A) Acceptance rates (error bars denote mean±s.e.m.) decreased with offer size for all subjects (grey; n=60, total-gain=26.55±10.29ILS) but for each offer size (except 19:1) were higher for the High-Gain group (blue; n=33, 34.24±5.15) compared to the Low-Gain group (red; n=27, 17.15±6.39). (B) Fair offers induced more positive emotions and less anger, unfair offers showed the reverse pattern, but also induced less positive emotions and more anger compared to fair offers (p<0.001). Additionally, anger increased in the second half of the game for both fair (p=0.006) and unfair (p<0.001) offers. (C) Total-gain accumulated in the game was positively related to participants' EVI, calculated as the ratio between (Positive Cluster - Anger Cluster) and (Positive Cluster + Anger Cluster), and (E) to the latency of the first above threshold SCR.

Table 4.4. Statistical results for SCR measures

	Fairness (fair/unfair)	**Gain-groups (LGs/HGs)**	**Interaction**
SCR Intensity	$F_{1,35}$=1.83, p=0.18, η_p^2=0.05	$F_{1,35}$=0.20, p=0.66, η_p^2=0.01	$F_{1,35}$=0.45, p=0.51, η_p^2=0.01
SCR Latency	$F_{1,35}$=0.68, p=0.42, η_p^2=0.02	**$F_{1,35}$=6.40, p=0.02*, η_p^2=0.15**	$F_{1,35}$=1.85, p=0.18, η_p^2=0.05

Table 4.4. For both SCR intensity and latency, the averaged response for the two fairness categories (fair/unfair) were submitted each to an ANOVA with gain-groups (LGs/HGs) as a between factor. The only effect found was a gain-groups main effect in SCR-latency (denoted by *).

4.3.5 Gain-group differences emerge from within the dynamics of the modified-UG

If the above detailed differences between gain-groups reflected a-priori predispositions unrelated to the interactive anger-paradigm, then one might expect to see these differences already at the first round of the game. Thus, acceptance rates of the first offer was submitted to a 2 (fairness: fair/unfair) × 2 (gain-groups: LGs/HGs) ANOVA and no main effect of gain-groups ($F_{1,56}$=0.36,

p=0.55, η_p^2=0.01) nor interaction effect ($F_{1,56}$=1.93, p=0.17, η_p^2=0.03) were found. There was no difference even when considering only the subset of first unfair-offers (t_{28}=0.47, p=0.64, *Cohen's d*=0.17). Next, the EVI of the first offer was submitted to a similar analysis and no main effect of gain-groups ($F_{1,56}$=0.02, p=0.88, η_p^2=0.00), no interaction effect ($F_{1,56}$=0.05, p=0.83, η_p^2=0.00) and no difference even when considering only anger or only positive ratings for the subset of first unfair-offers (anger: t_{29}=-0.86, p=0.40, *Cohen's d*=0.31; positive: t_{29}=0.55, p=0.58, *Cohen's d*=0.20) were found. In addition, there was no difference in sympathetic arousal in the first offer as measured by SCR intensity and latency (see section 4.2.6). Therefore, the differences found between gain-groups seemed to emerge from within the dynamics of the anger-infused UG.

4.3.6. Brain activation

To investigate the neural substrates of high vs. low total-gain the gain-groups main effect was examined, revealing as expected, increased activity in an anterior region of the vmPFC, but unexpectedly, also decreased activity in a region of the brainstem (BS), amongst HGs relative to LGs (Table 4.5.A; Figure 4.5.A). Furthermore, increased BS activity correlated with faster SCR latencies (r=-0.40, p=0.02; 4.5.B). In addition, a dissociated pattern of activation in the vmPFC and BS was found between gain-groups (LGs/HGs) and offers (fair/unfair; $F_{1,52}$=5.70, p=0.02, η_p^2=0.10; Figure 4.5.C) such that during unfair offers HGs displayed increased vmPFC activity and decreased BS activity (p<0.001), while LGs displayed the reverse pattern of activity (p<0.001). A correlation between BS activity and EVI was not found (r=-0.08, p=0.55). Importantly, however, the positive relation between vmPFC activity and total-gain was partially mediated by the EVI (Figure 4.5.D). In other words, with increased vmPFC activity, more positive and less angry feelings were reported (higher EVI), and more gain was accumulated throughout the game.

Next, it was examined whether there were differences in the neural correlates of unfair compared to fair offers with relation to the two gain-groups. It was found that HGs exhibited increased activity in the dorsal posterior Insula (dpI) during unfair offers (Table 4.5.B; Figure

4.6.A). There was no correlation between dpI activity and EVI (r=0.18, p=0.20), but there was a correlation with SCR-latency (r=0.40, p=0.02), which supports dpI's involvement in the physiological experience attributed to unfair-offers. Interestingly, a significant indirect path was found from BS to dpI via SCR-latency during unfair offers, indicating that the relation between BS and dpI during unfair offers was mediated by SCR-latency (Figure 4.6.B). In addition, dpI and vmPFC activity during unfair offers was positively correlated (r=0.31, p=0.02; Figure 4.6.C), which might be indicative of dpI's involvement in accepting unfair offers.

Finally, a triple interaction between gain-groups, fairness of offer and game-half revealed a cluster within the same spatial location of the vmPFC cluster identified by the gain-groups main effect, yet due to its' small size it did not pass the threshold (Table 4.5.D). This however led to the submission of the beta values extracted from the vmPFC gain-groups main-effect to a 2 (gain-groups: LGs/HGs) × 2 (fairness: fair/unfair) × 2 (game-half: $1^{st}/2^{nd}$) ANOVA. This triple interaction was found to be significant ($F_{1,52}$=7.43, p=0.009, η_p^2=0.12; Figure 4.6.B) indicating that amongst the High-Gain group vmPFC activity increased in the 2^{nd} half of the game to include also fair offers.

Table 4.5. Brain activity during the offer period for gain-groups related effects.

Brain Region	BA	Side	X	Y	Z	F(1,52)	p	Voxels
A. Main effect of gain-groups (LGs/HGs)								
Postcentral Gyrus	2	R	50	-14	24	14.165	0.0004	209
Postcentral Gyrus	2	R	47	-23	40	11.010	0.0017	234
Orbito Frontal Gyrus	11	R	14	49	-12	18.146	<0.0001*	554^
Brainstem		L	-7	-35	-18	18.079	<0.0001*	409^
Inferior Frontal Gyrus	47	L	-28	22	-15	12.934	0.0007	137
B. Interaction effect of gain-groups (LGs/HGs) × fairness of offer (fair/unfair)								
Parahippocampal Gyrus	30	R	30	-56	6	11.055	0.0016	63
Superior Frontal Gyrus	10	R	29	56	6	11.851	0.0012	85
Parahippocampal Gyrus	35	R	29	-29	-21	12.327	0.0009	117
Cerebellum		R	17	-68	-24	12.193	0.0010	649
Superior Frontal Gyrus	10	R	23	49	-3	11.340	0.0014	147
Orbito frontal gyrus	11	R	16	40	-12	12.253	0.0010	53
Subcallosal Gyrus	25	R	8	22	-12	13.380	0.0006	193

Cuneus	19	L	-1	-80	34	11.908	0.0011	56
Medial Frontal Gyrus	10	L	-13	58	1	18.466	<0.0001*	239
Superior Frontal Gyrus	10	L	-13	64	16	15.970	0.0002	195
Cerebellum		L	-16	-53	-15	12.422	0.0009	146
Posterior Insula	13	L	-31	-23	18	18.169	<0.0001*	562^
Middle Frontal Gyrus	6	L	-40	4	42	14.496	0.0004	369
Inferior Frontal Gyrus	10/45	L	-37	43	3	10.552	0.0020	81
C. Interaction effect of gain-groups (LGs/HGs) × game-half (1st/2nd)								
Posterior Insula	13	R	50	-23	19	11.272	0.0015	233
Posterior Insula	13	R	41	-17	19	16.217	0.0002	680^
Inferior Parietal Lobule	40	R	41	-35	45	12.794	0.0008	83
Fusiform Gyrus	37	R	32	-44	-11	23.848	<0.0001*	1685^
Superior Frontal Gyrus	8	R	23	19	42	13.127	0.0007	297
Fusiform Gyrus	19	R	26	-68	-12	12.359	0.0009	114
Precuneus	7	R	12	-71	39	11.628	0.0013	67
Cingulate Gyrus	23	L	-3	-20	30	14.083	0.0004	73
Medial Frontal Gyrus	10	L	-10	52	3	15.615	0.0002	102
Superior Parietal Lobule	7	L	-16	-65	57	11.438	0.0014	94
Superior Frontal Gyrus	8	L	-19	17	48	12.646	0.0008	104
Fusiform Gyrus	37	L	-28	-38	-15	12.128	0.0010	157
D. Interaction effect of gain-groups (LGs/HGs) × fairness of offer (fair/unfair) × game-half (1st/2nd)								
Middle Frontal Gyrus	10	R	41	53	-6	11.793	0.0012	55
Orbito Frontal Gyrus	11	R	14	46	-15	19.301	<0.0001*	108
Superior Occipital Gyrus	19	L	-32	-86	27	12.768	0.0008	174

Table 4.5. All regions arising from whole-brain random-effects gain-groups related effects (n=54), presented at a threshold of $p<0.005$ (uncorrected) with a minimal cluster size of 50 contiguous anatomical ($1mm^3$) voxels. Coordinates are of peak activity, given according to Talairach space with their F-scores and p-values. Beta values for subsequent ROI analyses were extracted for those brain regions with both peak voxel q(FDR)<0.05 (denoted by *) and minimal cluster size of 10 contiguous functional ($3mm^3$) voxels (denoted by ^; see section 4.2.7.). Anatomical locations were determined using Talairach Daemon (http://www.talairach.org/).

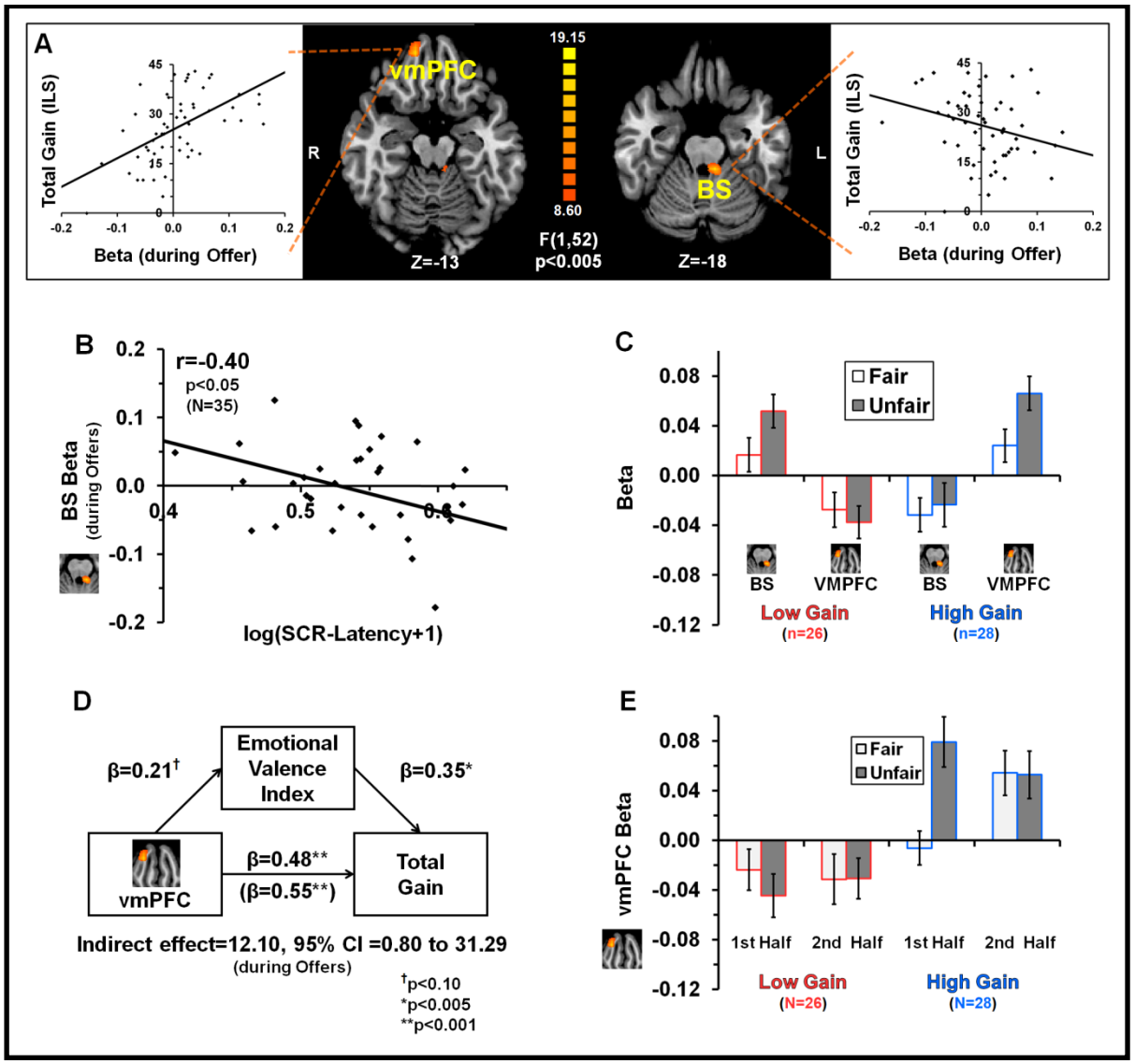

Figure 4.5. Brain activation results during the offer periods. During the offer periods, activity in the vmPFC and BS differentiated between gain-groups. (A) Gain-groups main effect (GLM with random effects, n=54) found activity in a ventral region of the PFC (vmPFC; Talairach coordinates x, y, z = 14, 49, -12) and in the brainstem (BS; x, y, z = -7, -35, -18) illustrated at a threshold of p<0.005 (uncorrected) and a minimal cluster size of 10 contiguous functional voxels. vmPFC activity (left) increased and BS activity (right) decreased with participants' increased total-gain. (B) BS activity negatively related to SCR-latency. (C) vmPFC and BS exhibited a dissociated pattern of activation. High-Gain group displayed increased vmPFC activation and decreased BS activation during unfair offers, while Low-Gain group displayed the reverse pattern of activation (p<0.001 for all these comparisons). (D) Mediation model depicting a significant indirect path from vmPFC to total-gain through EVI, during the offer periods. Such an indirect effect was not found for the BS. β indicates standardized regression coefficients and β in parentheses indicates the coefficient between vmPFC activity and total-gain before controlling for EVI. Indirect effect indicates the bias-corrected bootstrap coefficient and its' constructed 95% confidence interval (CI). (E) The triple interaction between gain-groups, fairness of offers and game half indicated that amongst the High-Gain group there was more activity in unfair compared to fair offers during the 1st half of the game (p=0.002). However, in the 2nd half, vmPFC activity increased to include also fair offers (p=0.58 compared to fair-1st half and p=1.00 compared to unfair-2nd half).

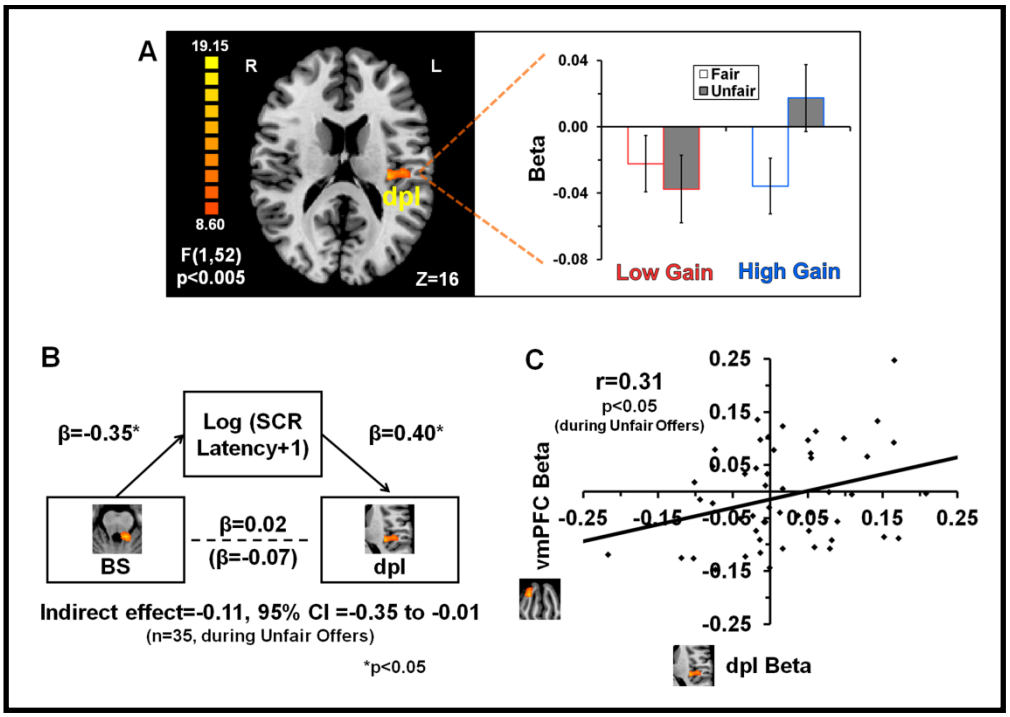

Figure 4.6. Brain activation results for the group by offer interaction. (A) The gain-groups by fairness interaction effect (GLM with random effects, n=54) revealed activation in the dpI (x, y, z = -31, -23, 18) illustrated at a threshold of p<0.005 (uncorrected) and a minimal cluster size of 10 contiguous functional voxels. dpI activity increased during unfair offers compared to fair offers, but only for the High-Gain group. (B) Mediation model depicting a significant indirect path from BS activity to dpI activity through SCR-latency, during unfair offers. (C) dpI activity positively correlated with vmPFC activity during unfair offers.

4.3.7. Functional connectivity:

A key aspect in the portrayal of an emotional experience is delineating the dynamic nature of its underlying neural manifestation (Raz et al., 2012). To further elucidate the neural dynamics of the anger-infused UG and to fully explore the relations between the vmPFC, BS and dpI and the entire brain, a task-dependant functional connectivity analysis using PPI was conducted. Using vmPFC, BS and dpI as seed regions in separate PPI analyses, no changes were found in connectivity related to total-gain when contrasting fair and unfair offers. Additional analyses were thus conducted on unfair offers relative to baseline, but included as covariate the specific gain accumulated during these unfair offers (Table 4.6.). A change in FC was found between the dpI and the medial Thalamus (mT), and more so as gain increased (Figure 4.7.A). In addition, the positive relation between dpI-mT connectivity during unfair offers and gain accumulated during these unfair offers was partially mediated by the subjective emotional experience specifically during the unfair offers (Figure 4.7.B).

Taken together, it seemed that two neural measures had a role in modulating the emotional experience during the game en route to increased gain. The first related to vmPFC activity throughout the entire game (all offers) and the second to dpI-mT connectivity during the more angering situations (unfair offers). To explore the relationship between these two measures and total-gain a regression analysis was conducted which indicated that although vmPFC activity during the offer period better explained the variance in total-gain than dpI-mT connectivity during unfair offers, together they explained significantly more (R^2_{vmPFC}=0.30, p<0.001; $R^2_{dpI\text{-}mT}$=0.17, p=0.002; R^2_{both}=0.44, p<0.001; R^2_{change}=0.14, p<0.001). This finding indicated that both these neural measures had a contribution in explaining variance in total-gain and suggested that they might reflect separate though related processes.

Table 4.6. Brain connectivity during the unfair offers in covariance with total-gain.

Brain Region	BA	Side	X	Y	Z	r(52)	p	Voxels
A. Seed=vmPFC								
Parahippocampal Gyrus	19	R	26	-41	-3	-0.494	<0.0001*	61
Lingual Gyrus	18	R	26	-77	-4	-0.413	0.0019	63
Lingual Gyrus	18	R	17	-83	-6	-0.417	0.0017	73
Anterior Insula	13	L	-34	10	15	0.441	0.0008	113
Fusiform Gyrus	19	L	-37	-65	-6	-0.452	0.0006	78
Fusiform Gyrus	20	L	-52	-20	-24	0.458	0.0005	61
B. Seed=BS								
No regions passed the threshold.								
C. Seed=dpI								
Middle Frontal Gyrus	6	R	20	-8	60	-0.456	0.0005	167
Paracentral Lobule	5	R	20	-44	51	-0.448	0.0007	414^
Cuneus	18	R	14	-95	9	0.443	0.0011	73
Precuneus	7	R	10	-44	51	-0.457	0.0005	252
Cerebellum		L	-1	-68	-15	0.458	0.0005	209
Medial Thalamus		L	-1	-23	5	0.557	<0.0001*	423^
Cingulate Gyrus	24	L	-19	-71	45	-0.457	0.0005	293
Cerebellum		L	-19	-74	-43	0.419	0.0016	53

Table 4.6. All regions arising from whole-brain random effects PPI analysis (n=54), presented at a threshold of p<0.005 (uncorrected) with a minimal cluster size of 50 contiguous anatomical (1mm^3) voxels. Coordinates are of peak activity,

given according to Talairach space with their r-scores and p-values. Beta values for subsequent ROI analyses were extracted for those brain regions with both peak voxel q(FDR)<0.05 (denoted by *) and minimal cluster size of 10 contiguous functional ($3mm^3$) voxels (deoted by ^; denoted by ^; see section 4.2.8.).

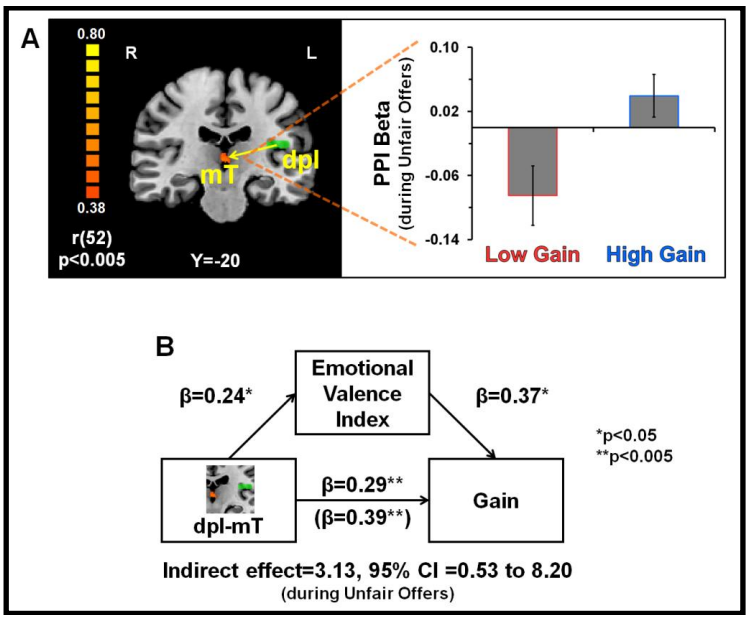

Figure 4.7. Brain connectivity results in covariance with total-gain during unfair offers. (A) Using dpI as a seed region for PPI analysis during unfair offers (GLM with random effects, n=54) revealed an increase in connectivity between the dpI and the medial Thalamus (mT; x, y, z = -1, -23, 5), illustrated at a threshold of p<0.005 (uncorrected) and a minimal cluster size of 10 contiguous functional voxels, for the High-Gain group, but not for the Low-Gain group. (B) Mediation model depicting a significant indirect path from dpI-mT connectivity to gain accumulated during the unfair offers of the game, through the EVI measure, also during the unfair offers.

4.4. Discussion

A naturalistic interpersonal conflict over monetary resources with an enhanced emotional turmoil was created by incorporating sequential on-line verbal negotiations with an obnoxious proposer intended to infuse anger in a repeated UG. Anger induction was validated by findings that participants reported more anger than other emotions, especially during unfair offers, and more so at the second half of the game. Moreover, in line with our expectations, as participants gained more money, they reported less anger and more positive feelings, had slower decision reaction-times and had slower sympathetic responses. These findings converge to indicate individual differences in emotional experience that relate to the final monetary outcome of the interpersonal conflict. Furthermore and as expected, participants who gained more money and also reported less anger showed increased activity in an anterior region of the vmPFC during the offer periods, but unexpectedly also decreased activity in a region of the BS. This opposite relationship between

vmPFC and BS was more accentuated during unfair offers. Lastly, specifically during unfair offers, high-gain participants had increased dpI activity and dpI-mT connectivity. Strikingly, both vmPFC activity during all offers and dpI-mT connectivity during unfair offers modulated the subjective emotional experience as depicted by the EVI, en route to a beneficial monetary outcome of the interpersonal conflict.

4.4.1. The tendency to accept anger-infused UG-offers is typified by a balanced emotional profile

While the idiosyncratic emotional profiles captured variability in how participants managed the interpersonal conflict, the question remains whether HGs had a different emotional reactivity pattern or whether they actively engaged in emotion regulation. Indeed, there is an open debate as to whether generation and regulation of emotions are separable processes, or intertwined in one another (Gross & Barrett, 2011). However, it is generally acknowledged that emotions unfold over time, and congruently the *process model of emotion regulation* (Gross & Thompson, 2007) suggests that regulatory processes may intervene at any time during this temporal dynamics, even before emotional response tendencies. It is thus implied that a less reactive person may in fact engage, whether implicitly or explicitly, in some form of regulation. Interestingly, similar to other studies implying spontaneous uninstructed emotion regulation (e.g. Drabant, McRae, Manuck, Hariri, & Gross, 2009) no differences were found between gain-groups in trait measures related to emotional reactivity, such as trait-anger or anxiety, nor to neuroticism. In fact, no differences were found in any trait measure except for agreeableness (see Table 4.2.), which is a personality measure generally related to pro-social orientation, but was also specifically associated with regulating anger and aggression during interpersonal conflict (Jensen-Campbell & Graziano, 2001; Meier, Robinson, & Wilkowski, 2006). Taken together, it is argued that a mental process with specific neural patterns emerged from within the dynamics of the interpersonal conflict and enabled HGs to end up with greater monetary outcome. In view of HGs' elevated Agreeableness scores, this might have involved recruiting pro-social thoughts as a means of self-regulation. Thus said, it does not mean

that HGs were not angry at all, but as evident, they seemed to have balanced between anger and positive feelings. Such an emotional balance corresponds to the notion that psychologically resilient people, those people who are able to efficiently adapt themselves to changing situational demands and thus able to cope with stressful events, do so by enhancing positive as well as reducing negative emotions (Tugade & Fredrickson, 2007).

