The role of the subgenual anterior cingulate cortex in dorsomedial prefrontal - amygdala neural circuitry during positive-social emotion regulation

Frank Scharnowski [1,2,3,4] *, Andrew A. Nicholson[1], Swann Pichon [5,6,7], Maria J. Rosa[8], Gwladys Rey [5,10], Simon B. Eickhoff [11,12], Dimitri Van De Ville [9,10], Patrik Vuilleumier [5,6], Yury Koush [13] *

[1] Department of Cognition, Emotion and Methods in Psychology, Faculty of Psychology, University of Vienna, Vienna, Austria
[2] Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zürich, Zürich, Switzerland
[3] Neuroscience Center Zürich, University of Zürich and Swiss Federal Institute of Technology, Zürich, Switzerland
[4] Zürich Center for Integrative Human Physiology (ZIHP), University of Zürich, Zürich, Switzerland
[5] Geneva Neuroscience Center, Department of Neuroscience, University of Geneva, Geneva, Switzerland
[6] NCCR Affective Sciences, University of Geneva, Geneva, Switzerland
[7] Faculty of Psychology and Educational Science, University of Geneva, Geneva, Switzerland
[8] Department of Computer Science, Centre for Computational Statistics and Machine Learning, University College London, London, UK
[9] Department of Radiology and Medical Informatics, University of Geneva, Geneva, Switzerland
[10] Institute of Bioengineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
[11] Institute of Neuroscience and Medicine, Brain & Behaviour (INM-7), Research Center Jülich, Jülich, Germany
[12] Institute of Systems Neuroscience, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[13] Department of Radiology and Biomedical Imaging, Yale University, New Haven, USA

Corresponding Authors:
* Frank Scharnowski, Department of Cognition, Emotion and Methods in Psychology, Faculty of Psychology, University of Vienna, Liebiggasse 5, 1010 Vienna, Austria. Email: frank.scharnowski@univie.ac.at
* Yury Koush, Magnetic Resonance Research Center, Yale University, 300 Cedar Street, New Haven, CT 06519, USA. Email: yury.koush@yale.edu

Running Title:

Subgenual anterior cingulate cortex in positive-social emotion regulation

Highlights:
- subgenual ACC (sgACC) is critically involved in the regulation of positive-social emotion
- top-down emotion regulation stems from dorsomedial prefrontal cortex (dmPFC)
- top-down emotion regulation influences amygdala directly and indirectly via sgACC
- activity and connectivity in dmPFC-sgACC-amygdala circuitry is linked to psychometric scores

Keywords:
Emotion regulation, positive-social emotions, subgenual anterior cingulate cortex (sgACC), dorsomedial prefrontal cortex (dmPFC), amygdala, functional magnetic resonance imaging (fMRI), connectivity, intrusive thought suppression, anxiety

Abstract

Positive-social emotions mediate one's cognitive performance, mood, well-being and social bounds, and represent a critical variable within therapeutic settings. It has been shown that upregulation of positive emotions in social situations is associated with increased top-down signals that stems from the prefrontal cortices (PFC) which modulate bottom-up emotional responses in the amygdala. However, it remains unclear if positive-social emotion upregulation of the amygdala occurs directly through the dorsomedial PFC (dmPFC) or indirectly linking bilateral amygdala with the dmPFC via the subgenual anterior cingulate cortex (sgACC), an area which typically serves as a gatekeeper between cognitive and emotion networks. We performed functional MRI (fMRI) experiments with and without effortful positive-social emotion upregulation to demonstrate the functional architecture of a network involving the amygdala, the dmPFC and the sgACC. We found that effortful positive-social emotion upregulation was associated with an increase in top-down connectivity from the dmPFC on the amygdala via both direct and indirect connections with the sgACC. Conversely, we found that emotion processes without effortful regulation increased network modulation by the sgACC and amygdala. We also found that more anxious individuals with a greater tendency to suppress emotions and intrusive thoughts, were likely to display decreased amygdala, dmPFC, and sgACC activity, and stronger connectivity strength from the sgACC onto the left amygdala during effortful emotion upregulation. Analyzed brain network suggests a more general role of the sgACC in cognitive control and sheds light on neurobiological informed treatment interventions.

