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Research Report

Attenuating anger and aggression with neuromodulation of the vmPFC: A simultaneous tDCS-fMRI study

Gadi Gilam [a,b,c,*,1], *Rany Abend* [a,b,d,1], *Guy Gurevitch* [a,b], *Alon Erdman* [a], *Halen Baker* [a], *Ziv Ben-Zion* [a,e] and *Talma Hendler* [a,b,e,f,**]

[a] *Tel Aviv Center for Brain Function, Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*
[b] *School of Psychological Sciences, Tel-Aviv University, Tel Aviv, Israel*
[c] *Division of Pain Medicine, Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Palo Alto, CA, USA*
[d] *Section on Development and Affective Neuroscience, National Institute of Mental Health, Bethesda, MD, USA*
[e] *Sagol School of Neuroscience, Tel-Aviv University, Tel Aviv, Israel*
[f] *Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel*

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ABSTRACT

Angry outbursts during interpersonal provocations may lead to violence and prevails in numerous pathological conditions. In the anger-infused Ultimatum Game (aiUG), unfair monetary offers accompanied by written provocations induce anger. Rejection of such offers relates to aggression, whereas acceptance to anger regulation. We previously demonstrated the involvement of the ventro-medial prefrontal cortex (vmPFC) in accepting unfair offers and attenuating anger during an aiUG, suggestive of its role in anger regulation. Here, we aimed to enhance anger regulation by facilitating vmPFC activity during anger induction, using anodal transcranial direct current stimulation (tDCS) and simultaneously with functional Magnetic Resonance Imaging to validate modulation of vmPFC activity. In a cross-over, sham-controlled, double-blind study, participants ($N = 25$) were each scanned twice, counterbalancing sham and active tDCS applied during administration of the aiUG. Outcome measures included the effect of active versus sham stimulation on vmPFC activity, unfair offers' acceptance rates, self-reported anger, and aggressive behavior in a subsequent reactive aggression paradigm. Results indicate that active stimulation led to increased vmPFC activity during the processing of unfair offers, increased acceptance rates of these offers, and mitigated the increase in self-reported anger following the aiUG. We also noted a decrease in subsequent aggressive behavior following active stimulation, but only when active stimulation was conducted in the first

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[*] *Corresponding author*. Systems Neuroscience and Pain Laboratory, Division of Pain Medicine, Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, 1070 Arastradero Road, Suite 200, MC 5596, Palo Alto, CA, 94304, USA.

[**] *Corresponding author*. Tel Aviv Center for Brain Function, Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center, Weizmann 6, Tel Aviv, 64239, Israel.

E-mail addresses: gadi.gilam@gmail.com (G. Gilam), hendlert@gmail.com (T. Hendler).

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experimental session. Finally, an exploratory finding indicated that participants with a stronger habitual tendency to use suppression as an emotion regulation strategy, reported less anger following the aiUG in the active compared to sham stimulation conditions. Findings support a potential causal link between vmPFC functionality and the experience and expression of anger, supporting vmPFC's role in anger regulation, and providing a promising avenue for reducing angry and aggressive outbursts during interpersonal provocations in various psychiatric and medical conditions.

1. Introduction

Anger is an omnipresent human experience, often aroused during interpersonal situations involving unfair treatment and personal insults (Averill, 1983; Baumeister, Stillwell, & Wotman, 1990; Fehr, Baldwin, Collins, Patterson, & Benditt, 1999; Gilam & Hendler, 2015; Miller, 2001). Aggression is the prototypical behavioral expression of anger in reaction to such provocations, potentially leading to unnecessary violence (Berkowitz & Harmon-Jones, 2004; Davidson, Putnam, & Larson, 2000; Rosell & Siever, 2015). While having an adaptive role in physical survival (Cannon, 1929) and in social relations (Keltner, Haidt, & Shiota, 2006; Novaco, 1976), the importance of anger (down) regulation is unequivocal. Unbalanced and excessive anger is prevalent in numerous psychopathological conditions, such as in Post-Traumatic Stress Disorder and various personality disorders (Novaco, 2010), as well as in other medical conditions, such as in cardiovascular disease (Williams, 2010) and chronic pain (Fernandez & Turk, 1995).

The neural bases of emotion regulation commonly engage regions of the prefrontal cortex (PFC) which exert control over regions involved in emotion reactivity such as the amygdala and insula (Buhle et al., 2014; Diekhof, Geier, Falkai, & Gruber, 2011; Etkin, Büchel, & Gross, 2015). This was similarly shown in the context of anger and aggression (Beyer, Münte, Göttlich, & Krämer, 2015; Fabiansson, Denson, Moulds, Grisham, & Schira, 2012; Jacob, Gilam, Lin, Raz, & Hendler, 2018; Morawetz et al., 2016). We previously demonstrated the recruitment of the ventro-medial prefrontal cortex (vmPFC) in modulating anger experience and aggressive expressions during an ecological induction of interpersonal anger (Gilam et al., 2015). Facilitating vmPFC recruitment during a naturalistic experience of anger may advance our understanding of the neural circuitry underlying anger and its regulation, and promote future development of brain-based treatments for conditions associated with excessive anger and aggression.

Transcranial direct current stimulation (tDCS) is a noninvasive method to safely modulate brain activity by applying a weak constant electrical current between electrodes placed over the scalp (Bikson et al., 2016; Shin, Foerster, & Nitsche, 2015; Woods et al., 2016). tDCS has been shown to increase neuronal excitability in the cortical area under the anode and decrease excitability in the area under the cathode. This emerging technique holds promise as an experimental means for causally manipulating neural activity for the study of cognition and behavior (Greenwood, Blumberg, & Scheldrup, 2018; Wörsching et al., 2016), as well as a potential treatment adjuvant for various pathological conditions such as major depressive disorder, chronic pain, and Alzheimer's disease (Fregni et al., 2015; Kuo, Chen, & Nitsche, 2017; Philip et al., 2017). Nevertheless, the overwhelming majority of studies do not include concurrent brain imaging to monitor and validate the effects of stimulation on targeted brain regions, presenting obstacles for effective implementation of neuromodulation (Shafi, Westover, Fox, & Pascual-Leone, 2012; Woods et al., 2016). In a recent exploratory study combining tDCS targeting the vmPFC with concurrent functional magnetic resonance imaging (fMRI) during a negative emotion induction task, anodal stimulation led to enhanced vmPFC activity coupled by decreased self-reports of emotion intensity and stress (Abend et al., 2018). Notably, these findings indicated tDCS could modulate vmPFC activity and influence subjective emotional states without instructing participants to regulate their emotions, complementing previous findings that tDCS targeting the dorsolateral PFC enhanced participants' explicit efforts to regulate emotions (Feeser, Prehn, Kazzer, Mungee, & Bajbouj, 2014).

Here, we applied anodal stimulation aiming to enhance vmPFC activity and implicitly facilitate anger regulation during an ecological induction of anger, thereby attenuating anger experience and expression. We conducted stimulation simultaneously with fMRI to monitor and validate its effect on vmPFC activity. Twenty-five healthy participants were each scanned twice in a cross-over, sham-controlled and double-blind design in which stimulation was applied while participants played the responder in an anger-infused Ultimatum Game (aiUG). In this task, a proposer decides how to split a sum of money between himself and a responder, who then decides whether to accept or reject the offer, thereby both players gain or lose the allocated money, respectively. Standard UG studies previously demonstrated that as offers become more unfair, they induce more anger and decrease the probability that responders accept (e.g., Dunn, Evans, Makarova, White, & Clark, 2012; Paz et al., 2017; Sütterlin, Herbert, Schmitt, Kübler, & Vögele, 2011). Moreover, rejecting an unfair offer is associated with aggressive retribution (e.g., Crockett et al., 2013; Mehta & Beer, 2010; White et al., 2015), whereas accepting unfair offers relates to down regulating the anger associated with such offers (e.g., Grecucci, Giorgetta, Wout, Bonini, & Sanfey, 2013; van't Wout, Chang, & Sanfey, 2010; Wang et al., 2011). Anger in the aiUG is further induced by means of interpersonal provocations embedded as short written messages congruent with the level of offer-unfairness, rendering the aiUG a more valid paradigm, compared to the standard UG, for inducing and assessing anger in an interpersonal context (Gilam, Abend, Shani, Ben-Zion, & Hendler, 2018). Using an aiUG, we demonstrated that vmPFC activity during unfair offers modulated the inverse relationship between anger and acceptance rates (Gilam et al., 2015).