One may argue that strict strategic reasoning caused LGs to reject offers to improve their stance in subsequent negotiations (Slembeck, 1999). If that was the case, one wouldn't expect LGs to report increased anger and decreased positive emotions, rather a more stable, perhaps even indifferent emotional experience. In addition, predicting that some participants might opt for the use of such strategies, our putative proposers were provided with specific scripts to handle such demands (see section 4.2.3.). Thus, even though strategic reasoning might have taken place at certain time-points along the game, it is unlikely that it determined the ample converging behavioral and physiological differences between gain-groups. On the other hand it is important to emphasize that since participants' decisions and negotiating skills did not have an actual influence on subsequent offers, though they were led to believe so, the results do not imply that HGs are better at strategic reasoning or better negotiators than LGs.

4.4.2. Neural substrates of the tendency to accept UG-offers modulate the emotional experience

As hypothesized, the vmPFC was found to have a major role in accepting UG-offers, supposedly by modulating the emotional experience, and in reflecting individual differences in managing interpersonal conflict beneficially. Nevertheless, in view of vmPFC's involvement in valuating reward (Rolls, 2004) and previous findings relating UG-behavior to reward sensitivity (Scheres & Sanfey, 2006), one might suggest that gain-groups differ in reward sensitivity. However, trait measures of sensitivity to reward and punishment, as well as a post-scan self-report of participants' desire to gain money in the game did not relate to vmPFC activity and did not differ between gain groups (see Table 4.2.). In fact, the only trait measure which did correlate with vmPFC activity was

the habitual use of expressive suppression as an emotion regulation strategy (see Table 4.2.). Indeed, the vmPFC has been generally implicated in implicit emotion regulation (Phillips et al., 2008; Gyurak et al., 2011; Etkin et al, 2015), and regulating anger and aggression in particular (Davidson et al., 2000; Siever, 2008). Notably, while functionalities such as reward processing have been commonly centered at rather posterior, subgenual regions of the vmPFC, here a more anterior aspect of the vmPFC was located. This alludes to previous studies that associated different roles for anterior and posterior regions of the vmPFC in decision-making. It has been suggested that posterior-vmPFC encodes concrete/material rewards while anterior-vmPFC encodes long-term/abstract rewards (Rolls, 2004; Moretti et al., 2009). An alternative proposition was that posterior-vmPFC encodes decision values, the value of choosing to reject or accept an offer, while anterior-vmPFC encodes experienced values, the actual reward or positive emotion in view of that decision (Baumgartner et al., 2011). However, these two alternatives seem to be in disagreement as decision values are relatively abstract while experienced values are rather concrete. From a different perspective, it is possible that an anterior-vmPFC region was identified because of its involvement in flexible adaptations to contingencies during dynamic decision-making (Boorman, Behrens, Woolrich, & Rushworth, 2009; Kovach et al., 2012). In other words, anterior-vmPFC seems to have a role in the ability to learn from on-going experiences and update behavior in a response-contingent manner. Interestingly, amongst HGs only vmPFC activity was found to increase between the 1st and 2nd half of the game extending to include both fair and unfair offers. Moreover, a meta-analysis of emotion regulation studies has revealed a rather anterior aspect of the vmPFC involved in the extinction of negative emotional responses to a previously conditioned stimulus (Diekhof et al., 2011). While speculative, this may suggest a flexible generalization in the application of an implicit process related to emotion regulation amongst HGs, especially since anger increased in the second half of the game for both fair and unfair offers.

In addition to the vmPFC, a cluster of activation was found in the BS, which was stronger for LGs compared to HGs. This cluster seemed to correspond to the anatomical location of the Locus

Coeruleus (LC; Keren, Lozar, Harris, Morgan, & Eckert, 2009), a subcortical nucleus located in the dorso-rostral Pons and the major source for noradrenalin in the brain, thus critically involved in arousal and stress response (Samuels & Szabadi, 2008a, 2008b). Localizing the LC from BOLD fMRI has been debated (Astafiev, Snyder, Shulman, & Corbetta, 2010; Minzenberg et al., 2010; Schmidt, Peigneux, Maquet, & Phillips, 2010), yet the specific location of the BS activation cluster, the relation found between its' activity and sympathetic arousal as measured by SCR-latency, and the fact that the LC has been consistently and reliably involved in human aggression (Haden & Scarpa, 2007), together supports that the BS activity indeed corresponds to the LC region. Interestingly, the inverse relationship found between vmPFC and BS/LC suggests that the vmPFC might have had a role in attenuating arousal-related brain activity.

The dpI was another cluster of activation which during unfair offers was stronger for HGs compared to LGs and also positively related to both SCR-Latency and vmPFC activity. The dpI, through its anatomical connection to the medial-Thalamus, which continues the pathway to the brainstem and finally to the spinal cord, is regarded as the primary region of interoception, that is attending to and representing the internal physiological state of the body (Craig, 2002, 2011). The neural-coupling found between dpI and mT corresponds to this anatomical pathway and contributes to accepting unfair offers by supposedly modulating the emotional experience, specifically during the more angering offers. Similarly, a recent study found that interoceptive awareness was related to UG behavior, moderating the relationship between SC and acceptance rates (Dunn et al., 2012), however an attempt to determine the link between interoceptive awareness and emotion regulation in regards to UG-behavior was inconclusive (van't Wout, Faught, & Menino, 2013). Interestingly, a study on experienced mindfulness meditators, considered to recruit emotion regulation through their practice of non-judgmental acceptance of internal and external experiences, found that they had higher acceptance rates and higher dpI activity compared to controls (Kirk et al., 2011). Consistently, the current results may suggest that dpI has a direct role in modulating the emotional experience during such volatile situations as unfair UG-offers, thus supporting theories of emotion

which emphasize bodily feedback via interoceptive processing (Barrett, 2006b; Craig, 2011, 2013; Damasio, 2010).

An additional note is in place regarding the possibility that low-gainers, those angry individuals who were more aroused and rejected more offers (thus gained less money), responded faster and rejected offers because the higher arousal directed their attention to do so. This interpretation is generally supported by the fact that low-gainers had higher LC activation, a major node of arousal suggested to be involved in directing allocation of automatic attention towards salient and threatening stimuli (e.g. Sara & Bouret, 2012). However, if low-gainers did respond faster because they were more attentive, one should consider to what their attention was directed at and why attention-dependant fast responding would specifically associate with the tendency to *reject* rather than to accept the offers. The goal of the modified UG as presented to participants was to gain money, not to respond as fast as possible (though they were generally instructed to respond within a 6second limit period). It thus seems reasonable that attention would be directed to the value of monetary offers. Therefore, it could be possible that low-gainers' attention was directed to the low amount of money offered to them compared to that of the proposer (while high-gainers could have directed their attention to the absolute value of their gain), making the offers more threatening and probably also more angering (compared to possibly being rewarding for high-gainers), and thus contributing to a fast rejection response. Such a rational does not pivot attention in contrast to anger, rather suggests that attention processes mediate the relationship between arousal and anger, leading to a fast reaction and a tendency for rejection.

Threat-related attentional bias paradigms have shown that some people, mostly anxious individuals, tend to direct attention more towards threatening stimuli and are thus more vigilant to such stimuli in their environment (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van Ijzendoorn, 2007). There is also documentation directly linking attentional bias toward anger-related cues, but only for high trait-anger individuals and following insults (Cohen, Eckhardt, & Schagat, 1998; Eckhardt & Cohen, 1997; van Honk et al., 2001). However, studies have shown that

the relationship between anger and attention tends to make people focus on rewards rather than threats (Ford et al., 2010). In other words, if attention indeed mediated the relation between arousal and anger, one would expect angrier individuals to be focused more on rewards rather than threats, which is counter-intuitive in the current case in which angrier individuals – low gainers – seemed to have been more focused on threats and thus rejected more offers. Nevertheless, it should be noted that no differences in sensitivity to reward or to punishment was found between low-gainers and high-gainers (Table 4.2.). In fact, there were also no differences in trait anger between low-gainers and high-gainers. Finally, here we did not find any differences between the low-gainers and high-gainers in cortical brain regions directly associated with attention and attentional control, such as the ACC, dlPFC or posterior parietal cortex (Knudsen, 2007; Miller & Cohen, 2001). In fact, elsewhere it was found that the vmPFC showed greater activation to angering stimuli which attention was direct to rather than ignored (Sander et al., 2005). In view of low-gainers having *less* vmPFC activation, these findings actually contend for the reverse interpretation whereby low-gainers were less attentive. Taken together, there is no clear evidence directly implicating attention processes as differing between low-gainers and high-gainers and the interpretation of attention mediating the relation between arousal and anger seems less plausible. A much more parsimonious and result-congruent explanation for the fast reaction times and arousal amongst angry low-gainers builds on impulsive reactions as part of an anger-related aggressive response (e.g. Ramírez & Andreu, 2006; Vigil-Colet & Codorniu-Raga, 2004; Wingrove & Bond, 2005), especially in view of the vmPFC results which has been similarly related with control of aggressive reactions (e.g. Best, Williams, & Coccaro, 2002; Kramer, Jansma, Tempelmann, & Münte, 2007).

4.4.3. The importance of naturalistic settings for neuroscience

In the current paradigm, within the confined environment of the MRI scanner, genuine interpersonal anger was infused to a social decision-making task by embedding on-line spontaneous verbal interactions as a negotiation phase after each ultimatum-offer. Importantly, there was separation

between a controlled and easily modeled period for analysis (the offer period) and an uncontrolled interactive period for the induction of an emotional experience (the negotiation period). A strong relationship was found in the subjective emotional experience during these two periods and there was no difference in the intensity of this experience between the two periods. Congruent with the dynamics of interpersonal conflict, this may suggest that the negotiation periods and the actual offers made intermingled in inducing the overall emotional experience. The study design did not enable to draw conclusions as to what neural processes engage during the actual interactions and it was not designed to directly compare the effects of having such interactions compared to a standard UG. This provides a promising path for future studies. Yet the high ecological validity of the decision-making process and of the emotional experience alludes to the significance of our findings to real-life situations. Moreover, the vmPFC and dpI results replicate previous findings, while it can be speculated that the BS/LC finding is related to the ecologically valid anger-infused manipulation since it was not previously reported in the UG-context. This study thus supports recent conceptual developments in shifting neuroscientific endeavor, especially in the neuroscience of affect, from an "isolated" to a "socially interacting" brain mode (Przyrembel et al., 2012; Schilbach et al., 2013; Gilam and Hendler, 2016).

4.4.4. Concluding remarks

The current study's findings point towards two possible processes that underlay the ability to reach a beneficial outcome to interpersonal conflict, possibly by modulating the emotional experience evoked during this kind of dispute. The primary process of this suggested mechanism is centered on the vmPFC and seems to be activated throughout the entire interaction, and might also have a role in attenuating BS/LC-related arousal. The secondary process is centered on the dpI and is particularly involved during the more volatile moments of the interaction. Results indicate that recruiting both processes is most effective for a beneficial outcome. These findings are particularly compelling as they relate to neural activity measured before the actual decision to accept or reject

an offer has been made. Moreover, since the paradigm enabled participants to spontaneously experience emotions during dynamic naturalistic social interactions, findings may relate to everyday life in which emotion regulation is engaged spontaneously (Gross & Thompson, 2007). Thus said, the paradigm is limited both in power due to its' ecological nature, and by the analysis which was focused on individual differences. These two methodological features could have determined the regions depicted by our whole-brain analysis. Indeed, others who utilized a more standardized version of the UG have found executive-function and emotion-reactivity related brain regions (e.g. Sanfey et al., 2003). A control task such as the standard single-shot UG was not employed and thus it is unknown to what degree results generalize to previous UG literature. Nevertheless, the converging results from behavioral, physiological and neural measures point to a multi-level mechanism that seems to be related to an implicit and spontaneous process of anger regulation, and might also increase the chances for cooperation rather than conflict escalation. Interestingly, findings indicate that such a process of emotion regulation consists of balancing both anger and positive feelings. Future research should scrutinize and generalize these findings to the population at large, by increasing the heterogeneity of the participants, such as comparing both genders and having a larger range of ages. In furtherance, open questions remain such as when and how people recruit the suggested processes, if and how do these processes interact and whether they represent an innate or an acquired tendency. Future studies could also investigate the relevance of these processes to individually tailored interventions focused on emotionally balanced pro-social interactions.

5. OBJECTIVE 2: Identifying the neural traces of anger experience

**** Excerpts from the current chapter have been submitted for publication in:**

Gilam G., Maron-Katz, A., Kliper E., Lin, T., Fruchter, E, Shamir, R. & Hendler T. Tracing the neural carryover effects of interpersonal anger on resting-state fMRI. *Brain Structure and Function*.

5.1. Introduction

As clearly established thus far, anger is daily experienced during social interactions, possibly leading to aggression and violence, but also to negative consequences on one's health, well being and social rapport. The importance of regulating anger and adapting it to socially accepted norms is unequivocal (Davidson et al., 2000; Gilam & Hendler, 2015). Notably, the challenge of coping with anger extends beyond the termination of the anger-inducing provocation since anger typically outlasts this event by about half an hour (Potegal, 2010). In fact, after anger has been triggered, people tend to engage in recurrent hostile thought patterns about the causes and consequences of the anger episode, involving fantasies of revenge and derogative labeling towards the persecutor, termed angry rumination (Deffenbacher et al., 2003; Denson et al., 2009; Snyder et al., 1997; Sukhodolsky et al., 2001). Angry rumination may be considered a specific case of *rumination*, broadly defined as a maladaptive regulatory response characterized by repetitive thinking about the meanings, causes and consequences of experiences inducing personal distress, which is common in depressive patients in regards to their symptoms (Lyubomirsky, Layous, Chancellor, & Nelson, 2015). Studies have shown that explicitly instructing participants to reflect about an angering event in its aftermath intensified anger and increased aggression (Bushman et al., 2005; Pedersen et al., 2011; Rusting & Nolen-Hoeksema, 1998). Interestingly, individuals who have a high habitual tendency to be angry (i.e. high trait-anger) are suggested to have an inclination for hostile interpretation of situations, for engaging in angry rumination and for impaired recruitment of inhibitory resources (Wilkowski & Robinson, 2010). Revealing the neural reorganization of the

brain following an angering episode provides an opportunity to expose neural processing of emotional experiences beyond their immediate occurrence and may inform efforts to mitigate the negative implications of anger and angry rumination on people's lives.

On a neural level, explicit instructions to engage in angry rumination revealed increased activation in several PFC regions including the mPFC and IFG, as well as in the ACC, PCC, insula and thalamus (Denson et al, 2009), and also a positive functional coupling between the IFG and both amygdala and thalamus (Fabiansson et al., 2012). Most notably the IFG, ACC, PCC and amygdala have been consistently associated with rumination in several experimental conditions including instructed rumination over negative experiences and testing for individuals' habitual tendency to ruminate (i.e. trait-rumination), both during active emotional as well as non-instructed "resting-state" tasks, and for both healthy (Freton et al., 2013; Hooker, Gyurak, Verosky, Miyakawa, & Ayduk, 2010; Johnson, Nolen-Hoeksema, Mitchell, & Levin, 2009; Kross, Davidson, Weber, & Ochsner, 2009; Kühn, Vanderhasselt, De Raedt, & Gallinat, 2012; Kühn, Vanderhasselt, Raedt, & Gallinat, 2013; Milazzo et al., 2014; Piguet et al., 2014; Ray et al., 2005) and depressed individuals (Berman, Nee, et al., 2011; Berman, Peltier, et al., 2011; Berman et al., 2014; Connolly et al., 2013; Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010; Mandell, Siegle, Shutt, Feldmiller, & Thase, 2014; Peters, Burkhouse, Feldhaus, Langenecker, & Jacobs, 2016; Siegle, Steinhauer, Thase, Andrew, & Carter, 2002; Thomas et al., 2011). In healthy participants grey matter volume of the IFG and ACC were similarly associated with trait-rumination (Kühn et al., 2012; Qiao et al., 2013). Notably, rs-fMRI periods in which participants let their thoughts wander while their brain is scanned (Gruberger, Simon, Levkovitz, Zangen, & Hendler, 2011) may be a particularly relevant paradigm to trace changes in neural processing related to a preceding emotional experience. A few previous studies that embraced such an approach to elucidate the sustained effects of acute stress on rs-FC revealed increased neural coupling between the amygdala and several brain regions including the medial PFC, ACC, PCC, precuneus, insula, hippocampus

and brainstem (Maron-Katz et al., 2016; Vaisvaser et al., 2013; van Marle, Hermans, Qin, & Fernández, 2010; Veer et al., 2011).

Here a whole-brain data-driven analysis was used to trace the changes in endogenous neural processing in the aftermath of an angering episode. Changes in FC between rs-fMRI scans before and after an interpersonal angering experience were examined expecting to reveal rs-FC modulations involving brain regions previously associated with angry rumination such as the IFG, ACC, PCC and/or amygdala. It was further expected that the identified neural carryover effects following the experience of anger would correspond to individuals' behavior during anger induction and/or to their associated reported anger experience. The anger induction paradigm was based on the anger-infused Ultimatum Game described above (section 4.2.2.), in which anger was induced by interpersonal provocations congruent with unfair monetary offers. One of the main results showed that as individuals rejected more of these angering unfair offers and thus gained less money throughout the game, they reported higher levels of anger. Notably, while monetary gain and self-report of angry feelings reflect state measures directly related to the induced experience of anger, individuals' grey matter volume and their habitual tendency to anger reflect trait-like measures. Therefore, individual differences in trait-anger and grey matter volume in the same brain regions in which anger related rs-FC modulations were identified were examined in correspondence to these identified rs-FC modulations. Thus a comprehensive neural account involving brain function and structure that may mediate coping with anger in the aftermath of anger provocation is provided.

5.2. Materials and methods

5.2.1. Participants

Participants consisted of the same 60 male participants (age 18.62 ± 0.88) that underwent the interpersonal anger-induction task as reported above (section 4.2.1.). Eleven participants were excluded due to technical problems with data acquisition of the rs-fMRI data, and an additional five

were removed due to excessive head movements (>2mm/2°) and therefore the final group for rs-fMRI analyses consisted of 44 participants (15 civilians and 29 soldiers).

5.2.2. Procedure

Two 6-minute resting state scans with eyes fixated on a cross were recorded before (rest1) and after (rest2) the interpersonal anger-induction task as extensively reported above (section 4.2.2.).

5.2.3. Behavioral measures

Total-Gain was calculated as the sum of money accumulated throughout the anger-infused UG by accepting offers and used as an objective measure of individual differences reflecting the final outcome of the anger-infused UG (section 4.3.1.).

Anger-experience was assessed based on the iterated version of the GEW scheme used to obtain subjective reports of the emotional experience during the anger-infused UG, on a round-by-round basis and in accordance with participants' actual decisions (section 4.2.4.). The average reported emotions for all periods and all rounds of the game in the anger-cluster were used here as the measure of anger-experience of each individual during the game.

Trait-Anger was assessed using the gold-standard STAXI-2 (section 3.3.1.) and comprised 10 items rated on a 4-point frequency scale from 1 (not at all) to 4 (very much) related to the frequency of angry feelings experienced over time. Trait-Anger was calculated as the sum score of these items and showed good internal consistency (Cronbach's α=0.74).

5.2.4. fMRI data preprocessing

fMRI data preprocessing was performed with SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). It included correction for head movements via realignment of all images to the mean image of the scan using rigid body transformation with six degrees of freedom, normalization of the images to Montreal Neurological Institute (MNI) space by co-registration to the EPI MNI template via affine transformation, and spatial smoothing of the data with a 6mm FWHM. The first six images of each functional resting scan were excluded to allow for T2*

equilibration effects. Before further analysis, BOLD signals were filtered to low frequency fluctuations (0.01–0.08 Hz) using DPARSF toolbox (Chao-Gan & Yu-Feng, 2010).

5.2.5. fMRI data parcellation

We used a whole brain functional parcellation reported by Craddock and colleagues (2012) , who applied a correlation-based clustering procedure on rs-fMRI data of healthy subjects that partitions the brain volume into 517 parcels. Parcels were masked to include grey matter voxels only using the WFU Pick Atlas Tool (Maldjian, Laurienti, Kraft, & Burdette, 2003; Stamatakis, Adapa, Absalom, & Menon, 2010) and 54 parcels that had less than 5 voxels in common with the grey matter mask were excluded, leaving 463 parcels. For each subject, average BOLD value across all grey matter voxels was calculated within each parcel at each time point of the two rest periods. These time series were used as the parcel's signal. In order to reduce the effect of physiological artifacts and nuisance variables, six motion parameters, cerebrospinal fluid, and white matter signals were regressed out of these parcel signals.

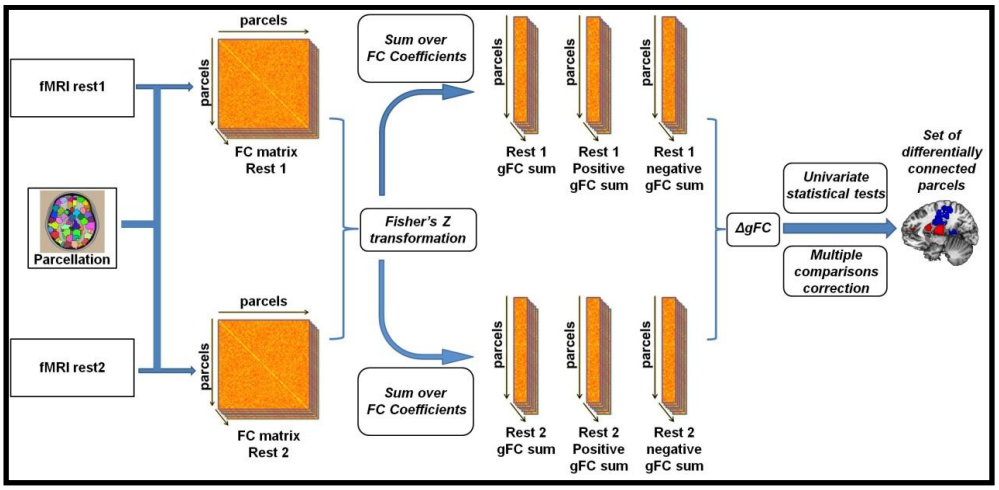

Figure 5.1. The global rs-FC analysis pipeline. Following parcellation, cross-correlation matrices were calculated for each subject and each resting-state session resulting in an rs-FC matrix. A Fisher Z transformation was subsequently applied to the correlation coefficients and global rs-FC (gFC) of the sum of each parcel (the sum of correlation of parcel signals with those of all other parcels) was computed. gFC values were also separated into positive-only and negative-only values, resulting in three gFC values per subject per session. Finally, a univariate one-sample t-test was conducted on the difference (ΔgFC=rest2-rest1) between each of the three values between rs-sessions applying an q(FDR)=0.05 multiple comparisons correction.

5.2.6. fMRI data analysis

We conducted a parcel-based univariate global functional connectivity (gFC) analysis (Figure 5.1.), in which a model is fitted independently to each parcel to assess evidence for experimental effects.

The relationship between each two parcels was estimated by calculating the Pearson correlation coefficient between their corresponding signals. This was done for each subject and each rest period separately. Coefficient values were next Fisher Z transformed to fit a normal distribution. Initially these coefficients were tested for changes in rs-FC between rest1 (before) and rest2 (after) but no result survived correction for multiple comparisons across over 100,000 pairs. Therefore a computation was carried out for each parcel and rest period of the sum of functional connections with all other parcels reflecting gFC. gFC is a commonly used approach to examine differences in whole brain rs-FC in a data-driven manner while maintaining statistical power (Cole et al., 2013; Cole, Pathak, & Schneider, 2010; Kotchoubey et al., 2012). The same gFC procedure was performed also for positive and negative rs-FC values separately, since the sum over all rs-FC values holds the risk of positive and negative changes cancelling each other out. Finally, the change in rs-FC was calculated by subtracting gFC level estimates of rest1 from the corresponding estimates in rest2, resulting in three gFC change values (denoted ΔgFC, ΔgFC^+ and ΔgFC^-) for each parcel and for each subject. To identify parcels that demonstrated significant change in gFC following the anger induction, a one-sample t-test was applied on the three change values of each parcel across all subjects. An FDR procedure was applied to account for multiple comparisons.

5.2.7. Volumetric data preprocessing and analysis

Volumetric analysis was performed using the FreeSurfer V5.3 image analysis suite (http://surfer.nmr.mgh.harvard.edu/), an automated software for brain segmentation based on probabilistic atlas and intensity values. Briefly, the automated procedure includes skull-stripping, intensity normalization, Talairach transformation, tissue segmentation, and surface tessellation (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell & Dale, 1999). The complete FreeSurfer analysis pipeline was performed with manual intervention and quality assurance of the data. Based on the automated segmentation and the fMRI data-driven results the volumes (mm^3) for each subject of the right amygdala, right IFG (pars

orbitalis) and intra-cranial were extracted. Subsequently the adjusted volume of amygdala and IFG was calculated by dividing each subjects' volume by his intra-cranial volume. To note, no differences in these two brain structures were found between civilians and soldiers (p-values>0.471).

5.3. Results

5.3.1. Anger-induced rs-FC modulations

Results of the parcel-based univariate gFC analysis revealed a single parcel located in the right medial amygdala (MNI coordinates: x=18, y=-3, z=-18) for which positive gFC significantly increased between rest1 (53.70±15.86) and rest2 (62.91±18.32; ΔgFC^{+}=9.21±14.51; t_{43}=4.21, p=0.127*10^{-3}, FDR q<0.05, *Cohen's d*=0.54; Figure 5.2.A). Subsequently, an examination of all 462 functional connections of the individuated right amygdala parcel in each rs-session was performed. A calculation of the t-value that represented the extent to which each specific connection was negative or positive in each rs-session was performed by testing if the average FC of each such connection across participants significantly differed from zero. This calculation accounted for inter-subject variance in each parcels' connectivity with the individuated amygdala parcel. Interestingly, 311 of these connections (67.32%) had an increase in connectivity between rest1 and rest2 (Figure 5.2.B). Moreover, there were 161 significant (t_{43}>2.017, p<0.05) positive connections at rest1 and 167 significant positive connections at rest2, of which 145 connections where significantly positive in both rs-sessions. The amygdala ΔgFC^{+} was recalculated based only on these 145 connections per subject per rs-session and a significant increase was found between rest1 (27.37±12.29) and rest2 (33.11±10.94; ΔgFC^{+}_{145}=5.73±9.79; t_{43}=3.88, p=0.350*10^{-3}, *Cohen's d*=0.49). This validated that the initial result of increased gFC^{+} in the individuated right amygdala parcel between rest1 and rest2 was neither a result of a possible influence of many small and insignificant positive connections nor of a difference in the connections between rs-sessions. To note however, irrespective of whether connectivity with a certain parcel increased or decreased

between rs-sessions or whether the connection was significant or not, the number of amygdala positive connections per subject showed a marginally significant increase between rest1 (253.39±30.47) and rest2 (266.25±36.80; Δ=12.86±45.03; t_{43}=1.89, p=0.065, *Cohen's d*=0.38). Finally, using a similar univariate analysis as implemented in the initial gFC analysis but now on all right amygdala FC coefficients, a single connection with a parcel located in the right IFG pars orbitalis (x=26, y=23, z=-18) was found to be significantly changed and showed an increase between rest1 (0.20±0.28) and rest2 (0.37±0.23; ΔFC=0.17; t_{43}=4.29, p=0.100*10^{-3}, FDR q< 0.05, *Cohen's d*=0.66; Figure 5.2.C).