Introduction

Positive emotions facilitate creative thinking, decision-making, problem solving, and social bounds (Ashby, et al., 1999; Carpenter, et al., 2013; Fredrickson, 2004; Gross, 2002; Nadler, et al., 2010). A more comprehensive understanding of the mechanisms underlying positive emotion upregulation in social situations (positive-social emotion upregulation) is critical as impairment of this ability might constitute a key factor contributing to the severity and maintenance of psychiatric disorders (Aldao, et al., 2010; Etkin, et al., 2015). For example, anhedonic symptoms are associated with depression, and emotion dysregulation symptoms are associated with posttraumatic stress disorder (PTSD) (Disner, et al., 2011; Etkin, et al., 2015; Nicholson, et al., 2017a; Treadway and Zald, 2011; Young, et al., 2017). Research investigating the psychological and neural processes underlying emotion regulation collectively point to the role of specific brain regions involved in the control of emotional experience, regulation and expression (Ochsner and Gross, 2005; Ochsner and Gross, 2008; Ochsner, et al., 2012; Schlosser, et al., 2008; Smith, et al., 2006). According to emotion regulation models, successful regulation is achieved through the modulation of emotional bottom-up responses by higher-order cognitive top-down processes (Etkin, et al., 2015; Gross, 2002; Ochsner, et al., 2009; Ochsner, et al., 2012; Taylor and Liberzon, 2007; Zilverstand, et al., 2017). Interestingly, numerous studies suggest that brain networks involved in the upregulation of positive versus negative emotions have both common and distinct components (Davidson and Irwin, 1999; Fossati, et al., 2003; Kim and Hamann, 2007; Koush, et al., 2019; Lane, et al., 1997; Ochsner, et al., 2012; Vrticka, et al., 2012; Yang, et al., 2020).

On balance, the sgACC, amygdala, and PFC areas typically show aberrant emotion regulation engagement associated with mood and anxiety disorders (Drevets, 2003; Gotlib and Hamilton, 2008; Lanius, et al., 2018; Ressler and Mayberg, 2007a; Yehuda, et al., 2015). The amygdala plays a central role in conscious and unconscious emotion processing (Glascher and Adolphs, 2003), and has been shown to be highly dysregulated in psychiatric illness, correlated to symptoms across a wide range of disorders (Etkin and Wager, 2007a; Fenster, et al., 2018; Phelps and LeDoux, 2005). Likewise, abnormalities in sgACC grey matter volume, activity, and connectivity, are associated with depressive and hyper-emotionality symptoms across a range of psychiatric illnesses (Disner, et al., 2011; Drevets, 2001; Drevets and Savitz, 2008; Etkin, et al., 2015; Fenster, et al., 2018; Wu, et al., 2016; Yehuda, et al., 2015). The sgACC has been used as a target region for treating chronic pharmaco-resistant depression with deep brain stimulation (Hamilton, et al., 2011; Ressler and Mayberg, 2007a). The sgACC has been suggested to transfer emotion information from the limbic

system to higher-order cognitive structures (Disner, et al., 2011; Greicius, et al., 2007). It has been implicated in functions related to emotion reappraisal (Banks, et al., 2007; Wager, et al., 2008b), positive emotion upregulation (Wager, et al., 2008a), fear extinction (Phelps, et al., 2004), monitoring internal states (Gillath, et al., 2005), anxiety and mood disorders (Drevets and Savitz, 2008; Etkin and Wager, 2007b), sadness induction (Ramirez-Mahaluf, et al., 2018), social interactions and social decision making (Lockwood and Wittmann, 2018), mediating autonomic arousal (Zhang, et al., 2014) and reward mechanisms (Azab and Hayden, 2018; Rudebeck, et al., 2014; Stevens, et al., 2011). In addition, the sgACC and rostral ACC have been shown to be implicated in the processing of negative and positive emotions, respectively (Etkin, et al., 2011; Grone, et al., 2015; Vogt, 2005), and together are involved in social cognition (Lockwood and Wittmann, 2018; Palomero-Gallagher, et al., 2015). Critically, both the sgACC and amygdala are densely connected (Beckmann, et al., 2009; Etkin, et al., 2011; Johansen-Berg, et al., 2008), and are thought to be a part of an automatic emotion regulation circuit, whereas the dmPFC has often been implicated in social-emotion processing (Amodio and Frith, 2006; Bzdok, et al., 2013; Goldberg, et al., 2006; Lockwood and Wittmann, 2018; Ochsner and Gross, 2008; Vrticka, et al., 2012), and has been associated with the voluntary regulation of motions (Braunstein, et al., 2017; LeDoux and Brown, 2017; Phillips, et al., 2008; Stevens, et al., 2011). Patterns of anatomical and functional connectivity collectively supports an important role of the sgACC in interacting with limbic regions, including the amygdala, and in communicating with prefrontal areas important for top-down forms of regulation (dmPFC), where the amygdala also has direct structural connections with the dmPFC (Eickhoff, et al., 2016; Etkin, et al., 2011; LeDoux, 2007).