Our primary hypothesis was that active anodal relative to sham tDCS during the aiUG would lead to increased vmPFC activity, particularly during the processing of angering unfair offers, thereby increasing acceptance rates of unfair offers and decreasing levels of self-reported anger following the task. In addition, we examined whether the effects of stimulation would extend to influence aggression in a subsequent provocation, as assessed using the Taylor Aggression Paradigm (TAP; Giancola & Parrott, 2008; Giancola & Zeichner, 1995). The TAP similarly engages the vmPFC in facilitating nonaggressive behavior (Beyer et al., 2015), and was previously shown to be susceptible to a preceding application of tDCS (e.g., Hortensius, Schutter, & Harmon-Jones, 2012). We therefore hypothesized that active stimulation targeting the vmPFC would lead to decreased aggression in the TAP. Finally, we examined the neural correlates of anger in the aiUG by exploring neural differences between offer types, and explored individual differences in trait anger and trait emotion regulation and their relationship to responsivity to stimulation.

2. Materials and methods

2.1. *Participants*

Twenty-five healthy participants (15 females; $M_{age} \pm SD = 26.16 \pm 3.63$ years; range = 21–33 years) recruited via social media advertisements took part in the study for monetary compensation. All participants had at least 12 years of education. They all completed a screening questionnaire to rule out any neurological or psychiatric disorders or contraindications to MRI or tDCS. The Institutional Ethics Committee of Tel-Aviv Sourasky Medical Center approved the study in accordance with the Helsinki Declaration and all participants signed an informed consent.

2.2. *General procedure*

Each participant completed two identical study sessions within 6–9 days ($M = 7.08 \pm .74$), in which active stimulation was applied in one, and sham stimulation in the other (see below; order of sessions counterbalanced across participants). Each study session was divided into several phases (Fig. 1A) beginning with a thorough explanation of the aiUG. We emphasized that at the end of data collection, the three participants who accumulated the largest sum of accepted offers would receive their actual monetary earning. Electrodes were then mounted and participants entered the scanner, beginning with anatomical scans and a 6-min rest scan (not analyzed here). Stimulation was initiated before the aiUG and continued throughout the task and associated emotion ratings. Finally, another rest scan was conducted. Upon exiting the scanner, participants completed a stimulation debriefing questionnaire to verify blindness to the stimulation conditions (see Supplementary material) and the TAP. Prior to the scan in the first study session, participants completed personality trait inventories (see Supplementary material). At the end of the second session, participants were debriefed. No participants articulated suspicion regarding the TAP or aiUG manipulations. Extended procedural information is detailed in Supplementary material.

2.3. *Electrical stimulation*

Electrical stimulation was applied during fMRI acquisition using an MR-compatible stimulation system (DC-Stimulator MR, neuroConn GmbH, Germany), via two 35 cm^2 electrodes with 5 kΩ resistors. High-chloride electro-conductive paste was applied under the electrodes to improve conduction. In line with previous studies targeting the vmPFC (Abend et al., 2016, 2018; Civai, Miniussi, & Rumiati, 2015), the anodal electrode was placed vertically over the forehead, with its side edges equidistant from the eyes, and the lower edge at the nasion line (Fig. 1B). The cathodal return electrode was placed extra-cephalically on the right shoulder. The electrodes were further kept in place with a head sweat-band (anode) and elastic band-aid (cathode). We used this montage to minimize both confounding effects due to stimulation of brain regions beneath the cathode and discomfort and head-movement during fMRI acquisition. Both computerized current flow modeling (Bai, Dokos, Ho, & Loo, 2014; Truong et al., 2014; Figure S1) and our previous study (Abend et al., 2018) indicate that this montage should result in enhanced vmPFC activity.

Participants were not explicitly notified that one session will involve active stimulation and the other sham stimulation, since we did not want their attention to focus on trying to identify stimulation type during the task, potentially yielding confounding and other interfering effects. Instead, we instructed them that both study visits may or may not involve stimulation at different time points. Stimulation initiated without informing the participants. During active stimulation, a direct current of 1.5 mA was delivered for 22 min with 30 sec of ramp up and down at the beginning and end of stimulation, respectively. During sham stimulation, the ramp-up was immediately followed by a 30-sec ramp-down of the current. Experimenters were blind to stimulation conditions as these were programmed and carried out automatically. Participants were blind to the stimulation conditions; successful blindness was verified using the stimulation debriefing questionnaire (see results in Supplementary material). Immediately before and after current ramp-up, participants rated their general stress levels on a 0 (not at all) to 10 (very much) scale. An increase in stress levels was noted across all sessions [before: $M = .77 \pm 1.21$; after: $M = 1.17 \pm 1.48$; $F(1,23) = 5.09$, $p = .03$; missing data for one participant] and this increase did not differ between stimulation conditions [$F(1,23) = .06$, $p = .80$]. This minor increase is in line with stimulation debriefing in which participants reported sensing the stimulation in 80% of all study sessions. Further information on debriefing is detailed in Supplementary material.