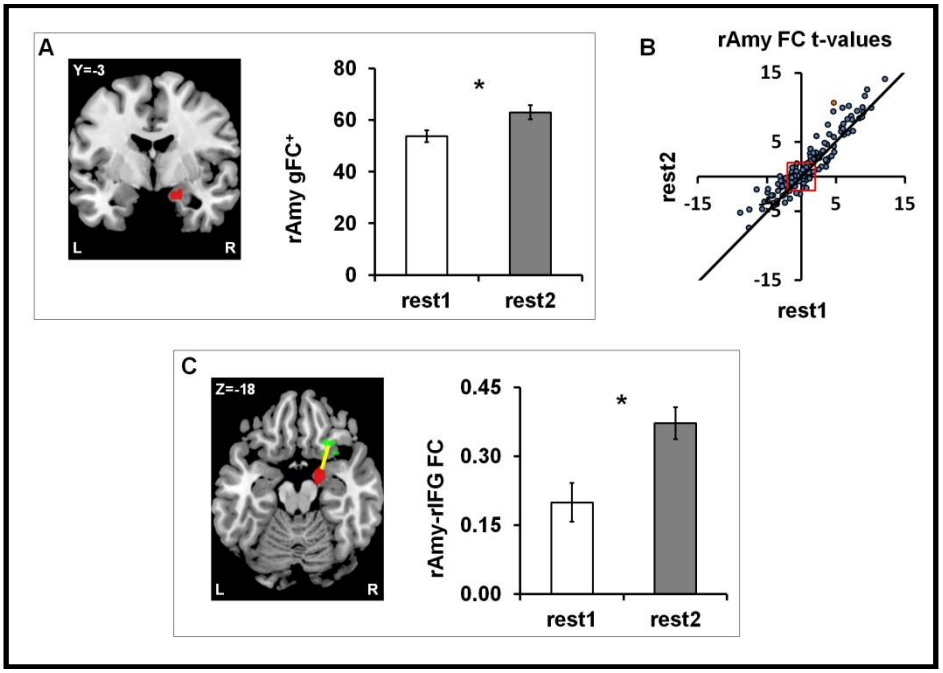

Figure 5.2. Anger-induced FC modulations. (A) A single parcel located in the right medial Amygdala (rAmy; to the left; MNI x=18, y=-3, z=-18) for which global positive FC (gFC+) significantly increased between rest1 and rest2 (the extent of change is shown on the right). (B) The scatter plot illustrates all 462 amygdala connections per rest1 (x-axis) and rest2 (y-axis) as t-values of the across participants FC calculated in comparison to zero. All dots above the diagonal (311 in number) reflect connections that increased between rs-sessions. All dots beyond the red square threshold (t_{43}=±2.017, p<0.05) have significant t-values. (C) Examining all pairwise FC changes involving the amygdala parcel revealed a single significant change characterized by an increase in FC with a parcel located in the right Inferior Frontal Gyrus (rIFG; MNI x=26, y=23, z=-18). The orange dot in panel (B) represents the rAmy-rIFG connection. * indicates q(FDR)<0.05; n=44 in all analyses.

5.3.2. Relation between anger-induced rs-FC modulations and state measures

The relation between the identified anger-induced rs-FC modulation, namely right amygdala ΔgFC^{+} and right amygdala-right IFG ΔFC, and state measures, namely total-gain and anger-experience was next examined. No significant correlations were found (p-values>0.319). Subsequently an exploratory analysis tested whether baseline (rest1) levels of right amygdala gFC^{+} and right

amygdala-right IFG FC were associated with these state measures. Significant correlations were found for the right amygdala gFC^{+}, negatively with experienced-anger (ρ=-0.332, p=0.027; Figure 5.3.A) and positively with total-gain (ρ=0.353, p=0.019; Figure 5.3.B). The other correlations with state measures were not significant (p-values>0.330). Notably, since there was also a significant negative correlation between anger and total-gain (ρ=-0.291, p=0.024; n=60; Figure 5.3.C), possible mediation models were tested but none were found significant.

To note, additional analyses were conducted to explore whether baseline levels of right amygdala gFC^{+} or of the identified right amygdala-right IFG ΔFC correlated with other measures shown to be associated with anger experienced during the anger-infused UG, including vmPFC, BS/LC and dpI activations and dpI-mT connectivity during unfair offers, SCR-latency, RT, agreeableness and ERQ-suppression. None were found to be significant (p-values>0.139). Also, no differences in these FC measures were found between civilians and soldiers (p-values>0.221).

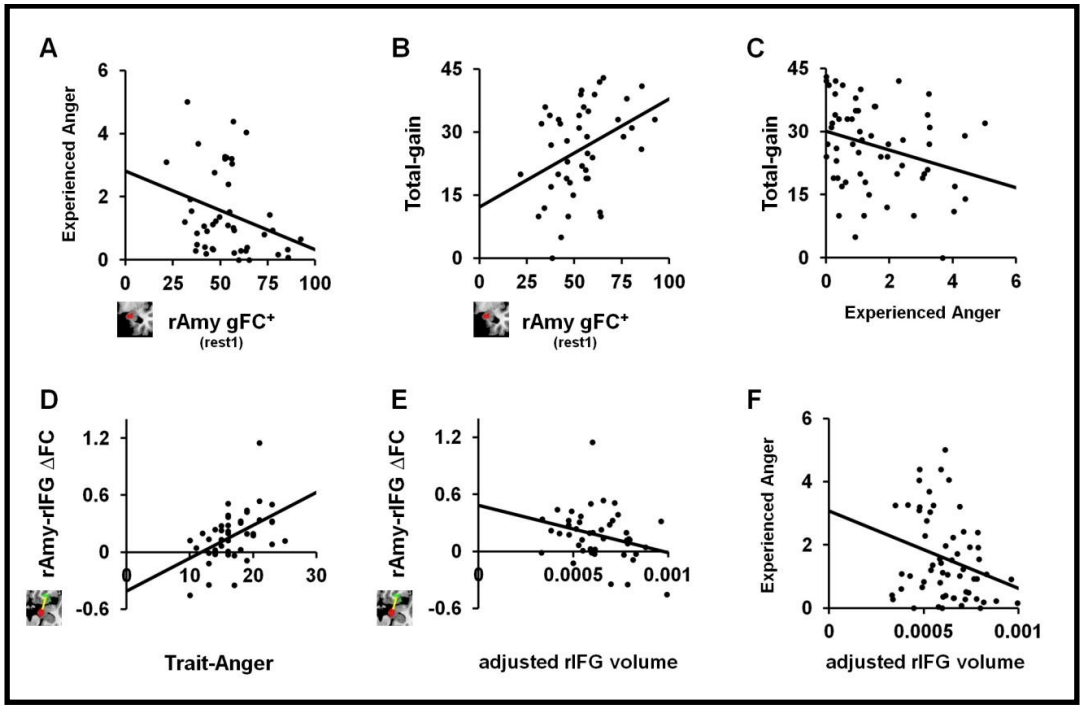

Figure 5.3. The relation between anger-induced FC modulations and behavioral measures. Higher gFC^{+} of the right Amygdala before (rest1) playing an anger-inducing Ultimatum Game predicted (A) lower experienced anger during the game (ρ=-0.332, p=0.027; n=44) and (B) higher total-gain accumulated throughout the game (ρ=0.353, p=0.019; n=44). Congruently, (C) total-gain and experienced anger were negatively related (ρ=-0.291, p=0.024; n=60). In addition, a greater increase in FC between right amygdala and right IFG between before and after the anger-induction (rest2-rest1) correlated (D) positively with trait-anger (ρ=0.469, $p=0.133*10^{-2}$; n=44) and (E) negatively with the adjusted volume size of the same right IFG (ρ=-0.304, p=0.045; n=44). Finally, (F) higher adjusted volume of the right IFG predicted lower experienced anger during the game (ρ=-0.278, p=0.032; n=60). To note, in plots (D) and (E) the highest dot is not an outlier and the correlations remain similar even when removing it: ρ=0.443, p=0.003, n=43 and ρ=-0.313, p=0.41, n=43, respectively.

5.3.3. Relation between anger-induced rs-FC modulations and trait-like measures

The relation between the identified anger-induced rs-FC modulations, and trait measures, namely trait-anger, adjusted right amygdala volume and adjusted right IFG volume was next examined. Significant correlations were found for the right amygdala-right IFG ΔFC, positively with trait-anger (ρ=0.469, p=0.133*10^{-2}; Figure 5.3.D) and negatively with adjusted right IFG volume (ρ=-0.304, p=0.045; Figure 5.3.E). The other correlations with trait measures were not significant (p-values>0.122).

5.3.4. Relation between state and trait-like measures

Finally the relation between state and trait measures related to anger was examined and a significant negative correlation was found between anger-experience and adjusted right IFG volume (ρ=-0.278, p=0.032; n=60; Figure 5.3.F). No additional significant correlations were found (p-values>0.111).

5.4. Discussion

The change in endogenous neural dynamics during rs-fMRI in the aftermath of an interpersonal anger experience was investigated by implementing a data-driven analysis approach to identify rs-FC modulations between before and after anger. In line with expectations, an increase in positive gFC of the right amygdala, and specifically an increase in the connection between the right amygdala and right IFG, was found following the anger-infused Ultimatum Game. It was further found that greater increase in this amygdala-IFG connection was associated with smaller volumes of the right IFG and higher trait-anger levels. Moreover, higher levels of right amygdala positive gFC at baseline predicted less reported anger and more monetary gain. Together, these findings indicate a link between neural dynamics in regions related to the traces of anger and both state characteristics of angry experience and trait-like measures of the habitual propensity to be angry.

The amygdala has a central role in processing emotional experiences (Davis & Whalen, 2001; Kober et al., 2008; Phelps & LeDoux, 2005) especially those associated with high arousal, possibly reflecting attention to and evaluation of motivationally salient stimuli (Lindquist et al., 2012; Pessoa

& Adolphs, 2010). As such, the amygdala was also shown to be the target of various emotion regulation processes, which engage the IFG in addition to other PFC regions (Buhle et al., 2014; Etkin et al., 2015). For example, it was shown that a positive association between IFG and amygdala predicted reduced cognitive control of affective responses (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). The IFG was also shown to be important for motor inhibitory control or response inhibition (Aron, Robbins, & Poldrack, 2004, 2014) and impairment of this region is known to contribute to impulsivity (Bari & Robbins, 2013). Interestingly, it was shown that both motor and affective inhibitory control positively mapped to IFG grey matter intensity (Tabibnia et al., 2011). These descriptions are congruent with a possible role of amygdala in mediating angry experience and subsequently contributing to reactive aggression (Rosell & Siever, 2015), while the IFG may be attributed a role in efforts to regulate anger experience and aggressive impulses.

5.4.1. Amygdala-IFG connectivity reflect neural traces of anger

Angry rumination outlasts anger provocation and typically involves repetitive thoughts and fantasies about the anger episode and possible retaliations. As in a previous study that explicitly instructed participants to ruminate over an angering experience (Fabiansson et al., 2012), an increase in amygdala-IFG neural coupling in the aftermath of an angering episode was revealed, but here by data-driven analysis and during task-independent rs-fMRI, which may reflect an implicit procedure of naturally occurring angry rumination if subsequent to an anger experience. In fact, results are congruent with a broader involvement of amygdala and IFG activity and connectivity in rumination, not necessarily specific to anger (Hooker et al., 2010; Kross et al., 2009; Kühn et al., 2012; Ray et al., 2005). Moreover, studies investigating neural dynamics during rs-fMRI following intense negative emotional experiences have similarly shown increased amygdala connectivity (Maron-Katz et al., 2016; Vaisvaser et al., 2013; van Marle et al., 2010; Veer et al., 2011). Together this suggests that the current finding of increased amygdala connectivity and specifically with the

IFG may reflect neural processing related to emotional coping following negative experiences, and possibly relates to rumination.

The congruency between findings reported in the literature and results found here further support the notion that the increased amygdala-IFG connectivity following interpersonal anger may indeed reflect a neural process associated with angry rumination. Of particular interest, Kühn and colleagues (2012) showed that high trait-rumination was associated with lower grey matter volume and overlapping lower resting-state activations in the right IFG. Here it was shown that a larger increase in amygdala-IFG rs-FC in the aftermath of an angering experience was associated with lower grey matter volume of the IFG, as well as with higher trait-anger. While there was a limitation since there was no direct measure of angry rumination, trait-anger was shown to have a strong positive association with such a measure (Sukhodolsky et al., 2001). In contrast to the results found here, others have shown that higher trait-anger was associated with lower rs-FC between amygdala and a region in the right orbital frontal cortex anterior to the IFG (Fulwiler, King, & Zhang, 2012). However, in that study only one rs-fMRI scan was acquired irrespective of an emotional experience, while here two rs-fMRI scans were probed before and after an experience of anger, which might explain this discrepancy. In this respect, it was also found that lower grey matter volume in the IFG, which was previously associated with more trait-rumination (Kühn et al, 2012), was associated with higher anger reported to have been experienced during the anger-infused game, in line with the general positive association between anger and angry rumination (Bushman et al., 2005; Fabiansson et al., 2012; Pedersen et al., 2011; Rusting & Nolen-Hoeksema, 1998).

Considering the lasting effects of anger, though one cannot know if participants actually engaged in angry rumination, it seems reasonable to assume that a resting period in which participants are simply asked to stare at a fixation cross may reflect an implicit procedure of angry rumination if it is subsequent to a validated anger-induction paradigm. Anecdotally, comments of several participants when exiting the scanner such as "Where is that second player? I have to see him!" or "Let me talk to that player, what was he thinking!?" led to believe that participants were

engaged to a certain extent in angry rumination during the rs-fMRI that succeeded the anger-infused Ultimatum Game, especially considering the comparison to the rs-fMRI that preceded that experience.

Notwithstanding, the role of the increased amygdala-IFG neural coupling in relation to angry rumination is still not clear, and in view of the above, several alternatives exist. One possibility is that such connectivity reflects unsuccessful and/or enhanced efforts to exert cognitive control over an emotional response. Another possibility emphasizes IFG's role in response inhibition, and thus the increased connectivity may reflect efforts to control motor impulses, such as when planning or imagining an aggressive revenge. Finally, an aspect of rumination that might be reflected by the increase in amygdala-IFG connectivity is the difficulty to disengage from an emotional experience, possibly due to persistence of the emotional content in working memory (Joormann, 2006). Each of these alternatives is viable and future studies will hopefully disentangle between these different processes.

5.4.2. Amygdala connectivity predicts behavioral indices of anger

An additional intriguing finding was that larger positive global connectivity of the amygdala before the anger-infused game predicted less reported anger and more gain accumulated throughout the game. There is an increasing interest in using task-independent neural activity and connectivity to predict individual differences in various behavioral measures (Fox, Snyder, Vincent, & Raichle, 2007; Wang et al., 2010), including in decision-making and self-regulation contexts (Gianotti et al., 2009; Daria Knoch, Gianotti, Baumgartner, & Fehr, 2010), and recently also to predict task-related neural activation (Tavor et al., 2016). The strength of such trait-like non-invasive measures of brain functionality is further boosted by findings that reveal predicted change in diagnostic criteria of clinical patients (Day et al., 2013). The findings presented here extend these results by predicting both behavior as well as the associated emotional experience, suggesting that amygdala connectivity during rs-fMRI may serve as an indicator for emotional predisposition. Alternatively,

since the amygdala seems to be part of a topologically central circuit involved in aggregation and distribution of information throughout the brain (Pessoa & Adolphs, 2010), our findings may be unrelated to amygdala's direct role in emotional processing. Notably, the amygdala parcel found here is rather medial, and based on previous connectivity analysis, the medial-amygdala and its' rs-FC network was suggested to be functionally distinct from a ventrolateral and dorsal amygdala networks, supporting pro-social affiliation rather than perception or aversion, respectively (Bickart, Hollenbeck, Barrett, & Dickerson, 2012). Therefore, amygdala connectivity at baseline may in fact reflect a pro-social orientation and thus explain the relationship to higher gain (i.e. accepting more offers from an angering counterpart) and lower reported anger. Although we had a measure of pro-social orientation, namely agreeableness (Jensen-Campbell & Graziano, 2001; Meier et al., 2006), no relation was found between this measure and global positive connectivity of the amygdala before the anger-induction. Additional inquiry is still needed to reach a more decisive interpretation.

5.4.3. Concluding remarks

In conclusion, the findings indicate that an interpersonal angering episode orchestrates increased amygdala-IFG connectivity during spontaneous task-independent neural processing. Interestingly, while it was shown above that coping with anger experienced during anger-provocation was associated with high vmPFC activation and increased dpI-mT connectivity (section 4.4.), coping with anger in the aftermath of provocation was here associated with different neural substrates. This may suggest the engagement of different processes during the on-going emotional episode compared to during recovery from that experience. Findings should be warranted by further investigations, especially considering their potential relevance to pathological conditions characterized by excessive anger and/or rumination such as depression, anxiety and personality disorders.

6. OBJECTIVE 3: Examining the influence of combat-training on neurobehavioral indices of anger

**** Excerpts from the current chapter were submitted for publication in:**

Gilam G., Ne'eman, Y.J., Raz, G., Lin, T., Fruchter, E., & Hendler T. Stoic regulation: The influence of military combat-training on neurobehavioral indices of anger. In *Anxiety and Anger: Predictors, Coping Strategies and Helath Effects*. Nova Science Publishers, Inc. NY.

6.1. Introduction

As clearly established above, anger is a common emotion experienced on a daily basis and serves as a primary precursor to aggression and violence. Anger is considered an instinctive survival response inherent in all living creatures (Darwin, 1872; Panksepp, 1998), which triggers the fight feature of the fight or flight reaction in view of threatening situations (Cannon, 1927; Carver & Harmon-Jones, 2009). Humans however, are endowed with the mental flexibility that enables them to control and regulate their anger and adapt it to socially accepted norms (Averil, 1982; Berkowitz, 1990; Gross, 1998; Davidson et al, 2000; Gilam and Hendler, 2015). However, as eluded by Aristotle's citation at the beginning of this work and as subsequently demonstrated, controlling, regulating or generally coping with one's anger is not an easy thing to do. Difficulties in balancing the levels of anger are apparent in normative development as in various pathological conditions (Potegal, Stemmler, & Spielberger, 2010). In fact, most people can probably testify that at certain incidents they lose control to anger. Some theorists go as far as suggesting that a certain type of personality, referred to as Type A personality, is specifically prone to anger expression and aggressive reaction (Friedman, 1996). Various emotion regulation therapeutic and pedagogical programs are existent to treat such emotional irregularities (Gross, 2015), yet over the years specific anger management frameworks have been developed to train people to manage their anger in various phases of prevention, intervention and postvention of anger (Fernandez, 2010; Kassinove & Tafrate, 2002; Potter-Efron, 2005).

Anger-management programs are reported to yield short and long term changes in patterns of angry and aggressive behavior (Blake & Hamrin, 2007; Potter-Efron, 2005). In such programs, four domains of intervention are generally outlined: cognitive reformulation to filter unnecessary anger triggers (e.g. identifying hostile thoughts), behavioral change of the actions taken during or after an anger episode (e.g. taking time-outs or learning to relax), affective modulation to prevent overstimulation and loss of control (e.g. exposure techniques teaching to remain calm when facing aversive stimuli), and personal growth by understanding the meaning of anger and aggression in a wider context (e.g. forgiveness practice). Seen through the theoretical prism presented above (chapter 1), the changes promoted by these intervention programs induce modulations in cognitive, physiological and behavioral components during or after anger experience. However, the level of internalization of anger-management strategies that such training programs can induce depends on their status and authority as socio-cultural institutions, as well as on their training pedagogy. Regardless of its moral end, military training, where Stoic-like pedagogy promotes emotional regulation and enhances the containment and control of anger (Darash, 2005; Sherman, 2007), offers a paradigmatic, and in Israel, an institutionalized case study of such anger-management programs. The aim of the current study was to investigate how military combat-training influences the neurobehavioral substrates of anger.

Contemporary military pedagogy nurtures a Stoic-like attitude, focused on self-control and fortitude in view of emotionally salient events, especially in regards to anger, with the goal of forming combatants that will be dedicated to carry out their defined missions under life-threatening situations (Ben-Ari, 1998; Darash, 2005; Sherman, 2007). Emotions may thwart the performance of military tasks and in the battle-field anger is specifically regarded as a sign of vulnerability. Thus emotion- and anger- regulation are considered critical for combatants and therefore they become a common and important objective in military pedagogy. This is clearly demonstrated in the US Army Leadership Manual (2006) which has a whole section on emotional self-control. In fact, the

manual quotes the 1917 Noncommissioned Officer's Manual, in that one "who loses his temper and flies into a tantrum has failed to obtain his first triumph in discipline" (there, page 52).

Indeed, training a combat soldier involves disciplined physical and psychological manipulations intended to maintain strength and endurance, and desensitize uncontrolled reactions (Ben-Ari, 1998; Darash, 2005; Lieblich, 1989; Sherman, 2007). Instrumental to this goal is a hierarchical authority implementing strong discipline and hazing. Hazing consists of a combination of treatments such as harassment, humiliation, insulting provocations, and physical and emotional degradation. Such manipulations trigger anger, fear and hostility, and while trainees are subject to verbal and physical violence, they are themselves permanently on the verge of aggressive reactions. At the same time, as part of their professional practice and similarly to the four domains of intervention outlined in anger-management programs: trainees must abstain from emotional storms (cognitive reformulation); trainees are punished for inappropriate reactions and uncontrolled outbursts (behavioral change); hazing can be thought of as an effective technique which trains soldiers to stay in control even under extreme conditions (affective modulation); and military lessons reflecting on outcomes of responses to combat incidents may advance contemplation on the disadvantages of uncontrolled anger outbursts in a wider context of problem solving (personal growth). Often publicly debated and morally condemned, the rational of this pedagogy can be thought of as a kind of exposure technique which effectively prepares soldiers for extreme combat situations because while trainees are subject to anger inducing manipulations, violent and egocentric manifestations of anger are sanctioned in favor of emotional control.

From a neural perspective, using an interactive and realistic anger-provoking paradigm based on the UG (section 4.2.2.), it was shown (chapter 4) that individuals with a tendency for aggressive reactions (i.e. rejecting angering unfair offers thus gaining less money throughout the game) were angry and had greater activation in a region of the BS corresponding to the LC and less activation in an anterior region of the vmPFC, while individuals with a tendency for conciliatory reactions (i.e.

accepting angering unfair offers thus gaining more money throughout the game) had an emotionally balanced response and the reverse pattern of brain activation – greater vmPFC and less BS/LC activation. This reverse pattern of activation led to the suggestions that the vmPFC is involved in regulating LC related arousal and aggressive reactions towards anger provocations. Interestingly, it was also shown (chapter 5) that high amygdala gFC during rs-fMRI before the anger-infused UG predicted higher conciliatory reactions (more gain) and lower reported anger in the game. There was also an increase in amygdala-IFG FC in the aftermath of the angering experience.

A prospective brain-imaging study was conducted to compare the neural and behavioral manifestations of anger before and after military combat-training. As described above (section 3.2.), participants were a-priori healthy newly drafter soldiers recruited to Duvdevan – a Special Forces unit in the IDF's Paratroopers Brigade, who's behavioral and neural responses were measured at two time-points: during the first two-weeks of boot-camp (pre-training) and approximately one year later at which they were about to complete their training program (post-training; Section 3.2.1., Figure 3.2.). Combat-training in this unit includes various psychological and physical practices such as strictly enforced discipline, survival challenges, Krav Maga training and a counter-terrorism course (Darash, 2005). The age-matched group of civilians recruited from Israeli civil-service programs and who did not partake in combat-training within a similar time period was used as control. While undergoing fMRI, participants performed the anger-infused UG at each time-point. Pre-training results (extensively reported above in chapter 4) indicated no differences between soldiers and civilians in any of the neurobehavioral measurements related to anger. Post-training results are reported here in light of these pre-exposure findings, focusing on the differences between LGs and HGs. It was expected that at the second time-point reported here, an increase in gain, a more balanced emotional response and a modulation in brain response to anger, such as an increase in vmPFC activation and decrease in LC activation during unfair offers, would manifest amongst LG-soldiers who pre-training had a tendency for more aggressive reactions, but not amongst HG-soldiers or civilians.

To note, the two rs-fMRI sessions before and after the game were performed in both time-points in order to test the influence of combat-training on the neural traces of an angering experience. Examining the rs-FC modulations individuated in the first time-point (extensively reported above in chapters 5), no significant interactions between the two experimental groups, the two gain-groups, and the two time-points were found (p-values>0.108), nor when considering the experimental groups separately (p-values>0.235). Therefore this chapter does not discuss this aspect any further. Also, due to technical malfunctions with the recording gear, the SC measure was not available at the second time-point.

6.2. Materials and methods

6.2.1. Participants

Of the 60 male participants that performed the anger-induction task in the first time-point, 46 participants were recruited and volunteered to take part in the second time-point, consisting of 29 Duvdevan soldiers (age 18.86±1.06 at time-point 1) and 17 civil-service civilians (age 18.24±0.44 at time-point 1). As for the participants who did not partake in the second time-point: five civilians and one soldier choose not to due to personal reasons; six soldiers were excluded from the combat-training course before its completion; and two soldiers had medical injuries which prevented their participation. Approximately one year passed in between time-points, at which soldiers were about to complete their combat-training but were not yet actively deployed and civilians were about to complete their civil-service programs. Both time points were approved by the Institutional Ethics Committee of the Tel-Aviv Sourasky Medical Center and of the IDF Medical Corps. As indicated above (section 4.3.), within the 60 participants of the first time point (38 soldiers and 22 civilians) there were no differences in any of the anger measures including behavior, emotional reports and brain activations. Low-gain (LG) and high-gain (HG) groups were defined based on the division of the first time-point (section 4.3.), resulting in 14 LGs and 15 HGs for the study group and 5 LGs and 12 HGs for the control group (see Table 6.1.).