The classification of emotion regulation differentiates self-regulation and social regulation of emotion (Reeck, et al., 2016). Self-regulation of emotion suggests that the regulator and the target are the same person, i.e. how people regulate their own emotions. Conversely, social regulation of emotion suggests that the regulator alters the emotional response of another target individual, that is, how people regulate the emotions of others. Positive stimuli with social content have been used to stimulate self-regulation of emotions in participants (Koush, et al., 2019). This was accomplished by passive viewing of displayed situations or effortful imagination of experiencing the depicted positive-social situations from a first-person perspective in an active and pleasant manner (termed as *positive-social emotion regulation*). Specifically, for positive-social scenes, participants were instructed to imagine a natural (spontaneous) interaction with a displayed single (multiple) person(s), for example, interactively carrying out a pleasant conversation, or leisure and sport

activities. For neutral inanimate scenes (no landscapes or food) participants were instructed to imagine oneself using the depicted neutral objects in an active and pleasant manner, for example, carrying out the favorite activity. This conceptualization is different from (i) instructions to naturally experience the exposed (non)social positive/neutral/negative scenes by watching and evaluating (Vrticka, et al., 2011; Vrticka, et al., 2012), (ii) instructions to increase emotional reactions to displayed positive stimuli (Kim and Hamann, 2007), and (iii) instructions associated with the social regulation of emotion (Reeck, et al., 2016).

It has been shown that regulating positive emotions is associated with increased top-down signals that stem from the prefrontal cortices (PFCs), which concomitantly modulate bottom-up emotional responses in the amygdala (Koush, et al., 2017c; Koush, et al., 2019; Young, et al., 2018; Zotev, et al., 2013). Consistently, positive-social emotion upregulation with a self-referential first-person perspective was associated with the direct influence of the superior frontal gyrus (SFG, lateral to the dmPFC), the ventromedial PFC and the dmPFC exerted onto the bilateral amygdala (Koush, et al., 2019). In addition, it has been shown that top-down influence of the dmPFC onto the bilateral amygdala could also be voluntarily regulated using positive emotion upregulation neurofeedback (Koush, et al., 2017c). However, it remains unclear if positive-social emotion regulation of the limbic system occurs through direct connections with PFCs or via indirect connections with the subgenual anterior cingulate cortex (sgACC), an area densely connected with the amygdala, which is often described as an important 'gatekeeper' between the cognitive and the emotional system (Disner, et al., 2011; Greicius, et al., 2007; Palomero-Gallagher, et al., 2015). This highlights the need to investigate further the specific role of brain areas implicated in positive-social emotion regulation and contribute to the identification of potential targets for future neurofeedback interventions based on positive-social emotion upregulation (Koush, et al., 2017c; Sitaram, et al., 2017; Stoeckel, et al., 2014). We hypothesized that a neural model engaging the sgACC in the dmPFC - amygdala neural circuitry would dominate over alternative models without this sgACC engagement, suggesting a gatekeeping role of the sgACC during the regulation of positive-social emotions.