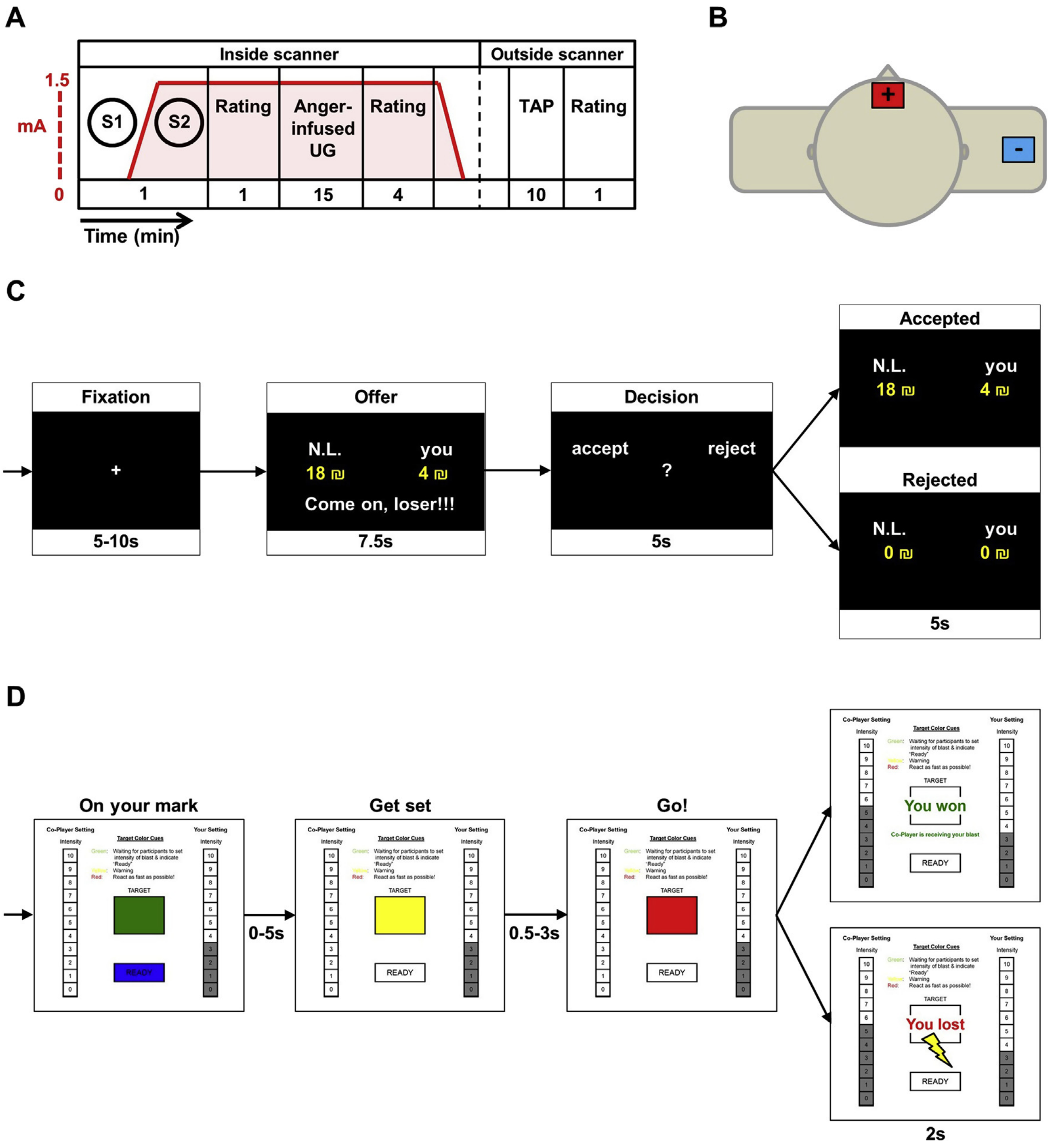

Fig. 1 – **Study design and task structure. (A) Illustration of the active stimulation experimental session, in terms of the intensity of applied current (in milliAmpere, red), time (minutes) and tasks both in and out of the scanner. Subjective stress levels were measured before and after initiation of stimulation (S1 and S2, respectively). (B) Illustration of electrode montage, with the anode (red) placed supra-orbitally and the cathode (blue) on the right shoulder. (C) Sequence of one trial in the anger-infused Ultimatum Game (aiUG). Each round began with a short fixation period, supposedly the time in which the computer draws offers from the pool of previous putative participants. A randomly drawn offer is then presented, coupled with an interpersonal message. Participants then had to decide whether to accept or reject the offer, and then viewed the outcome of their decision. This sequence was repeated 36 times in total. (D) Sequence of one round in the Taylor Aggression Paradigm (TAP). After participants chose the noise-blast intensity to inflict on their opponent if they won the round, and pressed a 'ready' button, the target at the center of the screen turned green. The target changed to yellow as soon as the putative competitor also pressed their 'ready' button, indicating the competition was about to begin. Once the target color changed to red, participants had to press the mouse button as quickly as possible. Finally, the winner was declared allegedly based on the shortest reaction-time. If the participant lost the round, the noise-blast (in the intensity chosen by their opponent) was administered through headphones for 2 sec.**

2.4. Anger-infused Ultimatum Game

The aiUG is a paradigm to induce and assess interpersonal anger with sound test-retest reliability and convergent validity (Gilam et al., 2018). Analogous to a typical UG, in the aiUG participants respond to randomly-drawn offers supposedly made by previous participants. All offers were in fact predetermined to include 12 fair offers (responder is offered 40–50% of the total sum), 12 medium offers (25–35% of the total), and 12 unfair offers (10–20% of the total). Stake size in each offer ranged between 20 and 30 Israeli New Shekel (ILS; equivalent to 5.5–8.5 USD). Offers were accompanied by the initials of putative proposers to avoid potential effects related to gender or names (Fig. 1C). Each offer also included a short written message (max of 35 characters) that was congruent with the offer type: fair offers included non-confrontational messages (e.g., *Let's split it equally*), while medium (e.g., *That's the offer*, *deal with it*) and unfair (e.g., *Come on*, *loser!!!*) offers included mild and intense provocations, respectively. We previously demonstrated that messages that are more provocative induced more anger (Gilam et al., 2018). Two sets of comparable offers (Table S1) and two sets of messages (Table S2) per each offer type were used and counterbalanced between sessions. Within each set and each offer type, coupling of offers and messages was randomized across participants, as was the order of presented offers. Upon completion of the aiUG task, participants were asked to rate their emotional response and fairness perception (presented randomly) in relation to each of the three types of offers, on a scale of 0 (not at all) to 10 (very much). Emotion categories included Anger, Fear, Sadness and Happiness (Gilam et al., 2018). See Supplementary material for additional information.

2.5. Taylor Aggression Paradigm

The TAP was used to assess transfer effects of stimulation on behavior in a subsequent interpersonal provocation. The TAP is a psychometrically sound task assessing reactive aggression as operationalized by the level of aversive noise intensity chosen to be administered to an ostensive opponent in a reaction-time competition (Beyer et al., 2015; Giancola & Parrott, 2008; Giancola & Zeichner, 1995). During the task, participants are led to believe they are playing against a real opponent in real time, supposedly an additional study participant in a different room, both competing to respond as quickly as possible (using a computer mouse) when a target on their screens simultaneously turns red. At the end of each task round (Fig. 1D), the winner is declared, and the level of noise intensity chosen by each player is revealed. In parallel, the player who lost the round is administered (through headphones) the noise blast at the intensity chosen by their supposed opponent, for 2 sec. The noise level set by the putative competitor was in fact predetermined to increase gradually across the ten task rounds. The task was programmed such that participants always lost the first and last rounds, while they randomly won 50% of the remaining rounds. Further information is detailed in the Supplementary material. Due to technical malfunction data were not acquired in one of the experimental sessions, leaving a total 24 participants with TAP data.

2.6. State emotion ratings

To assess changes in the ongoing emotional state of participants due to the tasks, they were asked to rate the same four emotion categories (presented randomly), namely Anger, Fear, Sadness and Happiness, on a 0 (not at all) to 10 (very much) scale. These emotion states were assessed before the aiUG, after the aiUG and after the TAP (Gilam et al., 2018). Due to technical malfunction, data were not acquired for six participants, leaving a total 19 participants with emotion rating data.

2.7. Behavioral data analysis

We first tested the effect of active versus sham stimulation on anger induced in the aiUG as assessed by behavioral and emotional measures of the aiUG. To this end, offer acceptance rates, decision reaction times (detailed in Supplementary material) and emotion and fairness perception ratings were each submitted to a separate repeated-measures analysis of variance (ANOVA), with offer type (fair, medium, unfair) and stimulation (active, sham) as within-subject factors. We also examined whether total gain in the aiUG differed between stimulation sessions as it captures individual differences in decision behavior (for example, one who accepted 13:14 and 9:19 offers has a different gain but equal acceptance rate compared with one who accepted 12:13 and 7:17 offers).

We next examined the effect of stimulation on subsequent aggression as elicited by the TAP. Chosen noise-blast intensities for the ten task rounds were submitted to a repeated-measures ANOVA, with round (1–10) and stimulation (active, sham) as within-subject factors. As reported previously (Gilam et al., 2018), three additional measures of aggression were examined using repeated-measures ANOVA. The blast intensity in the first round was used as a measure of unprovoked aggression following the aiUG as this round is unrelated to subsequent provocations (the opponent's noise blast intensities) in the TAP (e.g., Bushman & Baumeister, 1998; Konijn, Bijvank, & Bushman, 2007). The change in blast intensity between the first and last round of the TAP and the maximal blast intensity administered during the TAP were used as measures of provoked aggression following the aiUG.

Finally, we examined whether emotional states induced by the tasks were differentially influenced by stimulation. Emotion ratings were each entered to a repeated-measures ANOVA, with stimulation (active, sham) and period (pre-aiUG, post-aiUG, post-TAP) as within-subject factors. Two between-subject factors reflecting the order of stimulation (sham-then-active, active-then-sham) and the set order of aiUG offers (A-B, B-A) were added to all ANOVAs described above to test for possible differences associated with these factors. Significant higher-order ANOVAs were decomposed by lower-order ANOVAs, and associations between continuous measures were examined using Pearson correlation coefficients. All hypotheses tested were two-sided and significant effects were determined at $\alpha \leq .05$.