Table 6.1. Sample size of available data by type, experimental group and gain group

Time-Point	Data Type	#n Soldiers		#n Civilians		#n Total
		LGs	HGs	LGs	HGs	
#1	Behavior	19	19	8	14	60
	Brain	18	15	8	13	54
#2	Behavior	14	15	5	12	46
	Brain	10	10	5	10	35

Table 6.1. The sample size diminished between time-points and also according to the type of data acquired. Our initial sample of 38 soldiers and 22 civilians decreased to 29 and 17 respectively at the second time point and an additional reduction in sample size occurred for the brain data due to excessive head movements.

6.2.2. Anger induction and emotional rating

Anger was induced using the anger-infused UG and with the same post-scan emotional report to measure the induced emotional experience, both of which have been described above (section 4.2.). To note, the proposer of offers was one of two different professional actors compared to the first time-point and participants received the exact same offers as in the first time-point but in a different sequence (see Table 4.1.): participants who played the 1st sequence in the first time-point played the 2nd sequence in the second time-point and vice-versa, and similarly participants who played the 3rd sequence in the first time-point played the 4th sequence in the second time-point and vice-versa. Since there were no differences between the two actors and the four sequences in all measures they were collapsed across all analyses (p-values>0.151). Following findings from the first time-point **(**section 4.3.) total-gain and EVI were calculated for each soldier and civilian who participated in both time-points. Since the gain-groups × experimental groups × time-points interaction of these measures were not significant (p-values>0.193), the analysis was performed on the gain-groups × time-points interaction, separately for each experimental group. To note however, a general analysis of the second time-point as detailed below (section 7.3.2.) replicated results found in the first time-point indicating there was a relationship between behavior in the game and the corresponding emotional experience that validated the anger induction and did not differ between soldiers and civilians.

6.2.3. fMRI preprocessing and analysis

Preprocessing of data acquired at the second time-point followed the exact same steps as performed for the first time-point detailed above (section 4.2.7.). Five soldiers and one civilian were discarded from brain analyses due to excessive head-movements in the first time-point, and similarly additional four soldiers and one civilian were discarded from analyses of the second time-point. Therefore, the final sample for brain analyses for both time-points included 20 soldiers and 15 civilians (Table 6.1.).

Exploratory comparison of the two time-points was based on a random-effects GLM which included four regressors for each period of the game (offer, decision, result, negotiation), repeated twice to differentiate between fair and unfair rounds, and repeated again to differentiate between time-points. These regressors were convolved with a canonical hemodynamic response function. Additional nuisance regressors included the head-movement realignment parameters and the time course of averaged activity in cortical white-matter. The fixation period was used as baseline. A grey matter mask and a correction for temporal autocorrelations using a second-order autoregressive model were also used. Statistical analysis was conducted on the unfair-offer periods which were shown to induce more anger. The BOLD brain activity during the unfair offer period was then submitted to a 2 (gain-groups: Low/High) × 2 (experimental group: soldier/civilian) × 2 (time-point: $1^{st}/2^{nd}$) mixed-model ANOVA. Correction of brain activation maps for multiple comparisons was performed as detailed above (section 4.2.7.). Beta values were averaged across the entire ROI voxels for each significant cluster, separately for the difference experimental conditions.

6.2.4. ROI Analysis

Based on the two time-point GLM beta values were extracted for all the voxles in three ROIs identified in the first time-point: the vmPFC cluster which consisted of 554 contiguous anatomical voxels ($1mm^3$) with peak voxel located at the Talairach coordinate x=14, y=49, z=-12; the BS cluster which consisted of 409 contiguous anatomical voxels with peak voxel located at the

Talairach coordinate x=-7, y=-35, z=-18; and the dpI cluster which consisted of 562 contiguous anatomical voxels with peak voxel located at the Talairach coordinate x=-31, y=-23, z=18.

6.3. Results

6.3.1. Anger related behavior and emotional report

For total-gain, in line with expectation, for the soldiers there was a significant time-points × gain-groups interaction ($F_{1,27}$=10.32, p=0.003, η_p^2=0.28), but not for civilians ($F_{1,15}$=1.88, p=0.190, η_p^2=0.11; Figure 6.1.A. & B.). As expected, soldier LGs had a significant increase (p=0.014, uncorrected) in total-gain between pre (15.64±7.52) and post (24.71±13.34) combat-training. In addition, there was a marginally significant decrease (p=0.068, uncorrected) for HGs between pre (15.64±7.52) and post (24.71±13.34) combat-training, but there was no difference between LGs and HGs post combat-training (p=0.581).

For EVI, in line with expectation, for the soldiers there was a significant time-points × gain-groups interaction ($F_{1,27}$=7.43, p=0.011, η_p^2=0.22), but not for civilians ($F_{1,15}$=0.55, p=0.470, η_p^2=0.04; Figure 6.1.C. & D.). As expected, LGs had a marginally significant increase (p=0.076, uncorrected) in EVI between pre (-0.33±0.36) and post (-0.12±0.53) combat-training. In addition, there was a marginally significant decrease (p=0.054, uncorrected) for HGs between pre (-0.02±0.59) and post (-0.24±0.56) combat-training, but there was no difference between LGs and HGs post combat-training (p=0.546). Follow up analysis revealed that compared to pre combat-training, post combat-training LGs had a significant increase in reported positive-cluster of emotions (pre=0.56±0.27; post=0.88±0.58; t_{13}=-2.30, p=0.038, *Cohen's d*=0.73), while HGs had a marginally significant increase in reported anger-cluster of emotions (pre=1.45±1.33; post=2.07±1.49; t_{14}=-2.09, p=0.055, *Cohen's d*=0.43).

6.3.2. ROI analysis

Examining vmPFC activations during the offer periods, soldiers exhibited a marginally significant time-points × gain-groups interaction ($F_{1,18}$=3.43, p=0.081, η_p^2=0.16), but civilians did not

($F_{1,13}$=2.32, p=0.151, η_p^2=0.15; Figure 6.1.E. & F.). In line with expectations, LGs had a significant increase (p<0.014, uncorrected) in vmPFC activation between pre (-0.01±0.04) and post (0.02±0.03) combat-training. In addition, there was no difference (p<0.922, uncorrected) for HGs between pre (0.01±0.04) and post (0.01±0.04) combat-training, and no difference between LGs and HGs post combat-training (p<0.913, uncorrected). No other significant results were found, also when considering the BS/LC and dpI clusters' activations for both unfair offers and when averaging fair and unfair offers together (p-values>0.303).

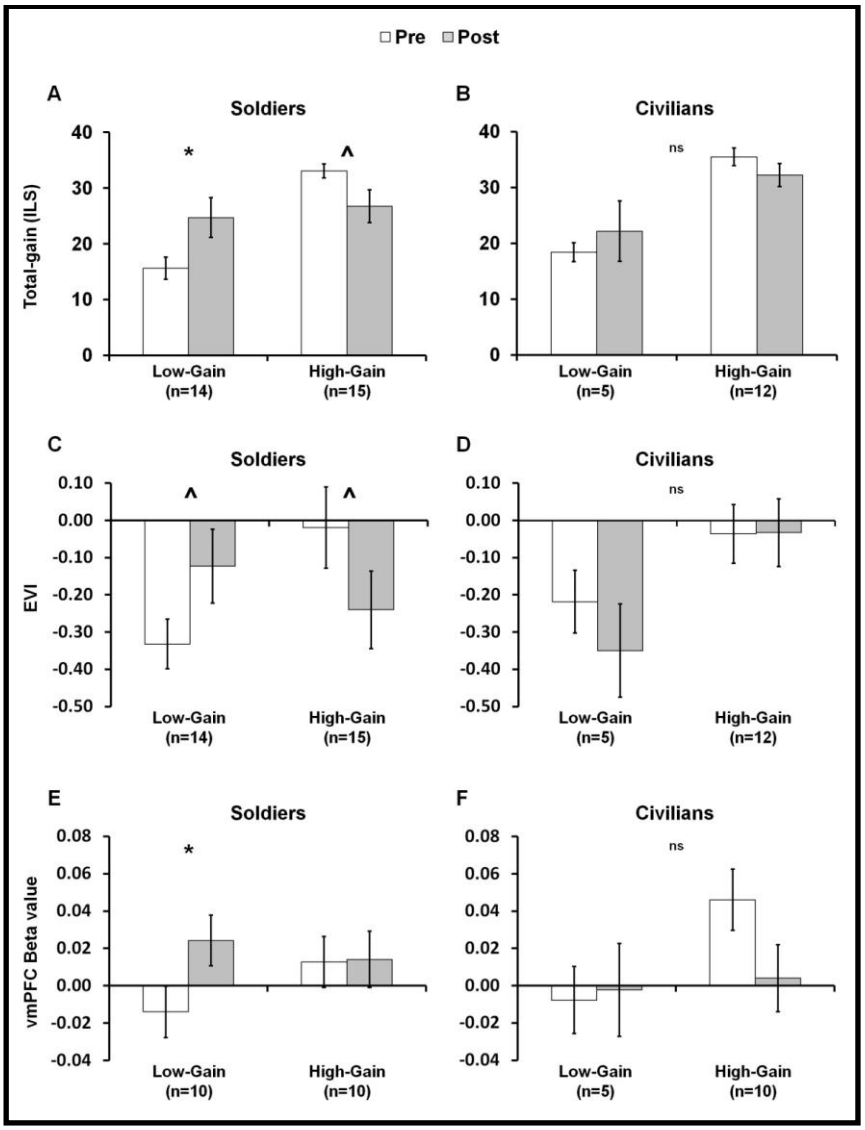

Figure 6.1. Behavioral and ROI results across time points. Considering total-gain accumulated throughout the anger-infused UG changes were detected for low- and high- gain soldiers (A) indicating LGs had increased gain between time-points while HGS had a decrease. (B) No changes were detected for civilians. Similarly (C) low- and high- gain soldiers showed an increase and decrease in EVI, respectively. (D) No changes were detected for civilians. Finally, (E) LG soldiers showed an increase in vmPFC activation during the offer periods, and again (F) no changes detected for civilians. * indicates p< 0.05, uncorrected; ^ indicates p< 0.10, uncorrected; ns=non-significant.

Table 6.2. Brain activation during unfair offer periods

Brain Region	BA	Side	X	Y	Z	F(1,31)	p	Voxels
A. Main effect of gain-groups (LGs/HGs)								
Precuneus	19	R	32	-71	36	17.359	0.0002	1165
Posterior Hippocampus		R	29	-29	-3	12.977	0.001	172
Orbito Frontal Gyrus	11	R	14	55	-12	16.288	0.0003	118‡
Brainstem		R	8	-32	-12	12.390	0.0013	156‡
Brainstem		R	8	-14	-15	13.673	0.0008	55
Brainstem		L	-7	-35	-15	12.378	0.0013	189
Precuneus	7	L	-7	-65	36	14.283	0.0006	99
Caudate Body		L	-16	10	9	11.554	0.0018	90
Caudate Tail		L	-24	-35	18	19.403	0.0001	203
Inferiof Parietal Lobule	40	L	-34	-38	39	14.904	0.0005	295
Precentral Gyrus	6	L	-36	-11	45	11.356	0.0019	50
Middle Frontal Gyrus	9	L	-52	16	30	24.150	<0.00002*	1199^
Middle Frontal Gyrus	8	L	-43	7	42	10.994	0.0022	68
Middle Frontal Gyrus	46	L	-43	20	19	14.039	0.0007	77
B. Interaction effect of time-points (1st/2nd) × experimental groups (soldier/civilian)								
Insula	13	R	36	28	9	10.990	0.0022	64
Caudate Head		L	-4	16	4	33.453	<0.00001*	2007^
Caudate Head		R	11	17	-6	12.501	0.0012	130
Lingual Gyrus	17	R	11	-95	-9	13.897	0.0007	71
Cerebellum		R	5	-56	-30	11.912	0.0016	97
Superior Parietal Lobe	7	L	-10	-65	61	12.562	0.0012	95
Superior Frontal Gyrus	10	L	-21	52	9	20.811	0.00007	1547
Insula	13	L	-25	28	9	17.389	0.0002	429
Superior Temporal Gyrus	38	L	-37	22	-24	12.497	0.0012	53

Table 6.2. All regions arising from whole-brain GLM (n=35), presented at a threshold of p<0.005 (uncorrected) with a minimal cluster size of 50 contiguous anatomical ($1mm^3$) voxels. Coordinates are of peak activity, given according to Talairach space with their F-scores and p-values. Beta values for subsequent ROI analyses were extracted for those brain regions with both peak voxel q(FDR)<0.05 (denoted by *) and minimal cluster size of 10 contiguous functional ($3mm^3$) voxels (denoted by ^; see section 4.2.7.). Though not significant, the gain-group main effect revealed two clusters in overlap with the vmPFC and BS clusters identified in the first time-point (denoted by ‡). Anatomical locations were determined using Talairach Daemon (http://www.talairach.org/).

6.3.3. Exploratory Brain activation maps

The gain-groups main effect revealed a significant cluster of activation in the left dlPFC (Table 6.2.A.). Follow-up examination of the time-points × gain-groups interaction during unfair offers, there was neither a significant effect for soldiers ($F_{1,18}$=7.43, p=0.011, η_p^2=0.22) nor for civilians

($F_{1,13}$=0.55, p=0.470, η_p^2=0.04). When averaging both fair and unfair offers together, there wasn't a significant effect for soldiers ($F_{1,18}$=1.56, p=0.227, η_p^2=0.08) but there was a marginally significant effect for civilians ($F_{1,13}$=3.42, p=0.087, η_p^2=0.21). Though no significant post-hoc simple effects were found (p-values>0.164), the interaction generally indicated a descriptive increase in activation of this region for the HGs in the second time-point. To note, though not passing significance threshold, the gain-group main effect revealed two clusters in overlap with the vmPFC and BS/LC clusters identified in the first time-point (Table 4.5.). The time-points by experimental groups interaction revealed a significant cluster of activation in the caudate head (Table 6.2.B.) but no significant effects were found in the follow-up examinations or in correlation with other measures obtained in this study (p-values>0.232). The interaction itself (Figure 6.2.) indicated no difference between groups at the first time-point (p=0.702), an increase in activation for the civilians (p=0.022), a marginal decrease for the soldiers (p=0.072) and more activation for civilians compared to soldiers at the second time-point (p=0.001). All the other generated maps related to the gain-groups by experimental groups by time-points interaction failed to produce any significant clusters of activation. Similarly, no results were found when examining maps generated separately for each experimental group on the gain-groups by time-points interaction.

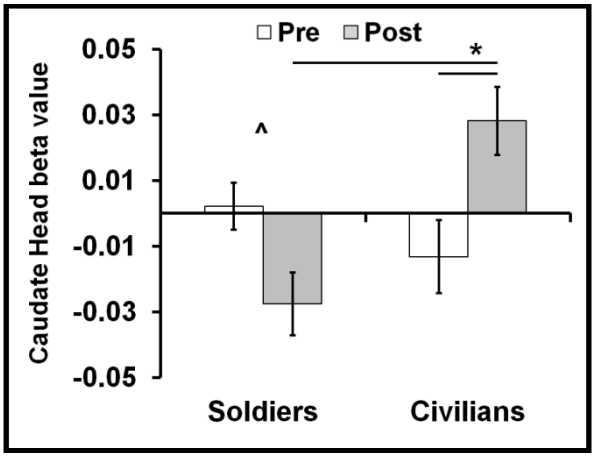

Figure 6.2. Caudate head brain activations. Caudate head activations during unfair offers differed between soldiers and civilians across time-points, indicating increased activation for civilians post combat-training compared to pre combat training (p=0.001) and compared to soldiers post combat-training (p=0.022). A marginal decrease in activation was apparent for soldiers post combat-training compared to pre combat training (p=0.072). * indicates p<0.05; ^ indicates p< 0.10.

6.4. Discussion

The aim of the current study was to examine the influence of military combat-training on neurobehavioral indices of interpersonal anger, assuming that such a training program would foster emotion regulation capabilities. To this end, a prospective neuroimaging study tested a group of combat soldiers and a group of civil-service volunteers at the beginning and end of a period of one year during which soldiers undertook their training (Figure 3.2.) and civilians were engaged in community service and educational programs. All participants at both time-points played the anger-infused UG which at the first time-point differentiated between HGs, who evidenced a regulated emotional and neural profile, with increased report of the EVI and increased vmPFC activation, while the reverse was found for the LGs who displayed an unbalanced profile and the reverse pattern of emotion and neural profile. Though some results were marginal in significance, a general confirmation of our expectations was obtained, indicating differences between the two time-points in the soldiers study group but not in the civilian control group. The low-gain soldiers evidenced an increase in total-gain, a marginal increase in EVI which reflected an increase in reported positive emotions, and an increase in vmPFC activation between the two time-points. In parallel, the high-gain soldiers displayed a marginal decrease in total-gain and in EVI, which reflected an increase in reported anger, between the two time-points. Moreover, no changes were found between LG and HG soldiers at the second time-point. Finally, a general result indicated that compared to the first time-point, civilians had an increase in activation in a region of dorsal striatum, namely the caudate head, while soldiers had a decrease such that at the second time-point they had less activation compared to civilians.

6.4.1. Stoicism and the effect of combat-training on neurobehavioral indices of anger

The findings presented are indicative of a pattern of modulation in the neurobehavioral indices of interpersonal anger suggesting that military combat-training has an influence on neural

processing associated with emotional experiences and hinting towards the possibility that military indoctrination indeed empowers emotion regulation. Anthropological studies (Darash, 2005; Sherman, 2007) inspired the assumption that military pedagogy nurtures a Stoic-like attitude which underlines self-control of emotional reactions and especially of anger. Stoicism (Baltzly, 2010; Sherman, 2007) contends that humans have complete power over their emotions and thus their goal should be to practice self-discipline in their emotional responsiveness to all events as they occur. Within this perspective emotions are viewed as destructive because they are regarded as evaluations or appraisals, ways of construing the world, and thus are inherently misrepresentations or misjudgments of the world. Cognitive, physiological and behavioral changes are inseparable from the stoic way of life in order to accomplish the goal of emotional containment.

The Stoic-militaristic synergism introduced in Sherman's "Stoic Warriors" (2007) following a period in the United States Naval Academy, is based on the notion that a soldier in the battlefield has little control of the turmoil and terror around him, but he does have full control of his own mind and body and therefore for his own actions and reactions to the unfolding of events in the battlefield. Therefore, regulating emotional reactions is a matter of life and death. Sherman refers to Seneca, one of the main Roman philosophers advocating Stoicism, as insisting that anger ought not to be part of the emotional repertoire of a stoic warrior (there, p. 67). Anger is seen as a major vulnerability in combatants since when lead by anger they may abandon their missions' goals or dismiss standard procedures and advance in an unsafe manner, thus putting themselves and their brothers-in-arms at risk. Anger regulation is thus considered critical for combatants in the battlefield and therefore becomes a common and important objective in military pedagogy.

In her interview-based work with Duvdevan combatants, the same unit from which the current sample of soldiers were recruited as participants, Darash (2005) provides ample support for Sherman's formulation, underlining the notion of both emotional and physical

control of internal and external events in one's mind and body as a result of being a professionally trained combatant. Together their work suggests that military indoctrination does not reach this end goal as a spontaneous outcome of the practical aspects of becoming a soldier (such as learning how to shoot) in a very large and hierarchical institute, rather it is a deeply ingrained and intended result of the discipline.

Interestingly, while initially reasoning that soldiers displaying a high-gain profile would not display changes in neuro-behavioral indices of anger since they were supposedly well regulated a-priori, at least in monetary gain and emotional report there seemed to have been a pattern of change in the opposite direction compared to the low-gain soldiers. In fact these high-gain soldiers displayed an increase in anger. This result may suggest that within the military practice, anger is not to be entirely abstained from, but perhaps knowing how to summon the right amount of anger for the right cause is the ideal. In this sense it provides a broader view of anger management where by too much containment is similarly unproductive and possibly unhealthy. Indeed, several examples evidence a negative influence of anger inhibition, such as an association between increased repression of anger and the diagnosis and development of cancer (Schlatter & Cameron, 2010; Thomas et al., 2000) or such as experimentally induced anger suppression amplifying pain sensitivity in both healthy and chronic pain patients (Burns et al., 2008; Quartana & Burns, 2007). Therefore, the ultimate effect of combat training may be to teach how to down-regulate as well as up-regulate anger in a contextual and idiosyncratic manner, according to the a-priori state of soldiers. Thus, LG soldiers who a-priori displayed an emotionally unbalanced pattern of response and increased anger, at the end of training they showed a HG pattern of response. At the same time, a-priori HG soldiers who were possibly repressing their expression of anger showed a decrease in gain and increase in reported anger. In this regards, while clear and distinct differences were apparent between LG and HG soldiers at the first time-point, no such differences appeared at the second time-point. Together the findings presented here may suggest that combat training aims to generate soldiers with a rather uniform response to

emotional perturbations, eliminating or decreasing their a-priori individual differences. Nevertheless, we do not actually know if there was explicit anger management training during the one year period of combat-training. Therefore, even though we had a control group of civilians, there is indeed a possibility that the results obtained among the soldiers are in fact not the results of the training regime, but rather a result of a natural adaptation to the exposure to salient emotional experiences that we may assume occurs during combat training. An additional alternative explanation for the changes found in the soldiers group could be regression to the mean, and since the control group did not consist of soldiers who did not undergo combat-training, the control group does not entirely refute this possibility. Future studies should aim to reproduce and confirm the stoic postulation compared to mere exposure, as well as add a control group, and test whether this may be the case for other institutionalized or pedagogical socio-cultural practices.

6.4.2. A progressive outlook on cultural neuroscience

Both Sherman (2007) and especially Darash (2005) emphasize the links between psychology, biology and culture, in that small-scale cultural environments such as the military practice can redesign a new body with a new mind, resulting in "local biologies". This later term, defined by Lock (Lock & Kaufert, 2001; Lock & Nguyen, 2010), refers to the mutual influences between the three core systems of human life, mind body and society, and underlines the fundamental change that soldiers undergo during their training. This formulation is primarily based on the general socio-cultural notion of "habitus" introduced by Bourdieu (1977) that professional and pedagogical practices continuously redesign an individual's internal psycho-biological dispositions, orchestrating lasting effects on the shape and form in which that individual perceives the world and reacts to it.

Markus and Kitayama's (1991) prominent psychological analysis has set the stage for investigating the socialization of emotions via the integration of one's mind or self and culture. Subsequently, with the advent of neuroimaging techniques such as fMRI, the subfield of

cultural neuroscience has generated evidence that humans neural processing of emotional stimuli differ cross-culturally. For example, Japanese and Caucasian Americans in their respective home country have greater amygdala response to fearful faces by members of their own cultural group (Chiao et al., 2008) Interestingly, Koreans reported experiencing more empathy and had stronger activation in TPJ, a region associated with mental state inference (Denny, Kober, Wager, & Ochsner, 2012), for stimuli involving their own cultural group members in pain compared to Caucasian Americans in pain while Caucasian Americans had the reverse pattern of TPJ activation (Cheon et al., 2011). Many similar investigations focus on cross-cultural differences in neural processing. In parallel other conceptualizations suggest instead to categorize individuals based on cultural personality dimensions such as individualism-collectivism, which has shown particularly reliable findings on various mental processes (Chiao et al., 2010).

The current study advocates a progressive view of socio-cultural differences which is determined not only by large-scale stable affiliations (e.g. Westerners vs. Easterners), but also within small-scale changing environmental surroundings, such as between civilians and soldiers, taxi-drivers and PhD students. It seems intuitive that such local biologies would have an impact on the response and subsequently the neural processing of emotional episodes. Though several theoretical considerations of cultural neuroscience as a field have previously echoed the importance of socio-cultural practices (Choudhury, 2010; Domínguez D., Lewis, Turner, & Egan, 2009; Kitayama & Uskul, 2011), experimental evidence is scarce. The only evidence except the current study found by this author is a study on gender differences in neural processing of compassion within the police force (Mercadillo, Alcauter, Fernández-Ruiz, & Barrios, 2015). The police force was assumed to reflect a socio-cultural practice that promotes specific codes of conduct intended for collective safety that should influence compassion. Results suggested than men and women are similarly influenced by police culture regarding the empathic behavioral expression of compassion. However, women manifested

more insular and prefrontal cortical activation, suggesting a more empathic experience of compassion. Interesting as these results may be, since there was no control group and it was not a prospective design it is unclear whether these results are a direct influence of police culture or general gender differences known to exist in empathic processing (Derntl et al., 2010; Schulte-Rüther, Markowitsch, Shah, Fink & Piefke, 2008). Though requiring further statistical support, results found here point at the possible modulation of vmPFC functionality following combat training in LGs, evident only for soldiers and not for civilians.

6.4.3. Concluding remarks

Though limited, the influence of combat-training on neural processing related to emotional systems has been reported before. In a pilot study comparing two soldiers at the end of training with two soldiers at the beginning of training, greater activation in premotor/prefrontal cortex, posterior parietal cortex, and posterior temporal cortex was found for the later over the former (Ćosić et al., 2012). Other studies focusing on task performance compared the neural response to emotional stimuli of elite SEAL combatants with healthy civilians, reporting differential activation of the insula and frontal cortex (Paulus et al., 2010; Simmons et al., 2012). To date however no systematic study tested in a prospective design the influence of combat-training on the neural response to emotional experiences. We found a differential pattern of activation across time-points between the soldiers and civilians in the caudate head which is part of the dorsal striatum. This region has previously been associated with motor, memory and addiction (Berke & Hyman, 2000; Seger & Cincotta, 2005; Voermans et al., 2004) as well as in processing of reward and emotions (Bartels & Zeki, 2000; Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009; Haruno & Kawato, 2006). However, since results indicate that the change was apparent mostly in the civilians' group activation rather than that of the soldiers, and since we found no relationship between activation in this region and other dependant measures obtained in this research program, it would be irresponsible to attempt an interpretation of the meaning of this

result. This underlines the critical limitation of this study - results were generally of low statistical power and marginal, probably due to the small sample size that ultimately participated in both time-points of this study. Therefore, this study desperately necessitates further replication and investigation. Notwithstanding, it offers a paradigmatic conceptualization of the influence of military pedagogy on neural and emotional processing, as on the integration of disparate fields of study such as psyho-biology and sociology / anthropology. Applying this conceptual framework to the study of emotions reverberates with modern psychological constructionist theories (Barrett, 2009) and allows a rapprochement to the subjective qualia-like characteristic of emotions.