To test this hypothesis, we investigated positive-social emotion regulation conditions, where participants effortfully enhanced their positive emotions by imagining to engage actively and pleasantly in social scenes in a first-person perspective, and different passive viewing conditions. We examined functional networks of two independent datasets, pertaining to (a) previously published data that consisted of positive-social and neutral non-social emotion upregulation conditions, and positive-social and neutral non-social passive viewing conditions of the same

condition duration (Koush et al., 2019), and (b) newly acquired data consisting of a similar positive-social emotion upregulation condition, a positive-social rapid passive viewing condition, and neutral non-social passive viewing and rapid passive viewing conditions. Passive viewing and rapid passive viewing conditions, attenuated and limited effortful emotion upregulation, respectively, i.e. self-referential engagement and active imagination. This design also uniquely allowed us to observe the role of the sgACC engagement in emotion upregulation with regard to dmPFC-amygdala neural circuitry interactions, and to confirm experimental findings within independent datasets. We also explored the link between psychometric scores associated with regulation of emotions and network activity and connectivity involved in positive-social emotion regulation.

Materials and Methods

Participants

In this study we examined (i) previously published experimental data (Koush, et al., 2019), with n=23 healthy individuals (11 female, age 27.7±6.2 years), denoted as the first experiment, and (ii) newly collected experimental data with n=14 healthy individuals (7 female, age 24.3±3.6 years), denoted as the second experiment. With regard to the second, unpublished dataset, healthy human volunteers were recruited from the local student/research community and gave written informed consent to participate to our study, which was approved by the ethics committee at the University of Geneva. All participants had normal or corrected-to-normal vision, and had no prior history of neurological or psychiatric illnesses. Before the experiment, participants received written instructions describing the positive-social and neutral images they were about to see and the experimental tasks. They were instructed to either passively look at these images, or to imagine positively experiencing the depicted positive-social situation as one of the main protagonist in a first-person perspective. After the experiment, participants were asked to fill in several questionnaires and inventories. Participants were paid 20 CHF/ hour for their participation.

Experimental stimuli

Emotional stimuli of both experiments consisted of two sets of photographs taken from the International Affective Picture Set (IAPS; (Lang, et al., 1993)), the Nencki Affective Picture System (NAPS; (Marchewka, et al., 2014)) and the Geneva Affective Picture Database (GAPED; (Dan-Glauser and Scherer, 2011)). Images in the first set depicted positive-social situations, and images in the second set depicted non-social neutral scenes and objects (no landscapes or food images were

selected). For the first experiment, we used 112 photographs per set (normative mean ± standard deviation; positive-social images of scenes with people: valence 6.92±.74, arousal 4.94±.75; non-social neutral scenes and objects: valence 5.21±.60, arousal 3.52±1.05). For the second experiment, we used 150 photographs per set (normative mean ± standard deviation; positive-social images of scenes with people: valence 6.71±.87, arousal 4.38±1.04; non-social neutral scenes and objects: valence 5.37±.69, arousal 3.61±.96). The number of images per set slightly differed between the experiments (112 vs. 150) due to their block-design differences (**Figure S1**). Importantly, because present research targets unveiling the role of sgACC using different emotion regulation paradigms, we do not compare associated brain activity and connectivity patterns between both experiments. Thus, to complicate the effortful upregulation of positive emotions so that participants had to apply more effort to induct positive feelings, positive-social images of the second experiment were selected slightly less positive (two-sample, two-tailed t-test, $t = 2.01$, $p = .045$) and less arousing (two-sample, two-tailed t-test, $t = 4.73$, $p < .001$) as compared to the first experiment. For both experiments, the order of stimuli presentation was pseudo-randomized, and each image was shown only once to a given participant to ensure a uniform distribution of stimuli valence and arousal in the picture subsets, and to balance potential color, intensity and scenery differences between pictures from the different databases. The images were presented centrally with a diameter of ~12° visual angle. In order to facilitate better stimuli recognition in both experiments, images depicting positive-social situations were framed in green, and images depicting neutral objects were framed in white. The order of passive viewing and upregulation epochs (first experiment) and runs (second experiment) was randomized across participants.

Experimental procedures

The first experiment consisted of two alternating functional runs with a 2×2 factorial design based on the factors stimuli (*positive-social* vs. *neutral non-social scenes*) and task (*passive viewing* vs. *effortful emotion upregulation*) (Koush, et al., 2019). The experimental runs were built of two epochs (**Figure 1A, S1A**), with each epoch consisting of either effortful emotion upregulation or passive viewing conditions (14 randomized blocks per epoch, 7 blocks per each stimuli category per epoch, 4 images per block, 6s image display duration, 11.3 min total run duration). The 6s image presentation time was chosen to facilitate imagination during the emotion regulation runs (Ochsner, et al., 2009; Vrticka, et al., 2012). During passive viewing conditions, participants passively viewed the presented images. During effortful positive-social and neutral non-social emotion upregulation conditions, participants imagined experiencing the depicted positive-social