2.8. fMRI data acquisition

Brain imaging was performed by a Siemens 3T Prisma scanner using a 20-channel head coil at the Wohl Institute for

Advanced Imaging, Tel-Aviv Sourasky Medical Center. Functional whole-brain scans were performed with gradient EPI sequence of functional T2*-weighted images (TR/TE = 2500/35 msec; flip angle = 90°; FOV = 220 × 220 mm; slice thickness = 3.0 mm, no gap; 38 interleaved bottom-to-top axial slices per volume). Anatomical T1-weighted 3D axial MP-RAGE sequence (TR/TE = 1860/2.74 msec; flip angle = 8°; FOV = 256 × 256 mm; slice thickness = 1 mm) was acquired to provide high-resolution structural images.

2.9. *fMRI preprocessing and analysis*

Preprocessing and statistical analyses were conducted using BrainVoyager QX version 2.8 (Brain Innovation). Each scan began with 6 volumes (15 sec) of fixation 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 application 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 6 mm FWHM Gaussian kernel. To avoid excluding participants based on excessive head-movements (>1 voxel), the data of two functional scans belonging to two participants were cut after 274 and 319 TRs (out of 360). In these two cases there were at least 7 repetitions of each offer type per each stimulation condition.

A single whole-brain random-effects General Linear Model (GLM) was computed which included 19 regressors: three for each phase of the task (offer/decision/result) repeated thrice for the different types of offers (fair/medium/unfair) and again repeated twice for the two stimulation scans (active/sham). The fixation period was used as baseline. Regressors were convolved with a canonical hemodynamic response function. Additional nuisance regressors included the head-movement realignment parameters and the time courses of averaged activity in cortical white matter and in cerebrospinal fluid. We applied a gray matter mask and corrected for temporal autocorrelations using a second-order autoregressive model. We then submitted the BOLD brain activity during the offer phase to an offer type (fair, medium, unfair) by stimulation condition (active, sham) ANOVA. We applied false discovery rate (FDR) of $\alpha = 5\%$ to correct brain activity maps for multiple comparisons and applied a minimal cluster size of $k \geq 10$ contiguous functional voxels (Lieberman & Cunningham, 2009). Subsequent analyses on the resulting regions of interest (ROI) were performed by calculating the average percent signal change (%SC) during the offer periods relative to the entire time course (averaged across all ROI voxels). To note, we performed functional connectivity analyses with individuated ROIs using psychophysiological interaction but no results survived statistical thresholds.

3. Results

3.1. *Offer acceptance rate and total gain in the aiUG*

To examine the effect of stimulation on participants' decisions to accept or reject aiUG offers, an ANOVA was performed on average acceptance rates. In line with previous UG findings, a significant main effect of offer type was revealed, F (2,42) = 30.35, $p < .001$, $\eta_p^2 = .59$, with follow-up analyses indicating decreasing acceptance rates with increasing unfairness of offers (fair: M = 93.33 ± 15.09%, medium: M = 61.00 ± 36.87%, unfair: M = 35.50 ± 43.23%), $ps < .001$. In line with our hypothesis, this effect was qualified by a significant offer type by stimulation interaction, F (2,42) = 3.36, $p = .04$, $\eta_p^2 = .14$ (Fig. 2A), with follow-up analyses indicating higher acceptance rates for unfair offers during active (M = 41.33 ± 45.12%) compared to sham stimulation (M = 29.67 ± 40.42%), t (24) = 2.03, $p = .05$, Cohen's $d = .27$. Acceptance rates for fair and medium offers did not differ between stimulation conditions, ts (24) < 1.00, $ps > .33$. The ANOVA on total gain in the task did not result in any significant effects ($ps > .27$).

3.2. *Emotion and fairness ratings to aiUG offers*

To examine the effect of stimulation on emotion ratings in response to the different offer types, as reported after completion of the aiUG task, an ANOVA was performed on emotion ratings, revealing a significant main effect of emotion category, F (3,63) = 18.60, $p < .001$, $\eta_p^2 = .47$. This effect was qualified by a significant emotion category by offer type interaction, F (6,126) = 58.43, $p < .001$, $\eta_p^2 = .74$ (Fig. 2B). Follow-up repeated-measures ANOVAs conducted within each offer type revealed a significant main effect of emotion category within each type, $Fs(3,72) > 6.02$, $ps < .001$, $\eta_p^2 > .20$. Among fair offers, happiness was rated significantly higher relative to all other emotions ($ps < .001$). Among medium offers, fear was rated significantly lower relative to all other emotions ($ps < .001$). Among unfair offers, anger was rated significantly higher relative to all other emotions ($ps < .006$). In addition, we noted a significant offer type by stimulation by stimulation order interaction, F (2,42) = 3.27, $p = .05$, $\eta_p^2 = .13$, with follow-up analyses indicating emotional ratings were generally higher for medium offers during sham compared to active stimulation ($p < .01$), but only if active stimulation was conducted in the first experimental session. No other significant effects emerged.

To examine the effect of stimulation on fairness perception, an ANOVA was performed on fairness ratings, revealing a significant main effect of offer type, F (2,42) = 324.78, $p < .001$, $\eta_p^2 = .94$, with follow-up tests indicating a decrease in fairness perception as offers became more unfair, $ps < .001$. This effect was qualified by a significant offer type by stimulation interaction, F (2,42) = 4.25, $p < .02$, $\eta_p^2 = .17$. Follow-up tests indicated that unfair offers were rated as more fair following active (M = 1.12 ± 1.88) compared to sham (M = .32 ± .56) stimulation, $p = .02$, $d = .58$. In addition, we noted a significant offer type by stimulation order interaction, F (2,42) = 9.81, $p < .001$, $\eta_p^2 = .32$. Follow-up tests indicated fair offers were