7. OBJECTIVE 4: Unveiling the relation between neurobehavioral indices of anger and combat-training stress symptoms

**** Excerpts from the current chapter were published in:**

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7.1. Introduction

The tendency to have uncontrolled angry outbursts accompanied by aggressive behaviors is an important feature of various anxiety and stress related disorders and most notably in PTSD (American Psychiatric Association, 2013; Olatunji et al., 2010). Research suggests that patients with traumatic and chronic stress related symptoms suffer from a profound difficulty in regulating their anger (Chemtob, Hamada, Roitblat, & Muraoka, 1994; Novaco & Chemtob, 2002), especially when interacting with other people (Beckham et al., 2000; Carroll, Rueger, Foy, & Donahoe, 1985; Jordan, Marmar, Fairbank, & Schlenger, 1992; Miles, Menefee, Wanner, Tharp, & Kent, 2015), during which even little provocation has shown to lead these patients to behave violently towards others (Beckham, Feldman, Kirby, Hertzberg, & Moore, 1997; Jakupcak & Tull, 2005; MacManus et al., 2015; McFall, Fontana, Raskind, & Rosenheck, 1999). Since anger is a major precursor to aggression and violence (Davidson et al., 2000; Gilam & Hendler, 2015; Rosell & Siever, 2015; Siever, 2008), it is possible that these patients are prone for such aberrant behaviors because of their poor capability to cope with anger-provoking interpersonal situations.

Using an interactive and realistic anger-provoking paradigm based on an anger-infused UG (section 4.2.2.), it was shown (chapter 4) that individuals with a tendency for aggressive reactions (i.e. rejecting angering unfair offers thus gaining less money throughout the game) were angry and had greater activation in a region of the BS corresponding to the LC and less activation in an anterior region of the vmPFC, while individuals with a tendency for conciliatory reactions (i.e. accepting angering unfair offers thus gaining more money throughout the game) had an emotionally

balanced response and the reverse pattern of brain activation – greater vmPFC and less BS/LC activation. This reverse pattern of activation led to the suggestions that the vmPFC is involved in regulating LC related arousal and aggressive reactions towards anger provocations. Interestingly, it was shown (chapter 5) that high amygdala gFC during rs-fMRI before the anger-infused UG predicted higher conciliatory reactions and lower reported anger in the game. There was also an increase in amygdala-IFG FC in the aftermath of the angering experience which is suggested to reflect a neural process associated with angry rumination.

The LC is the major source for noradrenalin (NA) secretion in the forebrain, critically involved in autonomic arousal and stress response (Berridge, 2008; Valentino & Van Bockstaele, 2008), and has been shown to have a specific role in propagating aggression (Haden & Scarpa, 2007; Haller, Makara, & Kruk, 1997). It was suggested that the LC-NA system represents a reorienting/alarm system in charge of averting attention towards and modifying behavior in view of salient, mostly threatening stimuli in the environment (Berridge & Waterhouse, 2003; Corbetta, Patel, & Shulman, 2008; Liddell et al., 2005; Sara & Bouret, 2012). Consistently, dysfunction in the LC-NA system has been associated with prototypical stress symptoms such as hyperarousal, hypervigilance and aggression (Arnsten, Raskind, Taylor, & Connor, 2015; Aston-Jones, Valentino, Van Bockstaele, & Meyerson, 1994; Berridge & Waterhouse, 2003; Southwick et al., 1999).

The vmPFC has been generally implicated in emotion regulation (Etkin, Egner, & Kalisch, 2011; Gross, 2015; Phillips et al., 2008; Quirk & Beer, 2006), including regulating anger and aggressive reactions (Davidson et al., 2000; Gilam & Hendler, 2015; Rosell & Siever, 2015; Siever, 2008), and was shown to be an important region displaying structural and functional abnormalities associated with increased stress symptoms (Admon, Milad, et al., 2013; Pitman et al., 2012). Moreover, vmPFC dysfunctionality in PTSD patients was associated with abnormal processing of emotions, especially fear (Etkin & Wager, 2007; Milad et al., 2009). Congruently, a leading psycho-biological model for the development and maintenance of stress symptoms has postulated an underlying dysfunctionality in the neural circuit subserving emotion and arousal regulation (Frewen

& Lanius, 2006; Pitman et al., 2012; Seligowski, Lee, Bardeen, & Orcutt, 2015), with the vmPFC playing a key role in such a circuit.

Interestingly, both vmPFC and IFG are involved in exerting regulatory control over the amygdala, in both healthy and patient samples (Etkin et al., 2015; Pitman et al., 2012). Recent meta-analyses on PTSD neuroimaging studies indicated that the bilateral amygdala together with the ACC were the most hyper-activated regions, whereas the vmPFC and right IFG were the most hypo-activated regions (Hayes, Hayes, & Mikedis, 2012; Patel, Spreng, Shin, & Girard, 2012). Moreover, several longitudinal and prospective studies indicate that abnormal amygdala functionality represents a predisposing risk factor for the development of PTSD symptoms (Admon et al., 2013). Therefore in PTSD hyper-responsive amygdala is thought to account for the exaggerated fear responses and the persistence of traumatic memories (Pitman et al., 2012). As described earlier (section 5.4.), based on extensive animal and human research, the amygdala is a core limbic structure that has a major role in mediating responses to emotionally and mostly threatening stimuli by orchestrating sensory and attentional resources (Davis & Whalen, 2001; Kober et al., 2008; Pessoa & Adolphs, 2010; Phelps & LeDoux, 2005). The amygdala was thus suggested as having a role in mediating angry experience and subsequently contributing to reactive aggression (Rosell & Siever, 2015).

Although there seems to be a correspondence between the neural circuits involved in processing anger during and after its provocation and those which are dysfunctional among patients with stress symptoms, studies to date have not yet investigated the neural trajectory of anger in relation to the development and manifestation of such symptoms. And since the development of stress symptoms is uniquely dependent on exposure to an acute or chronic stressful experience, such an investigation coincides with the opportunity to disentangle predisposing (pre-exposure) from acquired (post-exposure) neural abnormalities. Within this framework, recent reviews of PTSD prospective studies (Admon, Milad, et al., 2013; DiGangi et al., 2013; Schmidt et al., 2015) point out various pre-trauma risk factors for PTSD, including personality, environmental, genetic and

non-genetic molecular, and neural factors. Though only handful of such prospective studies on populations at risk of stress-exposure tested the involvement of anger, there is initial evidence suggesting that unbalanced levels of pre-exposure anger and aggressive tendencies are not only a consequence of, but may also causally contribute to the development of stress symptoms (Heinrichs et al., 2005; Lommen, Engelhard, van de Schoot, & van den Hout, 2014; Meffert et al., 2008; van Zuiden et al., 2011). However, these few studies assessed anger using self-reported questionnaires and not actual behavior during a provoking interpersonal situation. Therefore, the relationship between stress symptoms and individual differences in coping with anger, and specifically the neural correlates associated with reactivity towards and regulation of angering provocations, remains largely overlooked.

To directly investigate the relationship between the neural and behavioral indicators of interpersonal anger and the development and manifestation of stress symptoms, the current prospective brain-imaging study compared these neurobehavioral indicators before and after military combat-training. Combat-training is a highly intense period of chronic stress (Bernton et al., 1995; Day & Livingstone, 2001) impacting the development of stress-related symptoms (Lin et al., 2015; Taylor et al., 2007). Moreover, severe anger has been mostly, though not solely, associated with military personnel and veterans (McHugh et al., 2012). Therefore, measuring brain activation related to conciliatory or aggressive behavior during an interpersonal angering situation as well as stress symptoms before and after combat-training, and examining the relationship between them, may reveal neurobehavioral indicators of anger that predict the development of stress symptoms and/or change following exposure to combat-training related chronic stress. This may consequently shed some light on the functional role of anger in post-traumatic stress and may thus provide a neural basis for the development of therapeutic tools focused on coping with anger.

As part of the current prospective research program, participants were the same a-priori healthy soldiers recruited to a combat-unit in the IDF, whose behavioral and neural responses were measured at two time-points: during the first two-weeks of boot-camp (pre-exposure) and

approximately one year later at which they were about to complete their training program (post-exposure; Section 3.2.1., Figure 3.2.). The same age-matched group of civilians recruited from Israeli civil-service programs was used to control for nonspecific time effects, as detailed above (section 3.2.2.). To reiterate, at each time-point, participants undergoing fMRI performed the anger-infused UG and an rs-fMRI procedure before and after the anger-induction task. Pre-exposure results (extensively reported above in chapters 4 and 5) indicated no differences between soldiers and civilians in any of the neurobehavioral measurements related to anger. Here post-exposure results are reported in light of these pre-exposure findings, focusing on group differences between soldiers and civilians. It was generally expected to replicate findings from the pre-exposure time-point indicating that all participants accepted less unfair offers than fair offers, reported on angry feelings as the predominant emotional experience throughout the UG, especially for unfair offers, and that there was a relationship between the reported emotional experience and total-gain. Specifically for the soldiers, an increase in stress symptoms post-exposure to combat-training was expected, and that the neurobehavioral measures of anger revealed pre-exposure (such as total-gain and vmPFC and BS/LC activation during unfair offers) and the change in these measures between pre and post exposure, will correlate with stress symptoms measured post-exposure.

7.2. Materials and methods

7.2.1. Participants

As detailed above (section 6.2.1.), a total of 46 participants, 29 combat soldiers (age 18.86±1.06 at time-point 1) and 17 civilians (age 18.24±0.44 at time-point 1) volunteered to take part in both time points of this prospective study. Combat-training in these soldiers' unit, which includes various psychological and physical practices such as strictly enforced discipline, food and sleep restrictions and survival challenges, has been shown to induce elevated stress symptoms (Lin et al., 2015).

7.2.2. Procedure

Anger was induced using the anger-infused UG and a post-scan emotional report was used to measure the induced emotional experience, both of which have been described above (section 4.2. and section 6.2.2.). In addition, brain signals were also recorded from two rs-fMRI session before and after the anger-induction task (section 5.2.2.).

7.2.3. Stress symptoms questionnaires

The PDS (Foa, 1995; Foa et al., 1997; McCarthy, 2008; section 3.3.6.) assesses stress symptoms following specific traumatic events. After reporting on such an event respondents rate 17 stress symptoms items experienced in the past month in relation to this event, on a four-point frequency scale from 1 (not at all) to 4 (almost always).

The PCL – military version (Forbes et al., 2001; Weathers et al., 1993; section 3.3.7.) assess stress symptoms experienced specifically in relation to military experiences. Respondents rate each of 17 stress symptoms items on a 5-point frequency scale from 1 (not at all) to 5 (extremely), indicating the extent to which they have experienced a specific symptom during the past month of military service. This measure was evaluated only for the soldiers after combat-training.

7.2.4. fMRI preprocessing and analysis

Preprocessing of the anger-infused UG is detailed above (section 6.2.3). The final sample for analyses for this type of data for both time-points included 20 soldiers and 15 civilians. To reiterate, data for the first time-point was based on a GLM in which eight regressors were used for each period of the game (offer, decision, result, negotiation; Figure 4.1.), repeated twice to differentiate between fair and unfair rounds. These regressors were convolved with a canonical hemodynamic response function. Additional nuisance regressors included the head-movement realignment parameters and the time course of averaged activity in cortical white-matter. The fixation period was used as baseline. Data for comparison of the two time-points was based on a separate GLM

which included an additional duplication of the eight task regressors representing the second time-point. In both GLMs, beta values were averaged across the entire ROI voxels and for each experimental condition separately. Statistical analysis was conducted on the unfair-offer periods which were shown to induce more anger. Notably, the whole brain GLM combining both time-points revealed only two significant clusters of brain activation (section 6.3.3.) and both did not relate to stress symptoms (p-values>0.566). Therefore, analysis of the anger-infused UG focused on analysis of ROIs related to anger identified in the first time-point as detailed above (section 6.2.4.), namely the vmPFC, BS/LC and dpI.

Preprocessing and data parecellation of the rs-fMRI in the second time-point followed the exact same steps as performed for the first time-point detailed above (section 5.2.). Subsequently, values of the gFC^{+} of right amygdala and FC coefficient for the right amygdala – right IFG connection were extracted for both rs-fMRI sessions for each participants. The final sample for analyses of this type of data for both time-points included 14 soldiers and 9 civilians.

7.3. Results

7.3.1. Symptomatic effects of combat-training

In line with expectation, based on the PDS score a marginally significant increase in symptoms was observed in the soldiers group when comparing pre- (0.24±0.83) and post- (1.79±4.35) exposure to combat-training (Z=1.86, p=0.063; Figure 7.1.A.). There was no such change in the civilian group between pre- (0.65±1.54) and post- (0.29±1.21) exposure to civil-service (Z=1.34, p=0.180). Based on the PCL, soldiers showed an average symptoms-score of 28.38±11.55, ranging from asymptomatic to moderate stress symptoms levels (Figure 7.1.B.).

7.3.2. Anger induction related behavior and emotional report

To assess behavior in the anger-infused UG acceptance rates (in percentage) were averaged for each fairness category (fair/unfair). In line with standard UG results and similar to the pre-exposure time

point, fair offers (80.43±28.61) were accepted more than unfair offers (21.43±24.60), as noted by a main effect of fairness ($F_{1,44}$=217.29, p<0.001, η_p^2=0.83; Figure 7.2.A.). This result did not differ between soldiers and civilians ($F_{1,44}$=1.11, p=0.300, η_p^2=0.03) and for both groups this result did not change when comparing these participants between time-points ($F_{1,44}$=0.43, p=0.518, η_p^2=0.01). Next, the total-gain accumulated throughout the entire game was calculated and used that as an objective measure of individual differences reflecting the final outcome of the modified-UG. Similar to the first time-point, total-gain and overall acceptance rates were highly correlated (r=0.949, p<0.001).

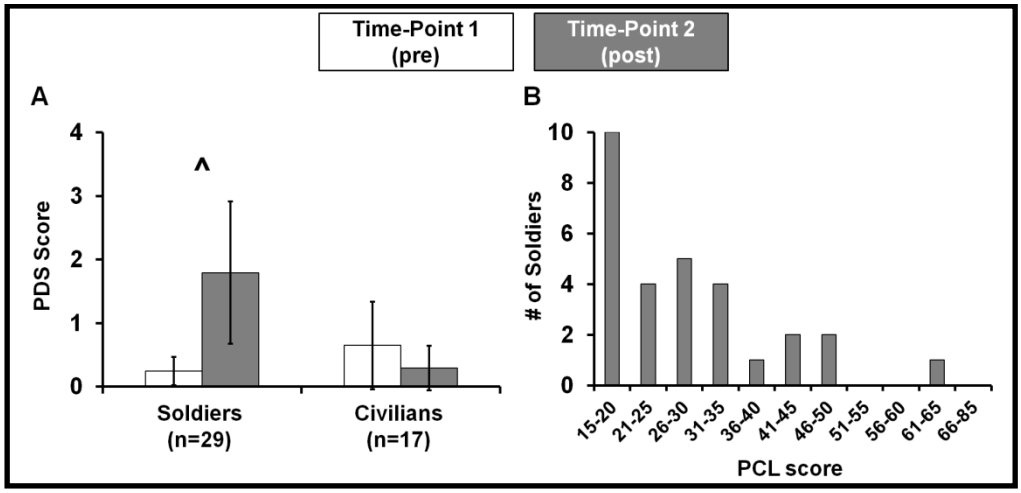

Figure 7.1. Stress symptom levels assessment. (A) Differences in stress symptoms scores between the two time-points for the soldiers and civilians as measured with the PDS. White bars indicate the first time-point and gray bars indicate the second time-point. Soldiers showed a marginal increase in PTSS (p=0.063 indicated by ^) while no change was apparent for civilians (p=0.180). (B) Distribution of stress symptom scores as measured with the military version among soldiers at the second time-point.

To revalidate the overall anger induction, the average reported emotions for all UG-rounds was examined based on the two GEW-axes of potency (high/low) and valence (positive/negative) and a significant potency by valence interaction was found ($F_{1,44}$=32.44, p<0.001, η_p^2=0.42; Figure 7.2.B.). Follow-up analyses indicated that the anger-cluster was the most reported category of emotions (1.69±1.34), compared to all other categories (p-values<0.001). In addition, there was no difference between the two positive clusters (high-potency=0.92±0.88; low-potency=0.90±0.77; p=0.998). This result did not differ between soldiers and civilians ($F_{1,44}$=0.01, p=0.914, η_p^2=0.00)

and for both groups this result did not change when comparing participants between time-points ($F_{1,44}$=0.45, p=0.507, η_p^2=0.01).

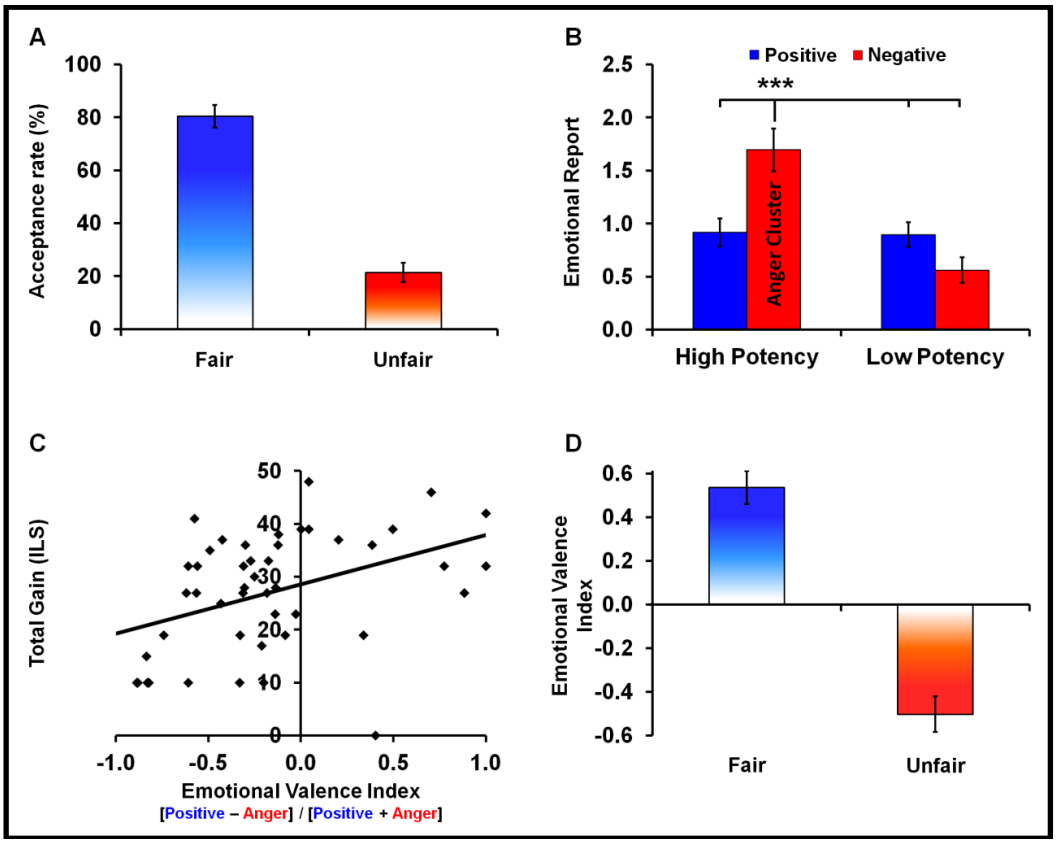

Figure 7.2. Anger induction related behavior and emotional report at the second time-point. (A) Participants playing the anger-infused UG accepted fair offers more than unfair offers (p<0.001). (B) A significant interaction (p<0.001) indicated that participants' emotional experience was mostly associated with angry feelings (p<0.001 for each comparison with the other clusters, indicated by *). (C) As participants reported a more positive and less angered emotional experience in the game, calculated as the Emotional Valence Index (EVI), so they had a higher total-gain (r=0.412, p=0.004) indicating more gain accumulated throughout the game. (D) Based on the EVI, fair offers were associated with more positive and less angry feelings while unfair offers were associated with more angry and less positive feelings (p<0.001). None of these results differed between soldiers and civilians, neither at the first time-point nor across time-points. In all results presented here sample size n=46.

The EVI was next calculated. A positive EVI indicated that more positive and less anger emotions were reported while a negative EVI indicated the reverse. The correlation between EVI and total-gain was examined to assess the relationship between the behavior and the emotional experience. For all participants, a more positive EVI correlated with greater total-gain (r=0.412, p=0.004; Figure 7.2.C.). In addition a significant difference was found between average EVI of fair (0.54±0.51) and unfair (-0.50±0.54) offers (t_{45}=12.59, p<0.001, *Cohen's d*=1.02; Figure 7.2.D.), indicating that unfair offers elicited more angry and less positive feelings and the opposite pattern for fair offers. Taken together, results indicated that similar to the pre-exposure time-point and in-

line with expectations, in the post-exposure time-point there was a relationship between behavior in the game and the corresponding emotional experience that validated the anger induction and did not differ between soldiers and civilians.

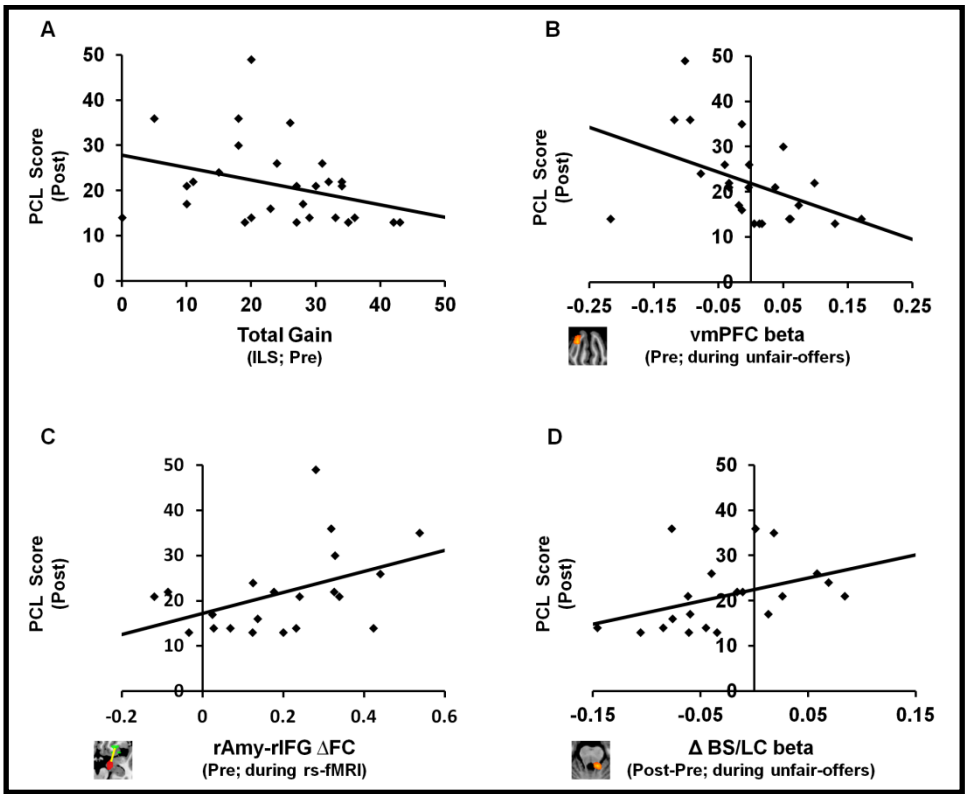

Figure 7.3. The relationship between soldiers' stress symptoms and their neurobehavioral indices of anger. (A), (B) and (C) show that lower PCL scores post combat-training was predicted by pre combat-training higher total-gain (ρ= -0.450, p=0.014, n=29), higher vmPFC activation during unfair-offers (ρ= -0.524, p=0.009, n=24) and higher amygdala-IFG ΔFC between rs-fMRI sessions (ρ= 0.459, p=0.036, n=21), respectively. (D) Higher increase in BS/LC activation during unfair-offers between pre and post combat-training (calculated as post – pre) was related to higher PCL scores post combat-training (ρ=0.495, p=0.027, n=20).

7.3.3. The relationship between soldiers' stress symptoms and neurobehavioral indices of anger

A potential methodological confound may exist in correlations between anger and stress symptoms measures since physical reactions, anger, hypervigilance and startleness are all anger and aggression concomitants as well as being symptoms of post traumatic stress symptoms (Jakupcak et al., 2007; Novaco & Chemtob, 2002). To avoid circularity between measures and refute this possible confound these symptoms' items (#5, #14, #16 and #17) were removed from the PCL score. First, the correlations between behavioral, emotional and brain indices of anger pre-exposure as measured by total-gain, EVI, vmPFC and BS/LC activation during unfair offers and soldiers' stress symptoms post-exposure as measured by the PCL score were assessed. Higher PCL score post-exposure

significantly correlated with lower total-gain (ρ=-0.450, p=0.014, n=29; Figure 7.3.A.), with lower vmPFC activation during unfair-offers (ρ= -0.524, p=0.009, n=24; Figure 7.3.B.), and with high amygdala-IFG ΔFC between rs-session (ρ= 0.459, p=0.036, n=24; Figure 7.3.C.). To assess whether the change in the same anger indices between post- and pre-exposure had a relationship with soldiers' stress symptoms post-exposure a difference score was calculated for each index between post- and pre-exposure and then the correlation with PCL score post-exposure was tested. Higher PCL score post-exposure significantly correlated with a greater increase in BS/LC activation during unfair offers between post- and pre- exposure (ρ= 0.495, p=0.027, n=20; Figure 7.3.D.) and had a marginally significant correlation with a greater increase in total-gain (ρ= 0.351, p=0.067, n=24). No other significant results were found (p-values>0.176).

7.4. Discussion

Embedding dynamic social interactions within the classic UG paradigm allowed inducing naturalistic anger, especially during the unfair offers, in both civilians and soldiers across two time-points. Moreover, in both time-points participants gaining more money along the game reported less anger as well as more positive feelings, suggestive of the idiosyncratic link between the subjective emotional experience and the tendency to accept or reject anger-infused UG-offers. In line with the hypothesis, an increase, though marginal, was found in stress symptoms among a-priori healthy soldiers over a one-year period of combat training assumed to induce chronic stress, whereas a similar period of civil service did not have such an influence on a matched group of civilians. Importantly, and further confirming the hypothesis, game related behavior and brain activation, as well as post-game neural traces reflected in FC, were found to correlate with the degree of stress symptoms among soldiers following combat-training. Specifically, as soldiers gained more money throughout the game, had more vmPFC activation during unfair offers pre-exposure and had a smaller increase in amygdala-IFG connectivity, so they reported less symptoms following combat-training. In addition, more symptoms among soldiers correlated with a larger increase in BS/LC

activation during unfair offers over time (between pre- and post- combat-training). These findings provide unique causal evidence that functionality of the vmPFC and BS/LC, as well as the amygdala and IFG, all major nodes in emotion and arousal regulation, contribute to the overall vulnerability of individuals to combat-training stress symptoms. Critically, the trajectory of this vulnerability is portrayed in a specific context of interpersonal anger, a critical symptom in anxiety and stress related disorders, thus providing an ecological framework for possible therapeutic intervention.