and neutral non-social scenes in a self-referential pleasant manner (Koush, et al., 2019). During effortful positive-social emotion upregulation condition, participants were instructed to imagine a spontaneous interaction with a displayed single (or multiple) person(s), for example, interactively carrying out a pleasant conversation, favorite leisure and sport activities. During neutral non-social emotion upregulation condition, participants were asked to imagine carrying out the favorite activity with the object and ensure that other people are not being engaged during imagination. For instance, if a bicycle is displayed, outdoor cycling could be imagined without other people.

The second experiment consisted of two alternating functional runs with periodic baseline and regulation conditions (**Figure 1A, S1B**). The effortful emotion upregulation run consisted of 10 blocks of *effortful positive-social emotion upregulation* conditions interleaved with 11 blocks of *neutral non-social passive viewing* conditions (4s image display duration, 3 images per block, 4.2 min total run duration). Thus, as compared to the first experiment, in the second experiment effortful emotion upregulation run, we slightly reduced the positive-social stimuli valence and arousal, reduced the stimuli display duration (6s vs. 4s), the number of stimuli per block (4 vs. 3 images per block), and presented baseline and condition blocks periodically to probe the feasibility of such a challenging experimental design. The rapid passive viewing run consisted of 10 blocks of *positive-social rapid passive viewing* conditions interleaved with 11 blocks of *neutral non-social rapid passive viewing* conditions (0.5s image display duration, 24 images per block, 4.2 min total run duration). The *effortful positive-social emotion upregulation*, and *positive-social and neutral non-social passive viewing* conditions were the same as for the first experiment described above. A critical manipulation was that the images in the rapid passive viewing run were presented more rapidly, and hence, were referred to as the *rapid passive viewing* conditions. This rapid passive viewing run was designed to limit participant self-referential engagement with the content of presented scenes, with the goal to simulate an automatic emotion regulation process (Braunstein, et al., 2017; Diano, et al., 2016). The latter renders the rapid passive viewing condition with 0.5s image display duration different from the passive viewing condition in the first experiment with 6s image display duration.

MRI data acquisition

Both experiments were performed on a 3T MRI scanner (Trio Tim, Siemens Medical Solutions, Erlangen, Germany) at the Brain and Behavior Laboratory (University of Geneva). At the beginning of the scanning session, we acquired for each participant a T1-weighted structural image (32 channel receive head coil, 3D MPRAGE, voxel size = 1 mm^3 isotropic, flip angle $\alpha = 9^\circ$, TR = 1900 ms,

TI = 900 ms, TE = 2.27 ms), and a double-echo FLASH fieldmap (TE1 = 5.19 ms, TE2 = 7.65 ms, voxel size = 3 x 3 x 2.2 mm^3). For the first experiment, functional images were acquired with a whole-brain single-shot gradient-echo T2*-weighted EPI sequence with 345 repetitions (TR = 2050 ms, 32 slices volume, matrix size = 120 × 120, 2 mm^3 isotropic voxel size, flip angle α = 75°, bw = 1.57 kHz/ pixel, TE = 35 ms, GRAPPA, iPAT = 3)(Koush, et al., 2019).

The EPI protocol of the second experiment was configured to ensure optimal sensitivity and precise segregation of the bilateral amygdala, dmPFC and sgACC brain areas (Weiskopf, et al., 2006; Weiskopf, et al., 2007). Thus, for the second experiment, functional images were acquired with a partial field of view (FOV) single-shot gradient-echo T2*-weighted EPI sequence with 252 repetitions (TR = 1100 ms, 18 slices volume, matrix size = 120 × 120, 1.8 mm^3 isotropic voxel size, flip angle α = 70°, bw = 1.54 kHz/ pixel, TE = 30 ms, GRAPPA, iPAT = 3). The partial FOV was chosen so that it covered our regions of interest (ROIs) given selected spatial and temporal resolution. In addition, data collection of the second experiment was optimized towards rapid data acquisitions typically required for real-time fMRI and neurofeedback applications (Koush, et al., 2017a; Koush, et al., 2017b; Koush, et al., 2017c; Koush, et al., 2013). This implies a compromise between the partial acquisition field of view (FOV) to cover target ROIs, relatively high spatial resolution (1.8 mm^3 isotropic voxels) and short repetition time (TR = 1100 ms) as compared to the whole-brain data acquired for the first experiment (TR = 2050 ms, isotropic voxel size of 2mm^3). The short TR also facilitates negligible EPI slice timing differences (Kiebel, et al., 2007; Sladky, et al., 2011).