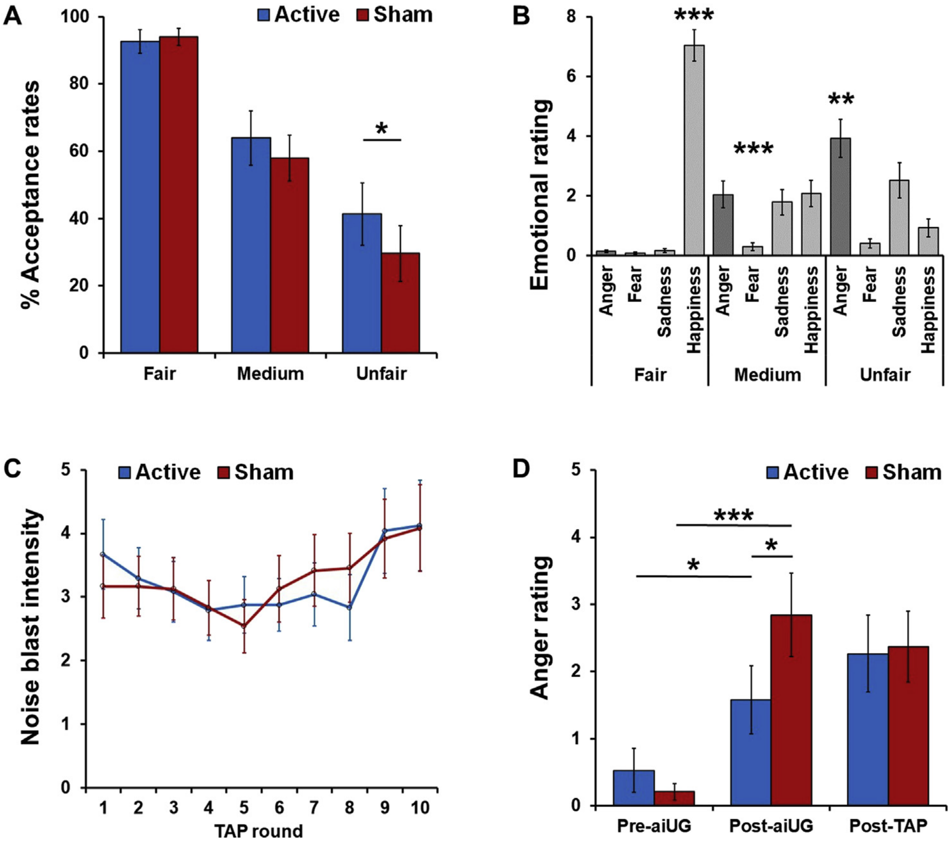

Fig. 2 – Effects of stimulation on behavioral and self-reported emotion measures. (A) Mean acceptance rates (%) per offer type ($n = 25$) in the aiUG, indicating decreased acceptance rates as offers become more unfair (*ps* $< .001$), but higher acceptance rates for unfair offers during active (blue) compared to sham (red) stimulation ($p < .05$). (B) Mean self-reported rating of the emotion categories (Anger, Fear, Sadness and Happiness) in response to the different offer types presented in the aiUG (Fair, Medium and Unfair; $n = 25$), indicating that among fair offers, happiness was rated significantly higher relative to all other emotions (*ps* $< .001$); among medium offers, fear was rated significantly lower relative to all other emotions (*ps* $< .001$); and among unfair offers, anger was rated significantly higher relative to all other emotions (*ps* $< .01$). An increase in anger is apparent as offers become more unfair. (C) Mean noise-blast intensity chosen by participants in each round of the TAP ($n = 24$), presented for the active and sham stimulation conditions, indicating an overall increase in noise intensities as the game progressed ($p < .001$). (D) Mean self-reported rating of state anger ($n = 19$) at pre-aiUG, post-aiUG, and post-TAP, indicating an increase in anger between before and after the aiUG for both active and sham stimulation conditions (*ps* $< .05$), but less anger following the aiUG for active compared to sham stimulation ($p < .05$). Error bars signify ±1 standard error of the mean. $^{*} = p \le .05$, $^{**} = p \le .01$, $^{***} = p \le .001$.

rated more fair ($p = .05$) and medium offers were rated less fair ($p = .02$) when active stimulation was conducted in the first experimental session (fair: $M = 9.88 \pm .43$, medium: $M = 2.04 \pm 2.32$) compared to when sham stimulation was conducted in the first experimental session (fair: $M = 8.83 \pm 2.44$, medium: $M = 3.88 \pm 2.09$). No other significant effects emerged.

3.3. *Noise blast intensity in the TAP*

To examine the effect of stimulation on subsequent aggression in the TAP, an ANOVA was performed on participants' chosen noise intensities in each round. In line with previous findings, a significant main effect of round was revealed, $F\ (9{,}180) = 4.92$, $p < .001$, $\eta_p^2 = .20$, with follow-up analyses indicating higher chosen noise-blast intensity to be administered to the putative adversary in the last two rounds of the task compared to all previous rounds (*ps* $< .05$; Fig. 2C). The main effect of round was qualified by a round by stimulation by stimulation order interaction, $F\ (9{,}180) = 2.24$, $p = .02$, $\eta_p^2 = .10$. In relation to this effect, the ANOVA using the provoked aggression measure of increase in blast intensity between the first and last round of the TAP indicated a significant stimulation by stimulation order interaction, $F\ (1{,}22) = 5.00$, $p = .04$, $\eta_p^2 = .19$. In partial support of our hypothesis, this effect indicated a decrease in blast intensity along the TAP during active stimulation when *active* stimulation was conducted in the first experimental session ($M = -1.00 \pm 3.38$), compared to an increase in blast intensity when *sham* stimulation was conducted in the first session ($M = 1.92 \pm 2.78$; $p = .03$, $d = .94$). No other significant effects emerged, including the other measures of unprovoked (1st round intensity) and provoked (max intensity) aggression.

3.4. *Effects of tasks on state emotions*

To examine the effect of stimulation on emotional states induced by the tasks (prior to aiUG, after aiUG, and after TAP), and on anger particularly, an ANOVA on emotion ratings revealed a significant main effect of period, $F(2,30) = 4.43$, $p = .02$, $\eta_p^2 = .23$, and a main effect of emotion category, $F(3,45) = 13.14$, $p < .001$, $\eta_p^2 = .47$. These effects were qualified by a significant period by emotion category interaction, $F(6,90) = 3.99$, $p = .001$, $\eta_p^2 = .21$. Follow-up repeated-measures ANOVAs conducted within each emotion category revealed a significant main effect of period for anger, $F(2,36) = 10.12$, $p < .001$, $\eta_p^2 = .36$, qualified by a significant time by stimulation interaction $F(2,36) = 4.58$, $p = .02$, $\eta_p^2 = .20$ (Fig. 2D). As hypothesized, break-down tests indicated that while anger increased following the aiUG in both active (pre-aiUG: $M = .53 \pm 1.43$, post-aiUG: $M = 1.58 \pm 2.19$, $p = .04$) and sham (pre-aiUG: $M = .21 \pm .54$, post-aiUG: $M = 2.84 \pm 2.71$, $p < .001$) stimulation sessions, less anger was reported following the aiUG for active compared to sham stimulation ($p = .03$, $d = .51$). No significant effects emerged for fear ($ps > .22$), happiness ($p > .33$) and sadness ($ps > .06$).

3.5. *Brain activity*

To examine the effect of stimulation on brain activity during the offer phase we tested a whole-brain ANOVA with offer type and stimulation as within-subject factors. The stimulation main effect and the offer type by stimulation interaction effect did not reveal any clusters of brain activity that survived the defined statistical threshold. Since the effect of stimulation on behavior was hypothesized and found in the unfair offer condition, we examined how this stimulation effect manifested on neural activity by testing the simple effect contrasting brain response to unfair offers during active versus sham stimulation. In line with our hypothesis, there was increased activity in the vmPFC during active compared to sham stimulation (Fig. 3; Table S3; illustrated in Fig. 3B). We also noted decreased activity in the anterior cingulate cortex (ACC) and left insula (in anterior, middle and posterior clusters; illustrated in Fig. 3B), two regions previously associated with processing unfairness and anger (Damasio et al., 2000; Denson, Pedersen, Ronquillo, & Nandy, 2009; Gilam et al., 2015; Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003), potentially indicating downstream effects of vmPFC stimulation.

The offer type main effect revealed numerous brain regions (Figure S1; Table S4). Follow-up ROI analyses to explore the pattern of activity (illustrated in Figure S1B) indicated that the main effect in most of these regions was driven by strongest response to fair or to unfair offers. A few regions, including the uncus, midbrain, right anterior insula and ACC, demonstrated strongest response to medium offers. Since medium offers had longer decision reaction times (RT) compared to fair and unfair offers (see Supplementary Material), it is possible that activity in those regions relate to additional cognitive processing, such as conflict monitoring in the ACC (Botvinick, Cohen, & Carter, 2004). To compare a non-angering with an angering condition directly, we contrasted between the fair and unfair offers, and most of the same brain regions as in the offer main effect reappear (Fig. 4; Table S5). Angering unfair offers recruited more activity in dorsomedial prefrontal cortex (dmPFC; illustrated in Fig. 4B), bi-lateral insula extending to inferior frontal gyrus (IFG), bi lateral temporal parietal junction (TPJ), thalamus and left temporal pole. These regions were previously associated with processing unfair offers (Feng, Luo, & Krueger, 2015), as well as with mediating the experience of anger (Gilam & Hendler, 2015). Fair offers recruited more activity in posterior cingulate cortex (PCC; illustrated in Fig. 4B), bi-lateral and medial PFC and regions in the bi-lateral parietal and temporal lobes.