7.4.1. Neural activation indices of anger during provocation as cause and consequence of stress symptoms

The findings of this prospective neuroimaging study support the suggestion that stress symptoms are characterized by an underlying dysfunctionality in the neural circuit subserving emotion and arousal regulation (Frewen & Lanius, 2006; Pitman et al., 2012; Seligowski et al., 2015). However, they also extend the understanding of the neural mechanisms that mediate the development and manifestation of stress symptoms in several novel aspects. First, since vmPFC activation predicted stress symptoms, in addition to the commonly demonstrated acquired neural abnormality of vmPFC following PTSD (Admon et al., 2013), it is possible to claim that vmPFC functionality may also serve as a predisposing risk-factor for the development of stress symptoms among soldiers exposed to combat-training. Strikingly, this predictive sensitivity of the vmPFC is demonstrated in a context of an angering interpersonal situation rather than the commonly studied context of fear (e.g. Etkin & Wager, 2007), which might explain why such a finding is currently absent from prospective neuroimaging studies on PTSD development (Admon et al., 2013). This also suggests that enhanced vmPFC activation which possibly reflected anger-regulation capabilities might buffer the accumulating influence of stress on the development of symptoms. This is consistent with previous more general findings indicating that emotion dysregulation is predictive of the development of

post-traumatic stress symptoms (Bardeen, Kumpula, & Orcutt, 2013; Kumpula, Orcutt, Bardeen, & Varkovitzky, 2011).

Second, when comparing the two time points, BS/LC activation which seemed to reflect arousal and aggression, increased following exposure proportionately to the level of stress symptoms following combat-training. Assuming that BS activation indeed corresponds to the LC, this is the first indication in humans of a causal relationship between alterations in the LC-NA system following chronic stress and the development of stress symptoms among a-priori healthy individuals. This result is congruent with previous findings showing enhanced reactivity of the LC-NA system in a validated rat model of PTSD (George et al., 2013). Moreover, a recent fMRI study in humans indicated increased LC activation during direct compared to indirect eye-gaze of a virtual character, in PTSD patients but not in healthy controls (Steuwe et al., 2014). Taken together the findings support the suggestion that prototypical stress symptoms such as increased arousal, vigilance and aggression are attributed to an acquired neural dysfunction and specifically heightened reactivity in the LC-NA system (e.g. Berridge & Waterhouse, 2003).

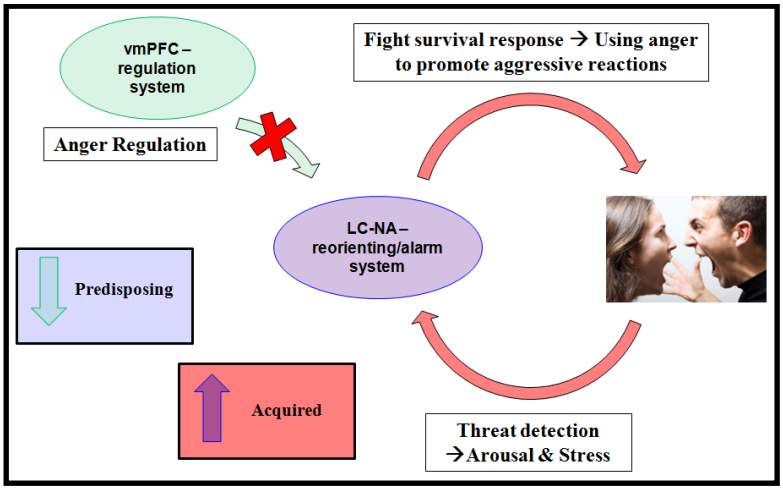

Figure 7.4. A speculative model for the role of anger during provocation in PTSD. The LC-NA system detects threat and generates arousal and stress response which lead to a survival mode that uses anger to promote aggression. Such a system evolved to respond to physical threats but possibly through enculturation also to interpersonal threat. The vmPFC is functionally and anatomically connected with the LC-NA system and through its regulatory capabilities may exert control over it. In PTSD the threshold for threat detection is lowered causing enhanced responsiveness of the LC-NA system leading to angry outbursts and aggression even in view of mild interpersonal provocations. If a-priori the vmPFC regulatory system is malfunctioning than this would further boost the proneness to such outbursts.

Taken together, result support the proposition that angry outbursts as a stress symptom might represent a failure to regulate low level reactivity to threat, and this reactivity in itself might be

excessive due to lowered threshold of threat detection (Chemtob, Novaco, Hamada, & Gross, 1997; Chemtob, Novaco, Hamada, Gross, & Smith, 1997; Figure 7.4.). Within such a framework, the LC-NA system which is involved in averting attention and modifying behavior in view of threatening stimuli, would be in charge of executing aggressive reactions and following a stress-related perturbation would be more sensitive to threat and thus more prone to such reactions. In parallel, the vmPFC which is involved in regulating angry and aggressive reactions, would possibly have more difficulty in successfully regulating these reactions due to their stress-related excess, and especially if such a regulatory role appears to be a-priori flawed. Further investigations are needed to solidify this proposition, especially in clinical populations.

7.4.2. Neural connectivity modulation in the aftermath of anger as a predictor of stress symptoms

An additional anger-related neural risk-factor for enhanced stress symptoms among soldiers exposed to combat-training is increased amygdala-IFG connectivity in the aftermath of anger. Though hyper-reactive amygdala and hypo-reactive IFG are of the most robust and consistent findings in studies comparing PTSD patients with healthy and trauma exposed controls (Hayes et al., 2012; Patel et al., 2012), amygdala-IFG connectivity as a predisposing factor is absent from prospective neuroimaging studies on stress symptom development (Admon et al, 2013), none of which have yet to consider rs-fMRI in such a prospective nature. Nevertheless, a growing number of studies consider rs-FC in PTSD patients in comparison to control groups (for a review see Peterson, Thome, Frewen, & Lanius, 2014). Such studies have demonstrated altered functional connectivity in brain regions such as the PCC/precuneus (Bluhm et al., 2009; Lanius et al., 2010; Zhou et al., 2012), thalamus (Yin et al., 2011), insula and vmPFC (Sripada, King, et al., 2012). Some studies (e.g. Lanius et al., 2010; Zhou et al., 2012) have shown that altered rs-FC between PCC and amygdala could be used as a prognostic index of symptomatology.

Several studies focused on altered amygdala connectivity (Brown et al., 2014; Sripada, Wang, Sripada, & Liberzon, 2012; Zhang, Zhang, Wang, Li, & Zhang, 2016) showing large scale

differences in amygdala FC and a specific weaker connectivity between amygdala and IFG among PTSD patients compared to controls. This finding is of specific interest in view of the result presented here which indicated that an increase in pre-exposure levels of amygdala-IFG connectivity following an emotional experience in a-priori health participants predicted more combat-training induced stress symptoms. Though participants' characteristics are obviously different between studies on PTSD patients and the current study, the results of the current study seem to be inconsistent with those previously found. However, unlike previous studies who analyzed rs-fMRI without an emotional context, here connectivity was examined during rs-fMRI before and after an emotional experience. Within this context, amygdala-IFC connectivity is suggested to be related to rumination and specifically about an angering event (section 5.4.).

PTSD patients are frequently troubled by incessant ruminative thoughts related to the traumatic events that led to their condition (American Psychiatric Association, 2013). While rumination is commonly attributed to the re-experiencing cluster of symptoms (e.g. Orth & Wieland, 2006), some theorists argue that intrusive memories about the trauma (re-experiencing) is functionally different than repetitive thinking about it (rumination; Ehlers & Clark, 2000; Joseph, Williams, & Yule, 1997; Speckens, Ehlers, Hackmann, Ruths, & Clark, 2007). It was postulated that rumination serves as a maladaptive strategy to avoid intrusive memories, therefore inhibiting the possibility to recruit adaptive coping strategies and subsequently leading to more of these intrusions (Ehlers & Steil, 1995). In support, several studies indicated rumination as a powerful predictor of persistent symptomatology (Clohessy & Ehlers, 1999; Murray, Ehlers, & Mayou, 2002; Nolen-Hoeksema & Morrow, 1991; Steil & Ehlers, 2000) over and above what could be predicted from initial symptom levels (Ehlers, Mayou, & Bryant, 1998; Ehring, Frank, & Ehlers, 2007), and it was also shown that rumination itself may trigger intrusive memories (Bennett & Wells, 2010; Michael, Halligan, Clark, & Ehlers, 2007). To date, only two studies aimed to integrate the relationship between anger, rumination and PTSD, resulting in inconsistent findings. In the first study, rumination was found to mediate the relationship between PTSD symptoms and anger (Orth et al., 2008) while in the second

no relationship was found between the three (Germain, Kangas, Taylor, & Forbes, 2016). Assuming the increased amygdala-IFG connectivity in the aftermath of anger indeed related to angry rumination, the results found here are the first to provide a causal neural link between anger, rumination and stress related symptomatology.

7.4.3. Disentangling predisposing from acquired neural abnormalities of PTSD

A model which aimed to disentangle predisposing from acquired neural abnormalities of PTSD was recently proposed (Admon et al., 2013), highlighting hyperfunction of amygdala and dorsal anterior cingulate cortex as predisposing factors and vmPFC-hippocampus hypoconnectivity as an acquired factor, with the insula, dorso-medial PFC and Nucleus accumbens (NAcc) suggested as possible mediators. The model was based on several research approaches most of which implemented paradigms such as viewing neutral and emotional faces or pictures. Only one prospective study implemented an interactive game, tapping into individuals' sensitivity to risk and reward, revealing that an acquired imbalanced relation between amygdala and NAcc best predicted stress symptoms following exposure to combat (Admon, Lubin, et al., 2013). The current study introduces yet another interactive paradigm, emphasizing the importance of social interactions in emotional experiences (Gilam & Hendler, 2016), and inducing genuine anger and aggressive retributions. This is especially important since it allowed to test for predisposing and acquired neural factors in a demanding and anger-provoking dynamic interpersonal situation that imitated real-life occurrences in which PTSD patients are prone for emotion dysregulation and maladaptive behavior. It is thus argued that to fully untangle the circular relation between trauma/stress and related psychopathologies, one should deconstruct psychological manifestations by their process domain and examine brain functionality in the relevant context (e.g. risk and reward, interpersonal anger). Such a context-dependant neurobehavioral approach may advance the characterization of trauma induced psychopathology and assist in tailoring personalized interventions in psychiatry, for example using neurofeedback (Keynan et al., 2016).

7.4.4. Concluding remarks

The results presented here support previous findings based on self-report questionnaires (Heinrichs et al., 2005; Lommen et al., 2014; Meffert et al., 2008; van Zuiden et al., 2011) that anger dysregulation has a specific contribution to stress symptoms, not only as a consequence of but also as a possible cause for their development. A step forward was taken by inducing interpersonal anger using a dynamic social-interactive paradigm and measuring its behavioral and neural concomitants, as well as its neural carryover effects, revealing specific anger-related brain activations and connectivity patterns sensitive to the development and manifestation of stress symptoms. Notwithstanding, several important limitations must be considered. The neurobehavioral indices of anger explained only about a third of the variability in combat-training stress symptoms, leaving a portion of variability to factors such as genetic predispositions which were not assessed (Lin et al., 2016). Additionally, the specific characteristics of the current sample, being rather small in size, all of male gender from a military cohort and reflecting stress symptoms following combat-training and not actual traumatic events, may limit the generalizability of these findings to clinical conditions and should be addressed in future studies. Nevertheless, the study revealed the importance of understanding functional impairment in sub-clinical symptomatic populations (Cukor, Wyka, Jayasinghe, & Difede, 2010; Grubaugh et al., 2005; Jakupcak et al., 2007). This is especially crucial in populations with high risk of trauma exposure. In conclusion, from a therapeutic perspective, since anger restricts and impedes treatment efficacy of PTSD (Forbes et al., 2008; McHugh et al., 2012), treating anger is of high priority as it may ultimately improve also other PTSD-related symptoms. This study may hopefully provide a springboard for the development of both pre-exposure inoculation treatment for at risk populations and post-exposure process-targeted interventions for patients with acquired deficits, based on the idiosyncratic behavioral and neural indicators of maladaptive interpersonal anger.

8. GENERAL DISCUSSION

**** Excerpts from the current chapter were published in:**

Gilam G. & Hendler T. (2015). Deconstructing anger in the human brain. In *Social Behavior from Rodents to Humans: Neural Foundations and Clinical Implications*. Eds M. Wöhr & S. Krach, Current Topics in Behavioral Neurosciences, pp1-17. Springer Berlin Heidelberg.

Gilam G. & Hendler T. (2016). With love, from me to you: Embedding social interactions in affective neuroscience. *Neuroscience and Biobehavioral Reviews, 68,* 590-601.

8.1. Overview of results

The current research program set as its goal to investigate how the human brain processes anger. Yet defining anger as a single psycho-biological phenomenon has continuously posed considerable theoretical and experimental difficulties. Therefore a framework for the study of anger was delineated in order to deconstruct and then to reconstruct this complex and multidimensional phenomenon based on key elements related to the profound interpersonal and dynamic nature of anger, to the inherent regulatory processes associated with anger management, to the alteration of anger experience following socio-cultural practices that empower emotion regulation, and finally to the conditions in which anger may manifest itself pathologically. To this end a prospective design was utilized in which IDF soldiers and civil-service volunteers were recruited at the begining and towards the end of a one year period of combat-training and of civil-service, respectively. It was initially assumed that no differences would be found between these two groups of participants at the first time-point, which would serve to characterize the psycho-biological mechanisms that mediate the experience and regulation of interpersonal anger. Conversely, at the second time-point differences would emerge between the two groups, at which soldiers would exhibit empowered regulatory capabilities associated with their training as well as chronic stress related symptoms. The later would subsequently allow the examination of the relationship between neurobehavioral indices

of anger and the development and manifestation of stress symptoms. In the sub-sections that follow an overview of the results is provided, as schematically depicted in Figure 8.1., within this deconstructed framework of anger.

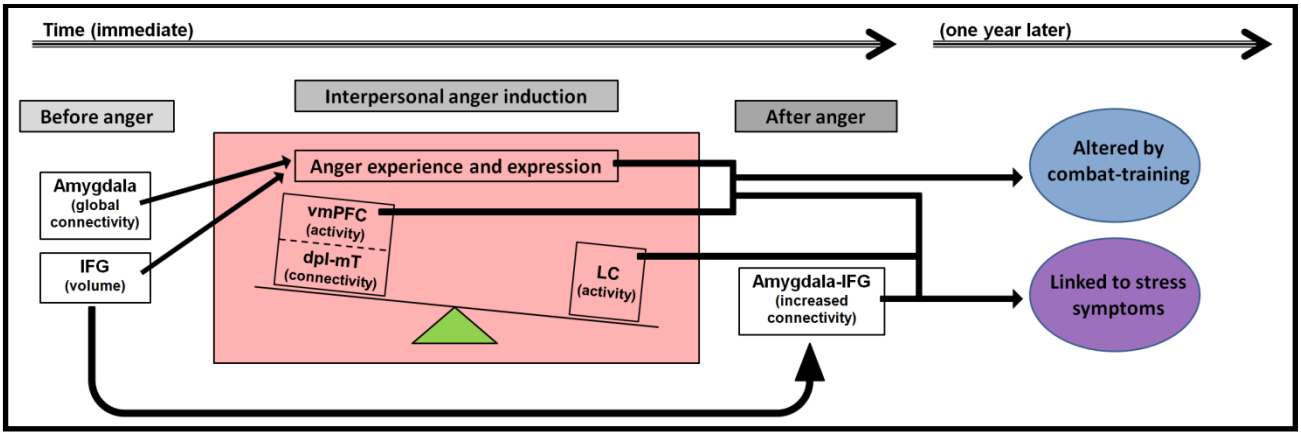

Figure 8.1. Schematic overview of results. During interpersonal anger (red square), anger experience and expression, as respectively measured by self report and monetary gain, is mediated by vmPFC and LC activity as well as dpI-mT connectivity. Regulation is achieved by balancing (green triangle) between these systems, whereby more vmPFC activity and dpi-mT connectivity attenuates LC activity and leads to less anger and aggression. Global connectivity of the amygdala and the anatomical volume of the IFG have a predisposing role in the experience and expression of anger (to the left of the red square). An increase in connectivity between these two regions in the aftermath of anger is associated with angry rumination and reflects the lingering and maladaptive effects of anger following provocation (to the right of the red square). Following combat-training, alterations in vmPFC activity and behavioral expression of anger are evident for soldiers but not civilians, indicating the malleability of these features to a pedagogical empowerment of emotion-regulation (blue circle). Finally, the vmPFC and behavioral expression of anger as well as the increased amygdala-IFG connectivity predicted stress symptoms following combat-related chronic stress, which is also in correlation with the change in LC activity following combat-training (purple circle). The black arrows indicate possible causal relations.

8.1.1. Anger experience and regulation

Characterizing the neural substrates of anger experience and regulation during a realistic interpersonal interaction by using multiple levels of measures, namely neural, physiological, behavioral and subjective measures, was the aim of the first objective (described in chapter 4 and in Gilam et al., 2015). Much effort was primarily invested in developing a naturalistic and interactive paradigm that will induce anger within the decision-making context of the UG. The UG is an ideal framework to model interpersonal conflict as it entails interdependency between two players that may have opposing goals. The bargaining nature of the game provides an opportunity to incorporate negotiations which can further escalate the conflict and evoke negative emotions, especially anger. In order to do that realistically, many training and pilot sessions were conducted with professional actors to achieve a reliable and authentic character

that would act as an obnoxious and competitive proposer, to refine the scripts that were the basis of improvisation during verbal negotiations, and to examine the agreement between these scripts and the sequences of offers played out in the UG. Furthermore, using individual differences as an objective measure, i.e. the total amount of money accumulated along the anger-infused UG, had several important implications. First and foremost, it represented the underlaying assumption that being able to accept offers and gain more money would reflect a capability to overcome the anger. Second, in the spirit of Averill's citation above (section 1.1.3.), it echoed the general notion that anger is not merely an "on"-"off" phenomenon, rather a continuum of variable responses which may have differential influences on peoples actions. In this regard much attention was directed at creating a large pool of angering categories within the negotiation phase in order to broaden the scope of anger beyond unfair treatment and underline the provocations themselves and not necessarily the form and fashion with which participants would respond to them. Third, it focused the analysis pipeline to converge other measures on an objective dependant variable reflecting actual behavior rather than self report which could be confounded by various factors such as demand characteristics. Finally, it is worth noting that the UG has been studied for more than three decades and the fact that it is one of the most well validated and replicated paradigms in the decision-making field (Güth & Kocher, 2013; van Damme et al., 2014) provided ample information to guide the development of the anger-infused UG.

The anger-infused UG was first validated in two important aspects. First, it replicated the classic UG findings in showing that as offers were more unequal so acceptance rates decreased. Second, it generated mostly angry feelings in participants' emotional report, feelings that escalated along the game and were particularly high for unfair compared to fair offers. These results confirmed hypotheses 1A and 1B, though the later only partially since no differences in sympathetic arousal were found between fair and unfair offers. Nevertheless the results were imperative to set the path and test the differences between high-gain and low-gain

participants. Interestingly, there were no differences between the two gain-groups neither in angry nor in positive feelings associated with the game, but while there were no differences between these clusters of emotion in the high-gain group, the low-gain group reported more anger compared to positive emotions. This is an important finding because it suggested that as a group the high-gain group reported being angry to an equal extent as the low gain group and thus provides important evidence indicating that the differences between the groups were not merely related to emotional reactivity rather to an internal balance between anger and positive emotions. This was further supported by showing that various personality measures related to emotional reactivity such as trait-anger and neuroticism did not differ between these groups. This result led to the calculation of a comprehensive emotional index reflecting both types of emotion-valence clusters. It was subsequently shown that as participants gained more money, they reported less angry feelings, but also more positive feelings and in addition made slower decisions and exhibited less sympathetic arousal, which supports hypothesis 1C. Moreover, in contrast to low-gain participants, high-gain participants displayed increased vmPFC and dpI activation, decreased BS/LC activation, and increased dpI-mT connectivity, especially during unfair offers, congruent with hypotheses 1D. Integrating these results, it was shown that vmPFC activity and dpI-mT connectivity contributed to increased gain, possibly by modulating the ongoing subjective emotional experience. This finding provided a model which triangulated neural, subjective and behavioral measures in the representation of anger and which could reflect a mechanism of anger regulation (see red square in Figure 8.1.). This was further supported by the correlation found between vmPFC activation and an independent personality measure of the habitual use of emotion regulation.

Considering the neural substrates of the tendency to accept anger-infused UG offers, a cluster of activation was revealed in the vmPFC which has been systematically implicated in emotion regulation, specifically in the case of controlling anger and aggressive inclinations and in particular during tasks where no explicit regulation instructions are given to participants (Davidson et al.,

2000; Diekhof et al., 2009; Etkin et al., 2015; Quirk and Beer, 2006; Rosell & Siever, 2015). On the other hand, the cluster of activation found in the BS/LC was in a sense unexpected since it is not commonly reported in fMRI studies and probably because of that it is missing from meta-analytic efforts on the brain basis of emotion (e.g. Kober et al., 2008). Though the current study was not the first to report LC's activations in fMRI studies (Steuwe et al., 2014; van Marle et al., 2010), it is argued that this brain region appeared here because of the genuine and interpersonal induction of anger. Importantly, this region has a key role in autonomic regulation and thus future neuroimaging studies should aim to further inquire into the LC's role in emotion generation and regulation and in to its large-scale functional connectivity within the brain. Finally, while meta-analytic studies on the neural structures involved in processing unfair offers commonly report activations in an anterior aspect of the insula (Feng et al., 2015; Gabay et al., 2014), here a cluster of activation in the posterior aspect of the insula was found and also showed increased connectivity with the mT. In view of these regions role in representing the internal somatic state of the body at a cortical level, the results provide initial evidence suggesting that interoceptive representation may have a direct role in shaping emotional experiences. This opens an interesting avenue of research that has been largely overlooked since it implicates an implicit interoceptive process in subjective emotional experiences, while many studies interested in interoceptive processing focus on explicit interoceptive accuracy which is associated with the AI (e.g. Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004). Together these findings support theories that place an important role for embodied states represented in the brain and body in emotional experience and expression (Barrett, 2006b; Craig, 2013; Damasio, 2010).

8.1.2. Short-term trajectory of anger - dynamic and lingering effects

The escalating and dynamic features of anger were portrayed by tracking the temporal unfolding of the reported emotional experience and using task dependant connectivity analysis (PPI) during anger provocation. In order to extend the understanding of the dynamic and

lingering effects of anger, the second objective (described in chapter 5) aimed to detect modulations in whole-brain connectivity during task-independent rs-fMRI. The data-driven analysis identified an increase in positive gFC in the right amygdala and specifically an increased in FC between the right amygdala and the right IFG. These changes in the aftermath of anger provocation (to the right of the red square in Figure 8.1.) replicated previous findings reported in the domain of rumination (Fabiansson et al., 2012; Kühn et al., 2012) and in studies investigating the influence of emotional experiences on endogenous neural processing (e.g. Maron-Katz et al., 2016). That the amygdala-IFG increase in connectivity reflected a process of angry rumination was further corroborated by showing in accordance with the literature that the extent of increase related to grey matter volume of the IFG (to the left of the red square in Figure 8.1.) and to trait anger, further illustrating the usage of multiple measures to converge results and guide interpretations. Interestingly, since this change in connectivity did not relate to actual behavior and emotional report in the anger-infused UG, it is suggested that different neural processes are engaged during the on-going emotional episode compared to in its' aftermath. This sheds new light on the understanding of the temporal unfolding of an emotional experience and may have implications in pathological conditions where emotions tend to linger on, such as in depression and anxiety disorders (Lyubomirsky et al., 2015). Notably however, amygdala's positive gFC at baseline predicted social decision-making preferences and emotional experiences (to the left of the red square in Figure 8.1.), demonstrating that individual variability may originate in neural predispositions. Here these predispositions manifested in levels of connectivity of an important limbic region which is central to core affect (Kober et al., 2008; Lindquist et al., 2012), hence providing the possibility to interpret and infer the neural and/or psychological processes that leads to such individual differences. Taken together, hypothesis 2A was partially confirmed since the neural modulations themselves did not predict anger and total-gain but the identified region did so at baseline, and hypothesis 2B was fully confirmed.

8.1.3. Long-term trajectory of anger – enhancing regulation and linking to stress symptoms

The influence of combat-training on neurobehavioral indices of anger was examined in the third objective (described in chapter 6). Inspired by anthropological studies (Darash, 2005; Sherman, 2007), it was assumed that military pedagogy nurtures a Stoic attitude that aims to regulate emotions and specifically to contain and control anger. Anger regulation is especially promoted in infantry and Special Forces units in which soldiers are trained and prepared to face extreme combat situations while maintaining focus in order to carry out their defined missions. Succumbing to anger in such situations would be detrimental to the mission and to the lives of the soldiers. This innovative formulation is based on a general postulation that military training, as other pedagogical, professional or other socio-cultural practices, continuously redesigns an individual's internal psycho-biological dispositions, orchestrating lasting effects on the shape and form in which that individual perceives the world and reacts to it (Bourdieu, 1977). It was therefore expected that this type of stylizing of one's mind and body would be reflected in neurobehavioral indices of anger. Supporting hypothesis 3A but not 3B, low-gain participants belonging to the soldiers study group indicated an increase in monetary gain, an increase in reported positive emotions, and an increase in vmPFC activation in response to the anger-infused UG at the end of combat-training compared to the beginning (note the arrows directed at the blue circle in Figure 8.1.). The civilians control group displayed no changes in any of the anger related measures between time-points. Interestingly, while initially reasoning that soldiers displaying a high-gain profile would not display changes in these indices since they seemed to be well regulated a-priori, at least in monetary gain and emotional report there seemed to have been a pattern of change in the opposite direction compared to the low-gain soldiers. In fact, these high-gain soldiers displayed an increase in anger. These results point towards the possibility that an intense socio-cultural practice with a clear aim of generating combat soldiers may in fact decrease variability in the forms and fashions which individuals respond to emotional perturbations. Moreover, regulating anger in

this militaristic sense is not avoiding it entirely but knowing when and how to utilize it. Though these results were generally the least powerful from a statistical point of view compared to the other objectives, and desperately necessitate further replication and investigation, they offer a progressive outlook on the notion of culture and its possible influence on emotion related neural processing (Kitayama & Uskul, 2011).