3.6. *Exploration of the relationships between traits, task behaviors and brain activity*

We explored individual differences in trait anger, and in the habitual tendency to use two emotion regulation strategies, namely trait suppression and trait reappraisal, and their association with the effects of stimulation on anger-related task measures (namely, acceptance rates for unfair offers, total gain, reported anger and fairness for unfair offers, post-aiUG anger and level of increase in noise-blast intensities) and brain activity (in vmPFC, ACC and left insula; see Table S6). To this end, we calculated difference scores (active minus sham stimulation) for each of these measures. Trait suppression correlated negatively with post-aiUG anger ($r = -.56$, $p = .01$), suggesting that participants who reported a stronger tendency to use suppression as an emotion regulation strategy, showed a greater effect of stimulation on reducing post-aiUG anger. In contrast, the same anger difference score did not correlate with trait reappraisal ($r = .15$, $p = .55$). The difference between these correlation coefficients was tested using the Fisher transformation and found to be significant ($Z = -2.60$, $p = .01$; Fig. 5A). We also explored associations within the calculated difference scores, specifically between the anger related task measures and brain activity, but no significant results emerged ($rs < .30$, $ps > .15$).

Finally, we explored individual differences in the measured traits and in the same anger related task measures, and their association with brain activity in regions associated with processing angering unfair offers (namely, in dmPFC, thalamus, bi-lateral insula/IFG, and bi-lateral TPJ; Table S7). Activity in the thalamus correlated positively with trait suppression ($r = .42$, $p = .04$), and not with trait reappraisal ($r = -.19$, $p = .36$). The difference between these correlation coefficients was found to be significant ($Z = 2.13$, $p = .03$). Activity in the left insula/IFG positively correlated with both trait anger ($r = .53$, $p = .01$) and post-aiUG anger ($r = .62$, $p < .005$). A follow-up bootstrap-based mediation test with 10,000 iterations (Hayes, 2012) indicated a significant indirect effect such that activity in the left insula/IFG mediated the direct relationship between trait anger and post-aiUG anger (Fig. 5B).

3.7. *Exploration of baseline differences between participants starting with either active or sham stimulation*

Additional analyses were conducted to compare the two randomly selected groups who either started first with the active stimulation condition ($n = 13$) or first with the sham

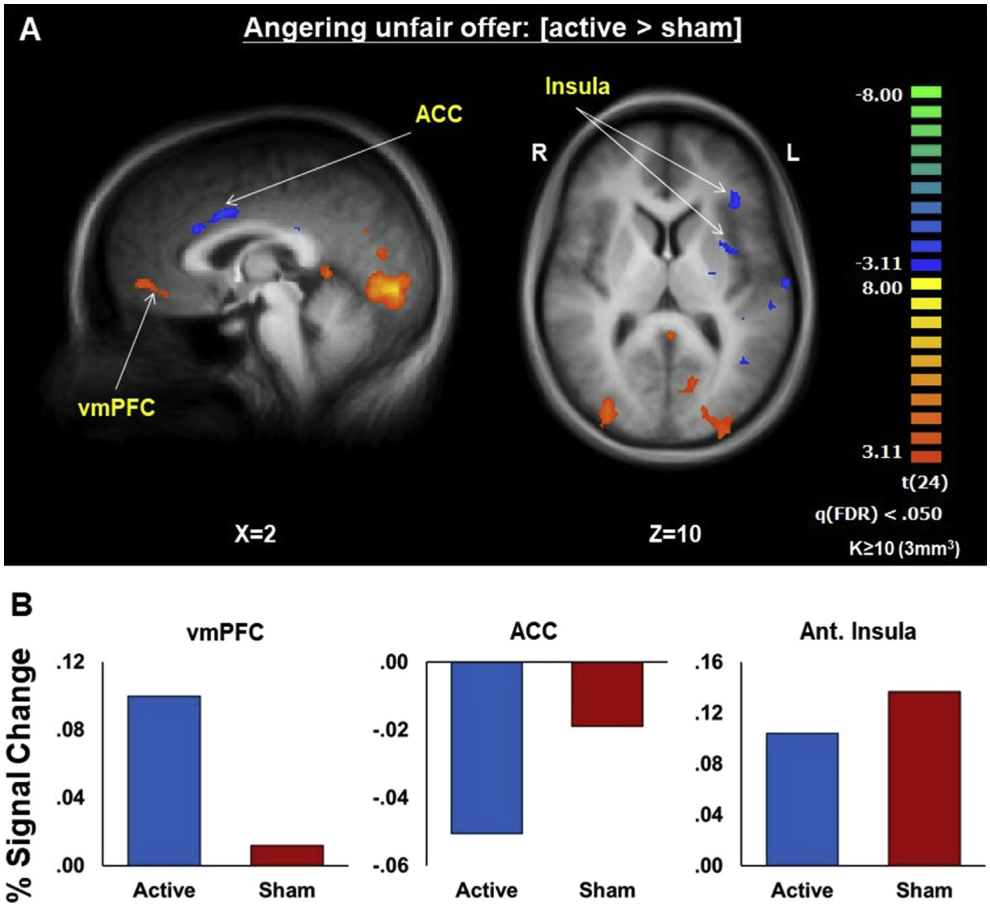

Fig. 3 – Active stimulation led to increased activity in the vmPFC. (A) Brain activity map presenting the simple effect of active versus sham stimulation on brain activity during unfair offer phase. Clusters are presented at a voxelwise threshold of q (FDR) < .05 with a minimal cluster size of k ≥ 10 contiguous *functional* voxels (3 mm^3; in Talairach space, overlaid on an average anatomical image of all participants). (B) Average percent signal change during unfair offers extracted for the vmPFC, ACC and left anterior Insula, demonstrating the effect seen in the brain activity map. vmPFC = ventromedial prefrontal cortex; ACC = anterior cingulate cortex; L = left; R = right.

stimulation conditions (n = 12). These two groups did not differ in any of the demographic and personality measures (*ps* > .12). We also repeated all the behavior and emotional self-reports analyses (as detailed above) for the first session only and found no group differences (*ps* > .10). To note however, in line with our findings for the entire data-set, the average acceptance rate for unfair offers was descriptively higher in the stimulation-first group (41.67 ± 44.88%) compared to the sham-first group (20.83 ± 31.08%, *p* = .19), and the level of anger increase following the task was descriptively lower in the stimulation-first group (2.92 ± 2.47) compared to the sham-first group (2.54 ± 3.13, *p* = .74). We repeated these analyses again, this time comparing the two groups for their behavior and emotional self-reports only for the sham stimulation condition, and found no group differences (ps > .11), though we did notice a trend indicating higher anger following the TAP in the stimulation-first group (4.10 ± 3.32) compared to the sham-first group (1.83 ± 1.90, *p* = .06). As such, we conclude that the reported findings are not a result of a priori baseline differences between those participants who began with the stimulation condition compared to those that began with the sham condition, nor of a potential “worsening of the sham” effect instead of an improvement caused by the active stimulation.

3.8. *Exploration of the consistency of active stimulation effects*

We categorized participants according to change in their total gain between the two stimulation sessions. Fifteen (60%) participants demonstrated an increase in gain in the active compared to the sham stimulation conditions. Eight (32%) participants showed a decrease in gain, and two (8%) participants showed no change. This distribution was significantly different from the chance expected distribution ($\chi^2 = 6.59$, $p = .04$), suggesting the effect of active stimulation was consistent across participants. We performed a similar analysis in regards to the anger ratings after the aiUG. Eleven (58%) participants reported less anger after the aiUG in the active compared to the sham stimulation conditions, while four (21%) participants reported the opposite, and four (21.05%) participants showed no change. Similarly, for vmPFC activity,

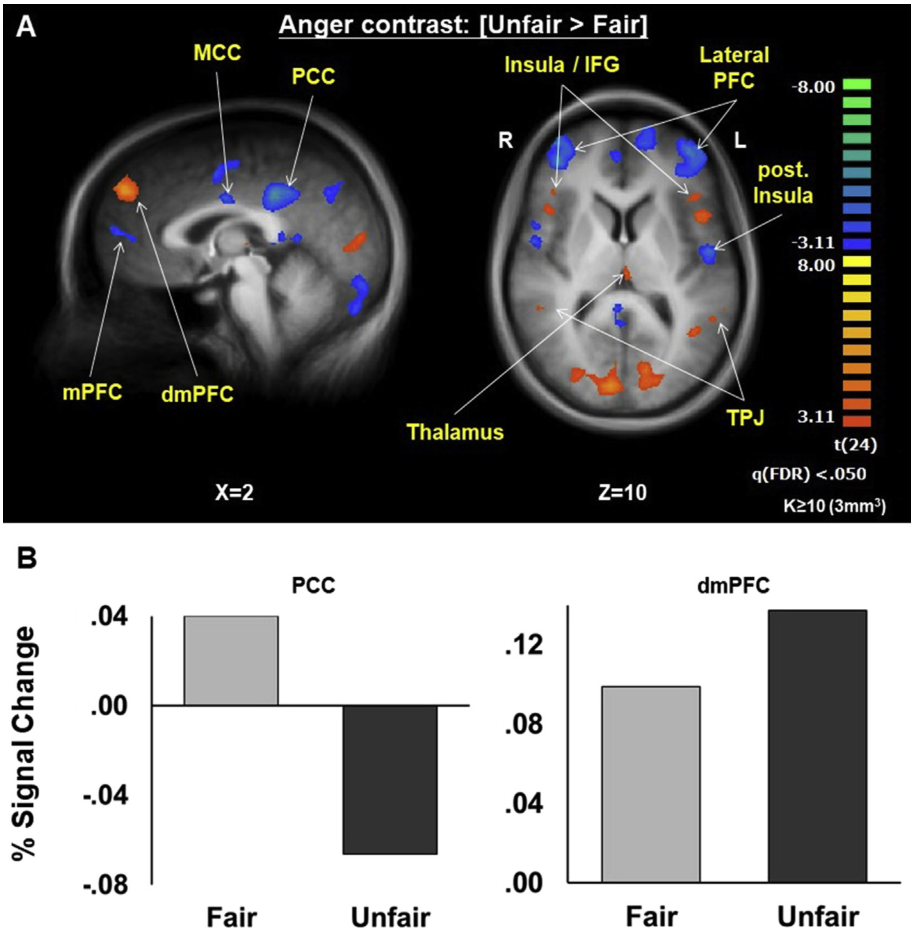

Fig. 4 – Brain regions associated with angering unfair offers. (A) Activity map in Talairach space depicting the contrast of brain activity during unfair versus fair offer periods, presented at a threshold of q (FDR) < .05 with a minimal cluster size of k ≥ 10 contiguous *functional* voxels (3 mm^3) and overlaid on an average anatomical image of all participants. (B) Average percent signal change during fair and unfair offers extracted for the PCC and dmPFC, demonstrating the effects seen in the brain activity map. MCC = mid-cingulate cortex; PCC = posterior cingulate cortex; mPFC = medial prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; IFG = inferior frontal gyrus; TPJ = temporoparietal junction; post. = posterior; L = left; R = right.

14 (56%) participants showed an increase in activity in the active compared to the sham stimulation conditions, while 11 (44%) participants showed the reverse. These two distributions for anger ratings and vmPFC activity were not significantly different than chance (χ^2s < .08, *ps* > .78) suggesting that the group-average observed effect of active stimulation was not consistent across all participants for these two measures.

4. Discussion

Prior work indicates the involvement of the vmPFC in increasing acceptance of unfair offers and attenuating anger during an aiUG (Gilam et al., 2015), suggestive of its role in implicit anger regulation, and in line with its broader role in self control (e.g., Maier & Hare, 2017) and emotion regulation (e.g., Etkin et al., 2015). In the current study, we applied anodal stimulation, concurrently with fMRI validation, to enhance vmPFC activity during the experience of interpersonal anger as induced by the aiUG. Results indicate that relative to sham, active stimulation increased vmPFC activity during the processing of unfair offers (coupled by changes in ACC and insula activity), increased acceptance rates of such offers, and mitigated the increase in self-reported anger following the aiUG, though only for about 60% of the participants. Notably, stimulation did not influence other emotion categories. Results also indicate that when active stimulation preceded sham, less aggression was noted in subsequent provocation (i.e., during the TAP). Finally, an exploratory finding indicated that participants with a stronger habitual tendency to use suppression as an emotion regulation strategy, reported less anger following the aiUG in the active compared to sham stimulation conditions. This result further supports a possible interpretation that the neurobehavioral changes induced by active stimulation may be associated with emotion regulation processes, as well as highlights a potential marker for individuals that may a priori benefit more from such intervention. Taken together, these findings provide evidence that application of non-invasive electrical stimulation targeting

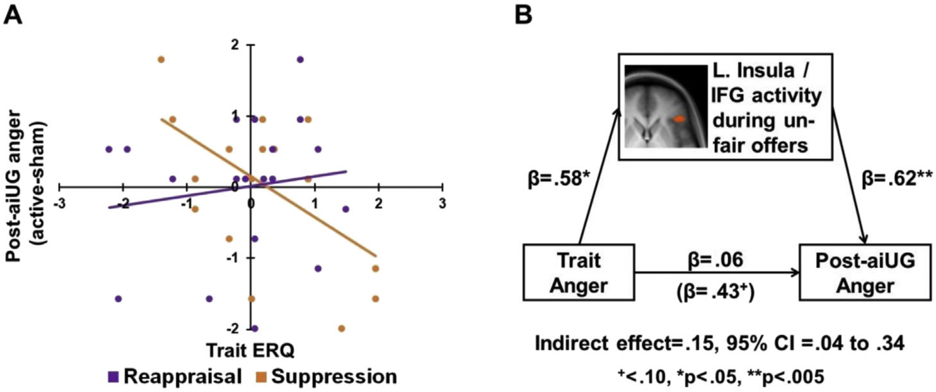

Fig. 5 – Post-hoc results relating traits, task behaviors and brain activity. (A) Association between emotion regulation traits of reappraisal (purple) and suppression (orange) as measured by the Emotion Regulation Questionnaire (ERQ) and the difference in post-aiUG anger between active and sham stimulation. The negative correlation with suppression ($r = -.56$, $p = .01$) was significantly stronger than the one with reappraisal ($r = .15$, $p = .55$; $Z = -2.60$, $p = .01$). Data is plotted using standardized values since trait suppression and trait reappraisal as measured using the ERQ have different magnitudes. (B) Mediation model depicting a significant indirect path from trait anger to post-aiUG anger through activity in the left insula/inferior frontal gyrus (IFG) during angering unfair offers. β indicates standardized regression coefficients and β in parentheses indicates the coefficient between trait anger and post-aiUG anger before controlling for brain activity. Indirect effect indicates the bias-corrected bootstrap coefficient and its' constructed 95% confidence interval (CI).

the vmPFC may attenuate anger and its related behavioral manifestations, and suggests a potential causal link between vmPFC functionality and the regulation of anger experience and expression.

Prior research examined the influence of stimulation on different aspects of anger, and aggression in particular. Anger and aggression have consistently been associated with greater left than right frontal cortical activation and approach motivation (Schutter & Harmon-Jones, 2013). Hortensius et al. (2012) showed that stimulation during rest aimed to increase approach-related anger by enhancing left versus right PFC activity, led to a stronger positive association between subsequent provoked aggression as measured with the TAP and self-reported anger. Complementing this result, Kelley, Hortensius, and Harmon-Jones (2013) showed that stimulation aimed to increase withdraw-related anger by enhancing right versus left PFC activity, led to an increase in anger-related ruminative thoughts. Two studies similarly targeting prefrontal asymmetry during the TAP yielded mixed results (Dambacher et al., 2015b, 2015a). Two additional studies examined the effects of anodal stimulation targeting right ventrolateral PFC (vlPFC), due to its recruitment in various forms of self-control (Cohen, Berkman, & Lieberman, 2013), evidencing less aggression compared to sham (Riva et al., 2015, 2017). While in the current study's electrode montage the anode was centralized to target the vmPFC, it is possible that positioning the cathode on the right shoulder could have led to a right lateralized current influx which may have impacted frontal asymmetry towards the right side, contributing to the observed reduction in anger and aggression. We note that the vmPFC cluster individuated here as well as in our previous study (Gilam et al., 2015) is marginally lateralized to the right side.