The relationship between neurobehavioral indices of anger and the development and manifestation of combat-training induced chronic stress symptoms was unveiled in the fourth and final objective of this research program (described in chapter 7). In-line with expectation, the anger-infused UG was found to be reliable in that behavioral and emotional results replicated between time points across both soldiers and civilians. In partial confirmation of hypothesis 4A, while no changes in stress symptoms were detected for civilians, soldiers displayed an increase in symptoms at the end of combat-training, but not following active duty in which no traumatic events were experienced. In furtherance, hypothesis 4B was confirmed indicating that soldiers with a high-gain profile assumed to be better equipped to cope with angering provocations, later developed less symptoms compared to low-gain soldiers (note the arrows directed at the purple circle in Figure 8.1.). While supporting initial evidence found in the literature that emergency service personnel with higher proneness for anger later developed more PTSD related symptoms (Heinrichs et al., 2005; Lommen et al., 2014; Meffert et al., 2008; van Zuiden et al., 2011), the results are meaningful from several additional points of view. First, it examines anger behaviorally and not by mere self-report questionnaires. Second, it emphasizes anger regulation and not anger response. Third, it places the psychopathological manifestation of anger in PTSD at the focus of inquiry since it is especially while interacting with other people that these patients suffer from the debilitating effects of anger that lead to extreme violence. Finally, and confirming hypothesis 4C, the behavioral findings were supported by neural findings indicating that vmPFC activation during anger provocations and amygdala-IFG connectivity increase in the aftermath of anger before exposure to chronic

stress, as well as the increase in LC reactivity to anger provocations between pre and post exposure, all correlated with the level of symptoms post exposure to stress. Using neuroimaging, these results triangulate the important link between anger, brain and pathological symptoms, suggesting that neural processing related to individual's anger regulation capabilities may buffer the negative implications of chronic stress, that neural processing related to the propensity to ruminate about anger may serve as a risk factor for the development of symptoms and that excessive neural reactivity of a deep structure in charge of autonomic arousal and threat detection is an acquired result of induced chronic stress. A speculative model for the role of anger experienced during interpersonal provocation in PTSD with predisposing (vmPFC) and acquired (LC) neural factors has been described above (Figure 7.4.), and future investigations should aim to test it in diagnosed PTSD patients. Interestingly, a recent study pointed towards the involvement of the LC in the consolidation of day-to-day memory (Takeuchi et al., 2016), offering the possibility that LC hyperactivation in PTSD may in fact have a broader role than described here in relation to the hyper-arousal cluster of symptoms, to include also the re-experiencing cluster of symptoms. Critically, neuropsychological research on PTSD in the last three decades has generated thousands of publications yet only about 1.5% directly dealt with anger (c.f. McHugh et al., 2010). Hopefully, these results may inspire future research to further elucidate the complex relationship between anger and PTSD, and provide a platform for the development of brain-based treatment, such as neurofeedback (Keynan et al., 2016).

Overall, the processing of human anger as evidenced here is in line with the general hypothesis suggested by previous meta-analytic efforts (e.g. Kober et al., 2008; Lindquist et al., 2012) and by the conceptual act model (Barrett, 2006b; both presented in section 1.2.4.) of being a result of integartion between brain regions belonging to several functional circuits that may interact during the dynamic unfolding of the emotional episode in the immediate experience of the emotion as well as well as in its' aftermath. In addition, results support the formulation of stoic pedagogy in

military practice as a program that empowers self-control and specifically anger regulation by modulating soldiers' neurobehavioral response patterns to an angering experience following combat-training. Finally, the findings consolidate the link between anger and stress symptoms via neural measures, which is to this author's knowledge the first and only evidence of its kind to date in humans.

8.2. Reconstructing the "angry brain"

In the introductory chapter of this manuscript human anger was deconstructed revealing its' physiological, cognitive, subjective and behavioral components, portraying a socially-contextualized regulated-prone multidimensional construct. However, the wide distribution of brain regions as reviewed above (section 1.2.) may suggest that brain imaging studies thus far have been limited to specific aspects of the emtion category of anger, without distinguishing between different modes of anger manifestation and without emphasizing the experience of anger during provocation. Notwithstanding, the contextualized multidimensionality of anger may point towards the involvement of several neural circuits in mediating this psycho-biological phenomenon. This lead to a deconstructed investigation of the neural correlates of anger as described in this research program, and together with the results found here, there seems to be several neural circuits that are fairly consistent across most sets of neuroimaging studies and meta-analyses that may provide the scaffolding for the reconstruction of the "angry brain" (Figure 8.2.). Initially, thalamic, limbic and brainstem regions seem to reflect a threat detection network which propagates the stress response (e.g. Berridge & Waterhouse, 2003; Corbetta, et al., 2008; Panksepp, 1998; Sara & Bouret, 2012) and has a critical role in reactive aggression (e.g. Nelson & Trainor, 2007; Rosell & Siever, 2015). Evidence is most strongly supported by animal models, though it seems a similar role for this network is apparent in humans, in which it is believed to have a role in mediating the experience of anger and negative affect (Davis & Whalen, 2001; Kober et al., 2008; Phelps & LeDoux, 2005;), especially by generating a state of arousal and possibly reflecting attention to, perception and

evaluation of motivationally salient stimuli (Lindquist et al., 2012; Pessoa & Adolphs, 2010). This is in line with results found here associating LC with aggressive behaviors and with sympathetic arousal (chapter 4), as well as being enhanced following stress (chapter 7). Similarly the amygdala and its global connectivity with the brain predicted anger experience and expression (chapter 5).

Studies on human aggression (Kramer, Jansma, Tempelmann, & Münte, 2007; Lotze, Veit, Anders, & Birbaumer, 2007) have shown the involvement of similar thalamic, limbic and brainstem regions, as well as of vmPFC and ACC. In fact, it was recently shown that across participants, activity in the vmPFC while viewing an opponent bearing an angry facial expression compared to a neutral expression during an interactive competitive aggression task was negatively correlated with aggressive behavior (Beyer, Münte, Göttlich, & Krämer, 2014). In addition, within participants and specifically during the angry-opponent trials, activity in the dACC was positively correlated with aggressive behavior. Yet studying reactive aggression, even in social contexts, does not directly reflect the subjective experience of anger. Similarly, perceiving anger in faces or voices is not necessarily experiencing anger though such stimuli may serve as a social signal of threat.

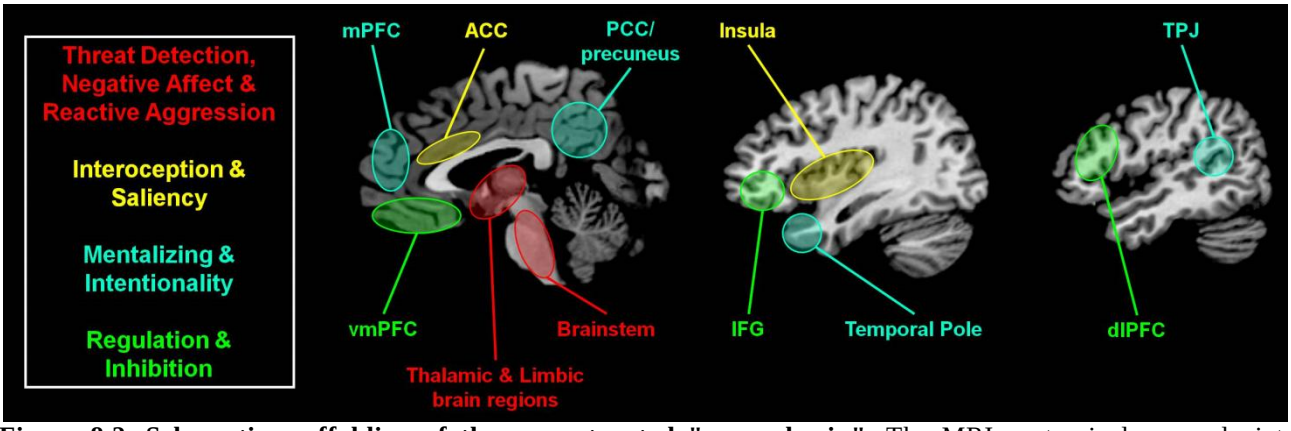

Figure 8.2. Schematic scaffolding of the reconstructed "angry brain". The MRI anatomical scans depict midsagittal (left; Talairach slice x=3), parasagittal (middle; x=37) and lateral (right; x=47) slices of the human brain. Four neural circuits seem to be involved in the subjective experience of anger: (1) threat detection, negative affect and reactive aggression (red) is mediated by thalamic (e.g. thalamus & hypothalamus), limbic (e.g. amygdala) and brainstem (e.g. PAG, LC) regions; (2) Interoception of the somatic state and saliency and perception of pain affect and emotion (yellow) is mediated by the posterior and anterior insula and the ACC; (3) Emotion regulation and inhibition (green) is mediated by the vmPFC and lateral-PFC, most notably the IFG, and dlPFC regions; (4) and mentalizing and understanding intentions is mediated by the mPFC, PCC/precuneus, temporal poles and TPJ regions.

Interestingly though, it seems that the same brain regions in the PFC are involved in the control and regulation of anger as of aggression. Most notably the vmPFC and the lateral PFC

(lPFC), including regions of the IFG and dlPFC, have been associated with such regulatory functions, commonly by targeting the amygdala. The vmPFC seems to be associated more specifically with regulation of anger experience and aggressive expressions of anger (e.g. Davidson et al., 2000; Rosell & Siever, 2015; Siever, 2008), as similarly found here (chapter 4), while the IFG seems to be engaged in maladaptive angry rumination in the aftermath of an angering experience (Denson et al., 2009; Fabiansson et al., 2012), again as similarly found here (chapter 5). Nevertheless all these regions have been related to implicit and/or explicit processes of emotion regulation in general, not necessarily related to anger (Etkin et al., 2015). Notably initial evidence provided here (chapter 6) suggests that these brain regions may also be altered and enhanced following a socio-cultural practice that aims to empower anger regulation such as combat-training.

The right dlPFC is considered a key region involved in domain general cognitive control (Miller & Cohen, 2001) and together with the IFG has been shown to involved in cognitive reappraisal of emotions (Buhle et al., 2014). The IFG was also shown to be important for motor inhibitory control or response inhibition (Aron et al, 2014) which has also led to the speculation that the enhanced amygdala-IFG connectivity in the aftermath of anger found here (chapter 5) refelcts increased efforts to either control the experience (affect) or the expression (inclination to do harm to a counter-part) following anger. Notablly, it is important to emphasize the findings found here regarding the temporal trajectory of the emotional episode which indicate a distinction between regulatory processes engaged during the experience of anger and those engaged in its aftermath. It is also interesting that the vmPFC has been consistently associated with the expected subjective value of many different types of rewards, including monetary payoffs, snacks and social rewards such as good reputation (Levy & Glimcher, 2012). The vmPFC's regulatory role may therefore reflect the expected value of the potential outcome of anger and aggression and thus direct behavior. Such a perspective is in line with recent conceptualization of emotion regulation as driven by valuation of the emotion itself (Etkin et al., 2015).

The reoccurrence in neuroimagaing studies of two highly interconnected regions, the insula and the ACC might be associated with their joint role in a neural network dedicated to detect salient sensory events (Menon & Uddin, 2010), which has been consistently involved in the perception of physical but also social pain (Iannetti & Mouraux, 2010; Legrain, Iannetti, Plaghki, & Mouraux, 2011). Notably both these types of pain are considered as primary antecedents of anger, yet the shared neural representation of physical and social pain in the dACC has been recently challenged and is currently under debate (Cacioppo et al., 2013; Lieberman & Eisenberger, 2015; Woo et al., 2014). Nevertheless there has been consistent evidence linking insula and ACC with pain experienced both from a first person perspective as well as with vicarious pain experienced from a third person perspective (Lamm & Singer, 2010; Rütgen et al., 2015), which is commonly regarded as a paradigm to study empathic processing. A division of labor between the insula and ACC has been suggested in which the insula is associated with the emotional experience, while the dACC is associated with allocation of control and modification of behavioral responses during challenging physical and cognitive situations (Gasquoine, 2013; Shenhav, Botvinick, & Cohen, 2013). This suggested role of the dACC is congruent with its co-activation with regulatory regions of PFC during both anger and aggression paradigms, though there is evidence that the ACC itself is a target for regulatory processes (Etkin et al., 2015). It is also important to recognize the functional segregation between anterior and posterior aspects of the insula. While the anterior aspect is suggested to be associated with the subjective and conscious representation of feelings, especially during social and motivational situations, and thus having a role in human awareness, the more posterior aspects of the insula has a role in the unconscious interoceptive representation of the internal somatic state (Craig, 2002, 2003, 2009, 2011). Here the dpI and its connectivity with the mT were found to have a direct role in modulating anger experience during provocation (chapter 4), illustrating the role of unconscious interoceptive representation in the subjective experience.

Finally, several regions associated with humans' capability to represent another person's mental state (i.e., mentalizing/theory of mind), including the mPFC, PCC/precuneus, temporal poles and

the TPJ (Amodio & Frith, 2006; Denny et al., 2012) have also reappeared in various anger induction studies, whether self-generated or induced, albeit to a lesser extent. The involvement of this system seems to reflect the interpersonal nature of angering events, but the exact role of mentalizing in the experience, expression and regulation of anger is still unclear. One possibility is that humans attribute the intention to do harm and the fault to another person, and thus blame him or her for the events that evoked the experience of anger (Cosmides & Tooby, 2005; Russell & Giner-Sorolla, 2011). For example, it was shown that unfair UG-offers randomly assigned by a computer were rejected less and also engaged less brain activity in bi-lateral AI compared to similar offers allegedly made by a human counterpart (Sanfey et al., 2003). In case of an incidental transgression, mentalizing may have a role in understanding the accidental nature of the event and thus in fact serve as a regulatory mechanism in avoiding or reducing an angry reaction (Haidt, 2003). The simplistic view would contend that mental-state attribution is necessary for anger by the mere fact that anger is mostly experienced during social interactions but this and other questions regarding the interaction between mentalizing and subjective anger deserves further scientific scrutiny. Interestingly, since in the anger-infused UG all provocations entailed a human counter-part, no direct evidence was found for this system. Yet the vmPFC has also been shown to be important for taking the perspective of other people and that lesions to this region may cause an increase in UG rejection rates (Shamay-Tsoory et al., 2012). Since the mediation model linking vmPFC to emotional experience to behavior in the anger-infused UG was partial (Figure 4.5.D), it is possible that having a measure of perspective talking could have explained additional variability in the link between the vmPFC and behavior in the game.

Taken together, this postulated "angry brain" provides a basis for hypothesis testing of anger experienced in various contexts and under a multitude of manipulations with the aim to tweak and refine our understanding of the idiosyncratic psycho-biological markers of the phenomenon. These efforts may hopefully serve as a springboard for the development of treatments and interventions in irregular and pathological conditions of anger. Moreover, it is apparent that this "angry brain"

model is constructed based on domain-general networks that are not specific to anger and might as well capture other emotional, social and motivational experiences. In fact, this model reverberates nicely and supports the neural circuits described in the introduction chapter (section 1.2.4.) as part of the conceptual act model (Barrett, 2006; 2009; Kober et al., 2008; Lindquist et al., 2012; Figure 1.2.). Whereas core affect resembles in structure and function the threat detection/reactive aggression and the interoception/saliency networks, conceptualization together with executive attention resembles in structure and function the mentalizing and regulation networks. Ultimately, it is emphasized that to capture the large variety in the forms and fashions in which human anger is experienced and expressed and to portray the neurobehavioral substrates of these anger- and related regulation modes, basic and translational efforts should embed social interactions to their investigations. This generally holds true to the neuroscientific scrutiny of emotional phenomena.

8.3. Embedding social interactions to the study of emotions

8.3.1. Social-Emotional overlap

The nexus between *social-cognition* and *emotion* has been acknowledged and demonstrated in the modern era of neuroscience by showing that brain regions that were associated with processing emotions were also associated with social-cognition (Adolphs, 2003, 2009; Barrett & Satpute, 2013). The amygdala, for example, has been considered as the core region of the "emotional brain" for many years (e.g. LeDoux, 1992), but at the same time has also been suggested to play a primary role in the so-called "social brain" (Brothers, 1990). Another example stems from findings that ascribe a role to the AI in processing subjective feelings but also when empathizing with others (Singer, Critchley, & Preuschoff, 2009). It was recently noted that the overlap between different functions and similar brain regions is also apparent when considering a network-based approach (Barrett & Satpute, 2013). For example, the so called "default mode" network, so named because of its' consistent appearance whenever people are not actively engaged in a goal directed task, possibly letting their minds wonder (Gruberger et al., 2011), has also been consistently engaged during tasks

requiring social-cognition, especially when attributing mental states to others and has thus also been termed the "mentalizing"/"theory of mind" network (Mars et al., 2012; Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008). Moreover, the main brain regions of this network, the medial prefrontal cortex (mPFC) and the PCC/precuneus, have also been shown to be engaged during various emotional states (Kober et al., 2008; Lindquist et al., 2012). In fact a meta-analysis converging on resting-state, social-cognition and emotion studies has shown that these two regions are the only ones to have direct statistical overlap in all three domains (Schilbach et al., 2012). Moreover, the mentalizing network was shown to have a role in mediating between a vicarious emotional experience and one's own emotional experience (Raz et al., 2014), providing a possible explanation for the overlap of this network in various social-emotional contexts.

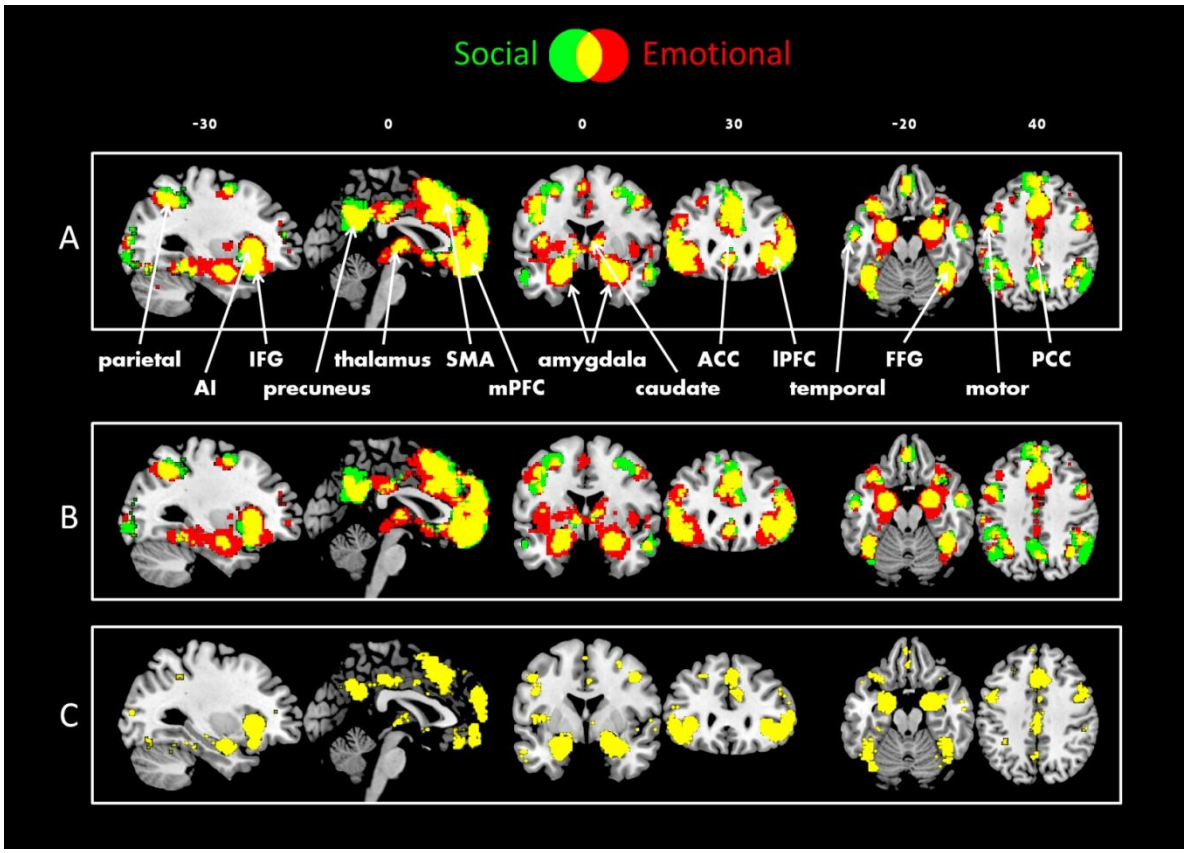

Figure 8.3. Social-emotional overlap in the human brain. Panel A illustrates NeuroSynth (http://www.neurosynth.org/) term-based forward inference meta-analytic maps for the terms social (green; 1000 studies) and emotional (red; 1340 studies). A forward inference map provides information about the likelihood of each voxel to activate if a study uses the term (i.e., P(activation|term), at a false discovery rate of 1%), alluding to the importance of the voxel to that term. There were a total of 11406 studies on December 5th, 2015 - the date the maps were downloaded. The overlap between the social and emotional maps is illustrated in yellow. Marked regions include the amygdala, thalamus, caudate, middle temporal lobe, FFG, IFG, AI, mPFC, ACC, SMA, PCC, precuneus, lPFC, and motor and parietal regions. The two left brain slices, the middle slices and the two right slices present sagittal, axial and coronal slices, respectively. The number above each slide refers to its MNI plane (x, y, z respectively). Panel B illustrates the same maps after removing 314 studies that were included in both terms thus presenting a mutually

exclusive subset (social=686 studies; http://neurosynth.org/analyses/custom/122a315b-0c06-4c78/; emotional=1026 studies; http://neurosynth.org/analyses/custom/1559b18a-a7b0-443f/). The overlap was apparent in similar brain regions though to a lesser extent. Panel C illustrates the meta-analytic map of the 314 studies shared by both the social and emotional terms (http://neurosynth.org/analyses/custom/9c442c82-bdbd-4f83/).

These observations are in line with the notion that the brain is not organized according to preprogrammed definitions of what is social or emotional. In other words, the brain does not seem to contain specific modules for processing *only* social or *only* emotional stimuli but rather is organized in more domain-general modules that have important functionalities for processing both emotional and social information. To provide support for this idea, NeuroSynth (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011) - a web-based platform for large-scale automated meta-analyses of fMRI data – was used to examine the overlap between meta-analytic maps of social and emotional studies pointing at extended and bi-laterally symmetrical overlap across the entire brain (Figure 8.3.). Even when removing a large subset of studies (314 in number) that were initially included in both the social (1000 studies) and emotional (1340 studies) meta-analytic maps, the overlap in these brain regions hardly changed. It is important to highlight that these meta-analytic maps are rough estimations and possibly provide an over generalization as no differentiation between various factors such as healthy and patient populations or between paradigms and induction methods.

Notwithstanding, while a comprehensive and in depth survey of the theoretical literature breaches the scope of this section and may be found elsewhere (Averill, 2012; Cunningham, 2013; Gendron & Barrett, 2009; Hareli & Parkinson, 2008; Moors, Ellsworth, Scherer, & Frijda, 2013; Parrott, 2001; Russell, Rosenberg, & Lewis, 2011), these meta-analytic maps resonate with the disagreement as to what defines the boundaries between social-cognition and emotions. It is suggested here to shift the discourse and instead of asking whether a specific type of emotion is social or not, or whether a social emotion is in itself a *type* of emotion, to embrace a broad perspective which views any emotional episode as social if it is somehow influenced by social context and/or if it might arise during social interactions. With this in mind, it is important to emphasize that all studies included in the meta-analytic maps generated with NeuroSynth, as well as

the vast majority of findings on the neurobiological underpinning of human social and emotional life are based on "offline" controlled laboratory paradigms during which participants' brains are studied in isolation from other agents in the environment. In recent years a growing number of researchers have addressed this problem and emphasized the need of a neuroscientific endeavor to study brain function in its naturalistic, socially interactive, "on-line" mode (Hari, Henriksson, Malinen, & Parkkonen, 2015; Hari, Sams, & Nummenmaa, 2016; Hari & Kujala, 2009; Hasson & Honey, 2012; Pfeiffer, Timmermans, Vogeley, Frith, & Schilbach, 2013; Schilbach et al., 2013; Zaki & Ochsner, 2009).

Notably, experimental and technological advancement has brought research closer to full social interactions in domains such as joint action (for review see Becchio, Sartori, & Castiello, 2010; Sebanz, Bekkering, & Knoblich, 2006) and joint attention (for review see Risko, Laidlaw, Freeth, Foulsham, & Kingstone, 2012; Schilbach, 2015) by using virtual reality scenarios and *hyperscanning*, in which two participants are simultaneously scanned in two separate MRIs while brain signals are acquired in synchrony with the behavioral interactions (for reviews, see Babiloni & Astolfi, 2012; Bohil, Alicea, & Biocca, 2011). These developments will be imperative for employing social interactive paradigms in neuroscience. The difficulty in designing such paradigms is determining where to draw the line between experimental control and real-world complexity. Joint-attention and joint-action tasks are highly controllable and provide an excellent starting point to study the building blocks of social interaction and coordination. However, creating a realistic situation in which participants can see, hear and talk to each other spontaneously, allowing engagement in interactive dynamics for the study of realistic emotional situations is more challenging. By loosening the structure of the experiment one might gain generalizability but also increase the complexity of data analysis and the amount of possible artifacts and confounds, hindering the ability to draw direct conclusions. To cope with these issues neuroscientific efforts must continue to aim for multilevel analysis (Cacioppo & Berntson, 1992; Cacioppo, Cacioppo, & Cole, 2013). That is, not only various neural signals such as combing fMRI and

electroencephalography (EEG) to accompany behavioral measures, but also autonomic, hormonal and genetic measures, etcetera. Such multilevel experiments, as was intended in the current research program, will allow for converging evidence that may negate alternative explanations and possibly compensate for diminished controllability.

8.3.2. The effects of social interactions on emotions

When William James asked in his seminal paper "what is an emotion?" he clearly recognized the basic sociality of human emotional life, yet he framed it as an emotional percept as any, without considering the possible role of social interactions within the emotional experience (1884). James seemed to argue that people themselves are not essentially different than other percepts as triggers of emotional experiences. However, when humans interact with other people in their environment they are not mere passive observers; they are able to spontaneously convey their thoughts, feelings and intended actions towards those people and in response to their own thoughts, feelings and actions, thus adapting their behaviors and cognitions within the unique dynamics of the situation. These dynamic interactions may alter how people perceive the intentions of other people and thus may influence the emotional episode, especially if the interactions themselves may hold unique information constitutive to how humans understand other agents (e.g. De Jaegher et al., 2010; Di Paolo & De Jaegher, 2012). For example, when someone bumps into you while walking down the street, both of you stumble and almost fall and you might think she did that on purpose and that she is directly responsible for you getting hurt. But she might immediately apologize and explain that she had a sudden loss of balance or she might be angry for hurting you because someone else pushed her. Certain information may come to light vis-á-vis the interaction which alters how you understand the sequence of events and may direct attention away from "what she did" and "how I feel" to focus on the momentary interdependency between you two.

In addition to the above postulation regarding the possible influence of social interactions on humans' emotional experiences, the nature of the relationship to the person with which one interacts

(friend or foe; familiar or stranger), the goal of the interaction (cooperative/competitive/incidental) as well as the possibility of past or future interactions, are all important factors that may influence peoples' emotional reactions to one another, which in turn may themselves alter the status of the relationship and the course of interaction (Fischer & van Kleef, 2010). Therefore, while emotions have an important role in shaping and motivating social interactions, the reverse similarly holds true – social interactions may fashion peoples' emotional experiences and expressions, and consequently their underlying neural manifestations. To date however, neuroscientific evidence regarding the experience and expression of emotions during truly interactive situations is still very limited.

In the realistic and interactive induction of anger developed within the current research program (section 4.2.), the involvement of the LC, a noradrenergic nucleus in charge of regulating autonomic arousal, was shown to mediate the experience and expression of anger, in addition to other brain regions including those involved in interoceptive processing and implicit emotion regulation. To the author's knowledge, this is the first neuroimaging evidence highlighting the association between LC and anger in humans, possibly because anger was induced during dynamic social interactions. Interestingly, it has been suggested that within its role in reorienting attention to salient events, the LC-NA system is also involved in driving attention to the intentions of other people as evidenced by the neural interaction between this system and regions involved in understanding other people, such as the TPJ and extending towards the PCC/precuneus (Corbetta et al., 2008). Notably these same regions have been suggested to encompass "all aspects of one's social persona" (Damasio, 2010).

There is no doubt that neuroscientific knowledge increased invaluably and will continue to do so by investigating brain function using highly controlled experimental stimuli such as pictures of scenes or faces. Nevertheless, there seems to be a qualitative gap between common paradigms used in neuroimaging to induce emotional experiences and how emotions are actually experienced in the real world. In view of the observation regarding the social-emotional overlap in the human brain, one may ask whether social interactions be the key for a clear dissection between the "social" and

"emotional" brain or if social interactions will further emphasize the inherent sociality of human emotions. Clearly however, a major concern for future empirical and theoretical progress of affective neuroscience is to reveal the neurobiological mechanisms that mediate emotional episodes during realistic interpersonal interactions. Such an endeavor may also hold implications for various psychopathological conditions with apparent emotional and social abnormalities such as anxiety disorders, autism and schizophrenia (Müller-Pinzler et al., 2016; Schilbach, 2016).

8.4. Limitations

While specific limitations were described in each chapter according to context, several additional limitations are existent when considering this research program. The current study was conducted on a sample of male IDF soldiers and civilians in pre-army national civil-service who volunteered and re-volunteered to participate in this prospective research program. Therefore it may not generalize and adequately represent the population at large, especially in view of the known gender differences in anger and aggression (Bernardez-Bonesatti, 1978; Frodi, Macaulay, & Thome, 1977; Lerner, 1980; Potegal & Archer, 2004, as apparent also in the UG paradigm Solnick, 2001). Our participants were also at an age of transition in to adulthood, a period characterized with remarkable changes in brain structure and function regarding social, emotional and cognitive functioning (Blakemore, 2012; Somerville, Fani, & McClure-Tone, 2011; Yurgelun-Todd, 2007), including decision making (Blakemore & Robbins, 2012; Hartley & Somerville, 2015) and in regards to the response to stress (McEwen & Morrison, 2013; Romeo & McEwen, 2006). Moreover, while starting with a rather large sample compared to standard neuroimaging studies, sample size was unfortunately reduced in between time-points thus weakening statistical power, and warranting future studies to recruit larger samples with possibly larger variability. This was especially apparent in regards to the possible influence of combat-training as a professional and cultural practice on neurobehavioral indices of anger (chapter 6).

The use of a-priori healthy sample of infantry soldiers minimizes the possibility of confounding factors such as comorbidity and medication use, but the circumstances led to low to moderate levels of stress symptoms following combat training, which ultimately did not develop into characteristic PTSD symptomatology. This limits our capability to infer from current findings about the neural substrates and relationship between anger and stress symptoms to actual PTSD patients. No study to date examined the neural response to anger in PTSD patients and this should be the priority of future work. Notably, while anger and PTSD have been mostly attributed to military personnel (McHugh et al., 2010), other emergency service populations such as policemen and firefighters, as well as other trauma related populations deserve a consideration. Therefore it is unclear if the identified neurobehavioral indices of anger and their relationship to stress symptoms may generalize to other such populations. A possible additional contingency is that the results found here may apply only to chronic but not to acute stress and trauma inductions.

In this regards, another important limitation to consider is the lack of an adequate assessment of stress symptoms. Symptoms were initially measured using the PDS questionnaire (Foa et al., 1997) which requires participants to report on at least one of a number of traumatic events before moving on to rate 17 items representing PTSD symptoms experienced in the past 30 days. The traumatic events include specific and discrete events such as a sexual or physical assault or an actual battle at war. Only before recruiting soldiers at the second time-point it was realized that these events would not necessarily be perceived as relevant for the period of combat-training. This can also explain the very low numbers of respondents in this questionnaire. To overcome this barrier the military version of the PCL (Forbes et al., 2001; Weathers et al., 1993) was administered as an additional assessment of symptoms. The PCL simply instructs respondents to indicate the extent to which they have experienced a specific symptom during the past month and in regards to their military experience in 17 items. While the PCL is considered a psychometric sound tool to assess PTSD related symptoms (Blanchard et al., 1996; Spoont et al., 2015), the version used here was before the publication of the 20-item version that corresponds to the DSM-5 characterization of PTSD.

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Finally, while the research presented here aimed for ecological validity by developing a realistic interactive task, these efforts were not void of experimental costs. The framework of anger induction using interpersonal conflict was similar for all participants but within this context it is probable that the provocations by actors playing as proposer had a differential effect. Though these variables were tested and showed not to have a significant effect the results, it is probable that they inflated variability and diminished statistical power. This holds true also in regards to motion artifacts during fMRI data acquisition. To address this limitation at least in part, anger was measured and characterized using multi-level measurements to converge on results and refute possible confounds and artifacts. However, as far as neuroimaging was concerned, only fMRI was used which has good spatial resolution but lacks in temporal resolution. Implementing simultaneous fMRI and EEG for example, could provide better and more reliable characterization of the neural substrates of anger. Future efforts should aim to develop a more controlled version of the anger-infused UG, and could harness combined fMRI and brain stimulation techniques to test for the causal specificity of the brain regions found here in relation to anger experience and regulation.

8.5. Significance

Anger proliferates in almost every aspect of human life and understanding what anger is, how it is generated and how it may be regulated, is of great importance for both normative and pathological conditions. The current research program advanced the neural, physiological and behavioral demarcation of inert individual versatility in emotion experience, expression and regulation as related to anger. Using a naturalistic paradigm to evoke anger through social interactions within the fMRI setting was a special feature of this research and its significance manifests both in ecological validity as in the advancement of interactive and realistic paradigms within laboratory experimentation in neuroscience and emotion inquiry in particular. Moreover, the scientific efforts described here opened a new avenue of research on the relatively scarce neuroscientific inquiry into the short and long temporal trajectories of

emotional experiences and their related neural substrates by implementing data driven connectivity analysis to investigate neural modulations in the aftermath of an angering experience and by using a prospective design inducing multiple instances of anger, respectively. Strikingly, no direct relationship was found between the neural substrates of anger experience and the neural traces of this experience further emphasizing the importance of the temporal dynamics in the experience of emotions. The longitudinal design enabled to scrutinize from a socio-cultural perspective the influence of collective practices and life experiences (such as military training) and has thus shed light on the way that acquired norms of conduct may influence neurobehavioral concomitants of prototypical human emotional experiences. Opting for a multi-modal methodological approach to study the dynamics of anger experience while taking into consideration the complexity of the construct, provided new insights on the relation between the various dimensions of emotion in general and specifically anger, and support a new platform to study other types of emotional experiences. Beyond basic scientific benefits, the advanced knowledge on anger and its regulation is expected to be useful for socially beneficial products. Identifying different modes of anger experience, in terms of their various features, may improve tools for the empowerment of anger regulation strategies at both the individual and the group levels, enabling focused and efficient intervention programs. Finally, a specific relation to stress related symptoms which feature unbalanced anger and aggression may prove beneficial in understanding the role of anger in the course and severity of stress and trauma induced psychopathology and its determinants.

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של "המוח הכועס". מערכת הפיגומים הזו שרטטה מספר מעגלים עצביים כלל-תחומיים שאינם בהכרח ייחודיים לכעס, ומציע שיחסי הגומלין ההדדיים בין האזורים המוחיים של רשתות אלו מתווך את הפרישה הדינמית של החוויה ושל ויסות כעס. בכך תמונות אפשרויות רבות לייצור ובחינה של היפותזות במחקרי המשך. באופן בולט, המבע הבינאישי על חוויות רגשיות אשר מאומץ כאן מציע למחקרי המשך לשבץ אינטראקציות חברתיות במחקריהם שכן זה יכול לדחוף קדימה את תחום החקירה מבחינה ניסויית ותיאורטית גם יחד. הממצאים גם תומכים בניסוח של פדגוגיה סטואית בפרקטיקה הצבאית כתוכנית המעצימה ויסות כעס על-ידי מודולציה של דפוס התגובה הנוירו-התנהגותית של חיילים לחוויה מכעיסה בעקבות אימון קרבי. לבסוף, הממצאים מגבשים את הקשר בין התשתית הנוירו-התנהגותית של כעס לבין ההתפתחות והביטוי של תסמיני סטרס בעקבות סטרס כרוני המקושר לאימון קרבי, ובכך מספק פלטפורמה לפיתוח טיפולים מונעים ומתערבים המבוססים על ביטויים אידיוסינקרטיים של כעס.

גישה זו והממצאים התומכים בה מציעים נקודת מבט ייחודית ומורכבת על מושג התרבות והשפעותיה האפשריות על עיבוד מידע עצבי ותגובות רגשיות.

מטרת היעד הרביעי והאחרון של המחקר כפי שמוצג בפרק השביעי הייתה לחשוף את הקשר בין מדדים נוירו-התנהגותיים לכעס לבין תסמיני סטרס שהתעוררו בעקבות אימון קרבי. בעוד שהתפרצויות זעם ואגרסיביות הינם ביטוי ברור של תסמיני סטרס, בייחוד בהפרעת דחק פוסט-טראומטית (PTSD) ובעיקר במהלך אינטראקציות בינאישיות, עדויות ראשונות מצביעות על כך שכעס יכול להווה גם סיבה וגם תוצאה להתפתחות של PTSD. עם זאת, עד היום הקשר בין כעס לתסמיני סטרס כפי שמתווך על-ידי המנגנון הפסיכו-ביולוגי של כעס לא נבדק. ההנחה הייתה שתקופה אינטנסיבית של אימון צבאי תעורר סטרס כרוני אשר יוביל לעלייה בתסמיני סטרס. ברמה הקבוצתית לא נמצאו הבדלים בין חיילים לאזרחים בין שתי נקודות הזמן במדדים הנוירו-התנהגותיים של כעס, דבר אשר מתקף מחדש את אינדוקציית הכעס על-ידי ה-UG, אך רק בקרב החיילים נצפתה עלייה בתסמיני סטרס. באופן חשוב, בקרב החיילים בנקודת הזמן הראשונה לפני החשיפה לסטרס כרוני, ככל שהם צברו יותר כסף, היו בעלי פעילות גבוהה יותר ב-vmPFC בתגובה להכעסה, והיו בעלי עלייה נמוכה יותר בקישוריות ה-אמיגדלה-IFG בעקבות ההכעסה, כך היו להם בנקודת הזמן השנייה בעקבות החשיפה לסטרס כרוני פחות תסמיני סטרס. לפיכך, נראה שחיילים אשר מצוידים טוב יותר להתמודד עם פרובוקציות מכעיסות ופחות רגישים להשפעות המתמשכות של כעס הינם עמידים יותר בפני התפתחות תסמיני סטרס. יתרה מזאת, נמצא שככל שלחיילים הייתה עלייה גדולה יותר בתגובת ה-LC לפרובוקציות כעס בין לפני לעומת אחרי החשיפה לסטרס כרוני, כך היו להם יותר תסמיני סטרס. תוצאה זו מהווה עדות סיבתית ראשונה בבני אדם למעורבות ה-LC בביטוי הנרכש של תסמיני סטרס. יחד, ממצאים אלו עושים טריאנגולציה לקשר החשוב בין כעס, מוח ותסמינים פתולוגיים, תומכים בתפקיד החשוב של ויסות רגשי ביחס להפרעות חרדה ומספקים מטרות עצביות לטיפולים התפורים להבדלים הבין-אישים בביטוי הפסיכו-פתולוגי של כעס.

לסיכום, הגדרת כעס כתופעה פסיכו-ביולוגית יחידה היוותה באופן מתמשך קושי תיאורטי וניסויי. מערך המחקר הנוכחי עשה דה-קונסטרוקציה של כעס למרכיבים הבסיסיים שלו, המתייחסים למהות הבינאישית והדינאמית שלו, לתהליכי הויסות האינהרנטיים לניהול כעס, לשינוי בחוויה של כעס בעקבות פרקטיקה חברתית-תרבותית אשר מעצימה ויסות רגשי, ולבסוף לתנאים שבהם כעס מתבטא בצורה פתולוגית, בפרט ב-PTSD. במקביל, הונהגה גישה רב-ממדית אשר השתמש במגוון מדדים, בדגש על מספר מדדים לתפקוד (פעילות וקישוריות) ומבנה המוח, כמו גם מדדים פיזיולוגים, התנהגותיים, סובייקטיביים ומדדי אישיות במטרה לכנס תוצאות יחדיו. תכנית המחקר הפרוספקטיבית על קבוצת מחקר של חיילים קרביים וקבוצת ביקורת של מתנדבי שירות לאומי, ותגובתם לחווית כעס בינאישית הובילה לרה-קונסטרוקציה

שכעס מתמשך מעבר לפרובוקציה ונוטה לגרום לדפוסי חשיבה שליליים. אנליזה מונחת-נתונים (data-driven) פותחה כדי לזהות שינויים בקישוריות התפקודית בכלל המוח בעיבוד עצבי אנדוגני כתולדה של חווית הכעס. נמצאה עלייה בקישוריות החיובית הגלובלית של האמיגדלה בסריקת המנוחה השנייה לעומת הראשונה, ובפרט עלייה בקישוריות בין האמיגדלה לבין ה-inferior frontal gyrus (IFG). באופן כללי האמיגדלה מקושרת לתפקיד חשוב בחוויות רגשיות שליליות ופעמים רבות מהווה מטרה לתהליכי ויסות עצבי, אשר למעשה מוצאים לפועל בין היתר על-ידי ה-IFG, אשר מקושר באופן כללי לאינהיביציה רגשית ומוטורית. ממצאים קודמים משייכים עלייה בקישוריות ה-אמיגדלה-IFG למאמצי שליטה ברגשות, לתהליכי רומינציה ובפרט רומיניציה של כעס. זאת ועוד ובהתאם לממצאים קודמים, גודל השינוי בקישוריות ה-אמיגדלה-IFG שנמצא כאן היה במתאם עם מדד אישיות של הנטייה היומיומית לכעוס ועם הנפח האנטומי של ה-IFG, אשר תומכים בפרשנות שהמודולציה הזו בקישוריות ה-אמיגדלה-IFG משקפת תהליך הקשור לרומינציה של כעס. השינויים בדפוסי הקישוריות של האמיגדלה לא נמצאו בקשר לתגובה הנוירו-התנהגותית לכעס אשר אופיינה על-ידי ה-UG, אשר מצביע על האפשרות שתהליכים עצביים שונים פועלים בעת אירוע המעורר חוויה רגשית לעומת ברגעים המידיים שבעקבותיה. לעומת זאת, מידת הקישוריות החיובית הגלובלית של האמיגדלה לפני ה-UG ניבאה את סכום הכסף הנצבר ואת מידת הכעס המדווח, אשר מצביע על המעורבות של האמיגדלה בהבדלים בין-אישיים במוכנות או בנטייה לתגובות וחוויות רגשיות.

מטרת היעד השלישי של המחקר כפי שמוצג בפרק השישי הייתה לבחון את ההשפעה של אימון קרבי על התגובה הנוירו-התנהגותית לכעס. בהשראת מחקרים אנתרופולוגיים, ההנחה הייתה שהפדגוגיה הצבאית מחנכת גישה סטואית שמטרתה לשלוט ולהכיל תגובות רגשיות. ביחידות קרביות ויסות כעס מקודם באופן יוצא דופן שכן חיילים מאומנים ומוכוונים להתמודד עם מצבי קרב קיצוניים תוך שמירה על מיקוד במטרה לבצע את משימתם המוגדרת, וכעס יכול לפגוע במטרה זו. אכן התוצאות מרמזות שחיילים אשר בתחילת האימון הקרבי היו בעלי פרופיל כעס בלתי מאוזן צברו יותר כסף, דיווחו על יותר רגש חיובי והראו פעילות גבוהה יותר ב-vmPFC בתגובה לפרדיגמת ההכעסה בסוף האימון הקרבי, ובכך בעצם הציגו לכאורה פרופיל מווסת. מעניין לציין שנראה שחיילים אשר בתחילת האימון היו בעלי פרופיל כעס מווסת צברו פחות כסף ודיווחו על יותר כעס בסוף האימון הקרבי, אשר מצביע לכאורה על פרופיל פחות מאוזן. כמו כן, באופן כללי בסוף האימון הקרבי לא נמצאו הבדלים במדדי הכעס השונים בין שתי קבוצות החיילים הללו. קבוצת הביקורת של אזרחים בשנת שירות לא הראו שינוי באף אחד ממדדי הכעס בין שתי נקודות הזמן. התוצאות הללו מצביעות על האפשרות שפרקטיקה חברתית-תרבותית בעלת עוצמה כגון זו של להפוך להיות חייל קרבי מעצבת את הגוף והנפש, כפי שמתבטא במדדים הנוירו-התנהגותיים של כעס, בצורה שמצמצת את השונות הבינאישית ומפיקה תגובה אחידה לכעס.

הרב על פרדיגמת ה-UG, לא רק שהיא תוקפה ושוחזרה פעמים רבות כהקשר אידיאלי לקונפליקט בין-אישי על משאבים כלכליים, אלא שבפרדיגמה זו הצעות לא שוויוניות מעוררות כעס, דחיית הצעות שכאלו משקפת התנהגות אגרסיבית, וקבלת הצעות שכאלה קשורה ליכולות ויסות רגשי של כעס ואגרסיביות. כדי לייצר אינטראקציה טבעית שתעורר כעס מעבר לחוסר ההוגנות של ההצעות, לאחר כל הצעה שולב משא-ומתן ספונטני ומילולי. אך בעוד שנבדקים האמינו שהשחקן השני הינו נבדק נוסף המציע את הצעותיו בזמן אמת, סדרת ההצעות הייתה קבועה מראש והשחקן השני היה למעשה שחקן מקצועי שאלתר במהלך המשא-ומתן באמצעות מגוון תסריטים במטרה לעורר חווית כעס בינאישית אותנטית בנבדקים. לפיכך, התבססה הנחה שנבדקים אשר יהיו מסוגלים למרות זאת לקבל הצעות לא הוגנות משחקן תחרותי ומעצבן כנראה יצליחו בצורה זו או אחרת לשלוט ולהתאים את הכעס שלהם לדרישות הקונטקסטואליות של המשחק.

הנבדקים כולם הביעו כעס והפגינו עליה בכעס ככל שהמשחק התפתח, ובעיקר כלפי הצעות לא הוגנות. כמו כן שוחזרו הממצאים הקלאסיים של ה-UG לפיהם ככל שהצעה הייתה פחות שוויונית כך הייתה נטייה גדולה יותר לדחות אותה. בנוסף, נמצא שנבדקים שצברו יותר כסף לאורך המשחק דיווחו על פחות כעס ויותר רגש חיובי, היו בעלי זמני תגובה איטיים יותר, היו בעלי תגובה סימפתטית איטית יותר אשר מצביעה על עוררות פיזיולוגית נמוכה יותר, היו בעלי פעילות גובהה יותר באזור ה-ventromedial Prefrontal Cortex (vmPFC) ונמוכה יותר בגרעין ה- Locus Coeruleus (LC), והיו בעלי קישוריות תפקודית גבוהה יותר בין ה-dorsal posterior Insula (dpI) לבין ה- medial Thalamus (mT), ודפוס הפוך בכל אלו לנבדקים שצברו פחות כסף. הטענה היא ששני דפוסי התגובה הנוירו-התנהגותיים הללו משקפים פרופיל תגובה מווסת לעומת חסר איזון, בהתאמה. באופן בולט, נמצא שפעילות ה-vmPFC וקישוריות **ה-**dpI-mT תרמו לצבירת יותר כסף באמצעות מודולציה של החוויה הרגשית. ממצא זה מספק מודל אשר עושה טריאנגולציה למדדים עצביים, התנהגותיים וסובייקטיביים המייצגים את חווית הכעס וכפי שנטען, משקף מנגנון עצבי לויסות כעס. תמיכה לכך מגיעה מהמתאם שנמצא בין פעילות ה-vmPFC לבין מדד אישיות בלתי-תלוי של הנטייה היומיומית להשתמש באסטרטגיות לויסות רגשי. תוצאות אלו משחזרים ממצאים קודמים בדבר תפקידו של ה-vmPFC בויסות רגשי אימפליסיטי, של ה-LC בייצור עוררות פיזיולוגית ותגובת סטרט לאור גירוי מאיים, ושל ה-dpI כאזור מוחי ראשוני לייצוג אינטרוספטיבי. מעבר לכך, מוצגות כאן עדויות לקשר הישיר בין ה-vmPFC, חווית הכעס והתנהגות ב-UG, למעורבות ה-LC בתגובת אנשים בריאים לכעס, וכן לתפקיד של ה-dpI בויסות החוויה הרגשית. נראה שכל אלו נובעים מהבסיס האותנטי והאינטראקטיבי של פרדיגמת הכעס שפותחה.

כלל הנבדקים השתתפו גם בסריקות fMRI במנוחה (resting-state) לפני ואחרי אינדוקציית הכעס, מתוך ידיעה

תקציר

בעוד שכעס מהווה תגובה הישרדותית הקיימת בכלל בעלי-החיים ומאופיין על-ידי רכיב פיזיולוגי מעורר, בבני אדם כעס התפתח לקונסטרוקט רגשי מורכב ורב-ממדי המושפע מאוד מהקשרים חברתיים-תרבותיים מצד אחד, ובעל השלכות אישיות ובינאישיות מצד שני. אכן, בבני אדם ובעלי-חיים גם יחד, כעס מהווה גורם ראשוני לאגרסיביות ולאלימות. לפיכך, כעס נתון ואף תלוי באופן אינהרנטי ביכולות הפרט לשלוט ולווסת אותו. בעוד כעס נוטה להסלים בצורה מהירה, הוא מתמתן באיטיות בצורה שמאריכה את חווית הכעס מעבר לפרובוקציה של כעס. במהלך זמן זה אנשים נוטים לאמץ דפוסי חשיבה שליליים חוזרים ונשנים, הידועים בשם רומינציה של כעס, ונחשבים לתגובה רגולטורית בלתי מסתגלת המקושרת לאפקטים הממושכים של כעס, ושיכולים בפני עצמם להוביל לאגרסיביות. אם כן, ההתמודדות עם כעס אינה קלה ומגוון תוכניות תרפויטיות ופדגוגיות התפתחו כדי ללמד ולאמן אנשים לוסת ולנהל את כעסם. יחד עם זאת, חוסר איזון ודיסרגולציה של כעס נפוצים במצבים פסיכו-פתולוגיים רבים, מה שמדגיש את מרכזיותו של חווית רגש זה בחיים הנפשיים של בני האדם, בבריאות ובחולי. הבנת המנגנונים הפסיכו-ביולוגיים המתווכים כעס אנושי מהווה אתגר תיאורטי וניסויי, אך גם מעלה תקווה בדבר המאמצים למנוע את ההשלכות השליליות של כעס על חייהם של אנשים.

במסגרת נקודת מבט זו, תכנית המחקר הבאה שמה לעצמה כמטרה לחקור כיצד המוח האנושי מעבד כעס, בדגש על נתיב הזמן המיידי והארוך בדינאמיקה של כעס וביחס להתפתחות ולביטוי של תסמיני לחץ (סטרס), באמצעות מערך ניסויי פרוספקטיבי המשלב הדמיה מוחית עם מדדים התנהגותיים, פיזיולוגיים וסובייקטיביים. הנבדקים היו חיילים קרביים מיחידת הצנחנים בצבא הגנה לישראל ומתנדבי שנת שירות לאומי אשר גויסו להשתתף במחקר בתחילתה ובסופה של תקופה בת כשנה של אימון קרבי ושל שירות לאומי, בהתאמה. ההנחה הייתה שלא ימצאו הבדלים בין שתי קבוצות אלו בתגובה לכעס בין-אישי ובדינאמיקה המוחית קצרת הטווח בנקודת הזמן הראשונה, כפי שאכן נמצא ביחס לשתי המטרות הראשונות של תוכנית מחקר זו. לעומת זאת, ההבדלים בין הקבוצות יתגלו בנקודת הזמן השנייה לאור החוויה הפדגוגית והסטרס הכרוני אשר מקושרים לאימון קרבי מתקדם, כפי שאכן נמצא ביחס למטרה השלישית והרביעית של תוכנית מחקר זו.

מטרות שני היעדים הראשונים של המחקר היו לאפיין את התשתית הנוירו-התנהגותית של חווית כעס בינאישית, כפי שמוצג בפרק הרביעי, ולזהות את העקבות העצביות של חוויה זו, כפי שמוצג בפרק החמישי. לשם כך, פותחה מטלת קבלת החלטות המעוררת כעס ואשר מבוססת על משחק האולטימטום (UG), במהלכה נבדקים העוברים סריקה באמצעות דימות תהודה מגנטית תפקודית (fMRI) צריכים שוב ושוב להגיע (או לא) להסכמה עם שחקן מתחרה נוסף על אופן חלוקת סכום כסף ביניהם, כאשר אם הנבדק דוחה את הצעת השחקן השני, שני הצדדים מפסידים. יש לקחת בחשבון שבהינתן הרקע

עבודה זו בוצעה תחת הנחייתה של

פרופסור תלמה הנדלר

אוניברסיטת תל אביב

הפקולטה למדעי החברה ע"ש גרשון גורדון

בית הספר למדעי הפסיכולוגיה

מחקר נוירו-התנהגותי פרוספקטיבי על חוויה ורגולציה של כעס בבני אדם – פרלוד לסימפטומים של הפרעת דחק פוסט-טראומטית

גדי גילעם

חיבור לשם קבלת התואר "דוקטור לפילוסופיה"

מוגש לסנאט אוניברסיטת תל אביב

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