Prior research also examined the effects of stimulation on different aspects of UG behavior. Knoch et al. (2008) applied cathodal stimulation over the right dlPFC in a standard UG, and Civai et al. (2015) used a similar electrode montage to ours, though with a reverse location of the anode and cathode, while participants were responding to UG offers for a “myself” versus a “third-party” condition. Both studies evidenced an increase in acceptance rates of unfair offers during active relative to sham stimulation.

The current study extends previous work in several ways. First, we acquired fMRI concurrently with stimulation to monitor and validate its neurobehavioral effect (Wörsching et al., 2016). To date, few studies combine fMRI with non-invasive stimulation, hampering effective implementation of neuromodulation as well as limiting inferences about observed behavioral effects. This is of particular importance in light of the ongoing debate about the reliability and efficacy of tDCS (Horvath, Forte, & Carter, 2015b, 2015a; Antal, Keeser, Priori, Padberg, & Nitsche, 2015). Second, the current study is the only one to use a within-subject, cross-over design, providing greater statistical power. Importantly, such designs should be used once reliability of applied paradigms is a priori established, as done for the current task (Gilam et al., 2018). Third, in addition to the main behavioral measure of the aiUG, we assessed different self-reported emotion categories, as well as transfer effects to a subsequent paradigm (TAP), to comprehensively characterize and converge the effect of stimulation on anger- and aggression-related constructs. The current study therefore complements and extends prior work, informing future efforts on applying noninvasive neuromodulation technology to study anger and aggression, and potentially reduce their maladaptive manifestations.

To note, the fact that current results and those of the two previous stimulation studies implementing a version of the UG (Civai et al., 2015; Knoch et al., 2008) all evidenced an increase in acceptance rates for unfair offers may suggest that the effect of stimulation on reactions to unfair offers is neither confined to a specific PFC region, nor to a specific type of stimulation (anodal, cathodal). However, because of the non-focal effects of tDCS and since prior studies did not implement concurrent brain imaging, it is difficult to conclusively contrast previous results with the stimulation effects on brain activation reported here. There are also contextual differences in the design of the studies, with ours focusing on the induction and assessment of an emotional experience. Additionally, unlike Knoch et al. (2008), we did note a difference in fairness evaluation to unfair offers between active and sham stimulation. Indeed, both fairness evaluations of, and anger reactions to, unfair offers have been shown to contribute to subsequent behavior in the UG (Srivastava, Espinoza, & Fedorikhin, 2009). Additional research is needed to disentangle the effects of various stimulation protocols and different brain regions on anger, fairness and UG behavior.

The current study provided an opportunity to examine the neural mechanisms underlying anger induction. Angering unfair offers recruited the dmPFC, bi-lateral insula/IFG, bilateral TPJ, thalamus and left temporal pole. These regions were previously associated with processing unfair offers (Feng et al., 2015), as well as with mediating the experience of anger (Gilam & Hendler, 2015). Exploratory analyses on individual differences revealed two intriguing results. First, activity in the thalamus positively related to the habitual tendency to use suppression as an emotion regulation strategy, suggesting that thalamus functionality during the experience of anger might be involved in anger regulation. In fact, this rather medial aspect of the thalamus is in direct overlap with a previous finding in which the connectivity between the thalamus and left posterior insula attenuated the experience of anger en route to increased monetary gain in an aiUG (Gilam et al., 2015). Alas, our functional connectivity analyses did not result in any significant results. Nevertheless, it may suggest that the thalamic involvement in the experience of anger is not necessarily one of evoking the associated negative affect, as might have previously been suggested (Gilam & Hendler, 2015).

An additional result indicated that activity in the left anterior insula extending to the IFG pars orbitalis (BA47), fully mediated the relationship between trait anger and self-reports of anger following the aiUG. In other words, participants with high levels of trait anger had higher levels of insula/IFG response to angering unfair offers, which supposedly resulted in higher self-reports of anger following anger-induction. This result confirms previous findings indicating this brain region's involvement in mediating the experience of anger (Damasio et al., 2000; Denson et al., 2009; Sanfey et al., 2003), as well as in mediating the association between the tendency to anger upon provocation and maladaptive recovery from anger (Gilam, Lin, Fruchter, & Hendler, 2017). Therefore, though post-hoc in nature, this result supports the validity of the aiUG as a task to induce and assess anger experience. To note, while there was an overlap of 113 voxels between this insula/IFG cluster and the insula cluster influenced by stimulation, in each region separately as well as in the specific overlap, we did not find a significant interaction effect between stimulation conditions and offer types. Future studies will hopefully target these effects with more power, experimentally as well as technologically (i.e., stronger stimulation effects).

4.1. *Limitations*

Several limitations and future directions should be considered. We had a larger sample size than most published simultaneous tDCS-fMRI studies (Woods et al., 2016), and we implemented a within-subject design which yields greater statistical power than a between-subjects design. Nevertheless, the sizes of the effect of stimulation on aiUG behavior and related emotional experience were small to medium, and no associations were observed between neural and behavioral responses to stimulation. Moreover, the effects of active stimulation on behavior, subjective reports and brain activity appeared in about 60% of the participants, but were not statistically strong enough to generate a consistent effect across all participants. This further emphasizes the need to personalize stimulation parameters, since individual differences in physiological parameters (e.g., skull thickness) may lead to heterogeneous stimulation responsivity. Findings should therefore be considered with caution. Moreover, the crossover design did have a cost since the order of stimulation, whether active or sham was applied at the first stimulation session, had an influence on some measures (e.g., TAP noise-blast intensities and fairness evaluations). Future studies should aim to further increase sample size and statistical power, but also to systematically investigate stimulation order effects, as well as to compare single stimulation sessions with repeated multiple exposures (Monte-Silva, Kuo, Liebetanz, Paulus, & Nitsche, 2010). This is crucial in order to develop effective stimulation protocols for potential therapeutic implementation which may require repeated stimulation sessions. Another limitation is the lack of an additional active stimulation site, which could have further improved specificity and potentially resolved conflicting findings between our own and others' studies. In this regard, concurrent fMRI is necessary to validate the engagement of the targeted brain region, especially since tDCS has lower spatial resolution compared to other neurostimulation techniques, such as transcranial magnetic stimulation (TMS). Replicating our results using concurrent TMS-fMRI (Bestmann et al., 2008), or alternatively by the use of focal high-definition tDCS electrodes (Minhas et al., 2010), may prove beneficial. Finally, we must consider that there still exists a possibility that the observed effects are not necessarily an effect of enhancing emotion regulation, rather reducing emotional reactivity. This is an inherent problem to naturalistic settings in which there is no explicit instructions to regulate emotions, and may also relate to one's theoretical perspective in regards to the relation between emotion generation and emotion regulation processes (Gross & Barrett, 2011).

4.2. *Conclusion*

The simultaneous tDCS-fMRI approach implemented in this study combines complementary methodologies to causally manipulate the brain and monitor its activity (Shafi et al., 2012), thus providing a comprehensive approach to investigate and validate vmPFC's role in attenuating the experience and expression of anger, indicative of its potential role in anger regulation. While it is important to replicate, validate and extend the findings presented here, they may advance the potential application of tDCS in the clinical field (Brunoni et al., 2012). Angry and aggressive outbursts during interpersonal provocations are prevalent in numerous psychiatric disorders and medical conditions. In some cases, anger may even restrict and impede treatment efficacy (Forbes et al., 2008; McHenry, 1994). We previously demonstrated that combat-soldiers with more vmPFC activity and better anger-coping capabilities developed less traumatic-stress symptoms following chronic stress (Gilam et al., 2017). The current study therefore provides a promising platform towards using tDCS as a non-invasive adjuvant to improve anger coping capabilities in individuals with pathological manifestations of anger, and perhaps also for therapeutic inoculation for populations at risk of developing such pathology.

Conflict of interest

None.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2018.09.010.

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