Visual stimuli and instructions were displayed using a rectangular projection screen at the rear of the scanner bore with a mirror positioned within the head-coil. All participants were instructed to breathe steadily and to remain as still as possible.

Activity analysis

For both experiments, data analyses were performed using SPM12 (Wellcome Trust Centre for Neuroimaging, Queen Square, London, UK). The fMRI analysis of the first experiment is described in detail elsewhere (Koush, et al., 2019).

For the second experiment, a similar fMRI analysis was performed. The first 10 EPI volumes were discarded to account for T1 saturation effects. The remaining images were spatially realigned to the mean scan of each session, coregistered to the standard MNI structural template using DARTEL (Ashburner, 2007), corrected for geometric distortions (Jenkinson, 2003; Jezzard and Balaban, 1995), and smoothed with an isotropic Gaussian kernel with moderate 5 mm full-width-at-half-

maximum (FWHM). The regressors were modeled as boxcar functions convolved with the canonical hemodynamic response function (HRF). For the subject-level analysis, we specified general linear models (GLM) with regressors for positive-social emotion upregulation and passive viewing conditions, and the neutral non-social passive and rapid passive viewing baseline conditions, respectively. The model included covariates derived from head movement parameters.

For the whole-brain group level analysis of emotion upregulation and rapid passive viewing runs of both experiments, we performed a factorial ANOVA with a fixed factor 'condition' and a random factor 'subject'. Statistical maps were corrected for multiple comparisons using family-wise error correction (FWE, $p < .05$). Small volume correction (SVC) at the peak-level (FWE, $p < .05$) was also applied to the dmPFC using a sphere of 10 mm radius (Koush, et al., 2019; Pichon, et al., 2012; Poldrack, et al., 2008) centered on independent coordinates defined with Neurosynth database ([2, 58, 32], MNI coordinates for association test, entry 'emotion regulation'), to the amygdala using Talairach Daemon atlas (Lancaster, et al., 2000), and to the sgACC using anatomically referenced rectangular 16×27×12 mm box centered at [0, 14, - 6] (Beckmann, et al., 2009; Palomero-Gallagher, et al., 2015). The SVC correction was based on the corresponding contrast maps ($p < .005$ unc.) with 10 voxels extent threshold. Recent findings suggest that cognitive reappraisal of social emotions might recruit the left amygdala more than the right, where additionally, the interaction between valence and social content is more pronounced in the right amygdala (Vrticka, et al., 2011; Vrticka, et al., 2012; Young, et al., 2014). Hence, we tested for lateralization of amygdala activation during emotion upregulation conditions. To accomplish this, we compared individual hemisphere contrast images with their contralateral counterparts using paired t-test in SPM12.

ROIs definitions and time-series processing for DCM analysis

For both experiments, we considered four ROIs: the bilateral amygdala, the dmPFC, and the sgACC. The dmPFC and bilateral amygdala ROIs were the same as in the first experiment (Koush, et al., 2019). Specifically, the dmPFC ROI was defined as a sphere with 10 mm radius around the corresponding cluster center of gravity (main effect of stimuli, positive > neutral). The bilateral amygdala ROIs were defined anatomically based on the Talairach Daemon atlas (Lancaster, et al., 2000) because it is a small region for which a spherical ROI would have likely included non-amygdala voxels in close proximity. The centers of gravity were defined for the clusters of the thresholded activation maps ($p < .005$ unc.) as implemented in the Anatomy toolbox (Eickhoff, et al., 2005). Based on the generic functional and anatomical labeling of the sgACC (Beckmann, et al., 2009; Palomero-Gallagher, et al., 2015), the sgACC ROI was defined as 16×27×12 mm box centered

at [0, 14, - 6]. For each ROI, we extracted the first principal component of the individual local multivariate time-series from both experimental groups using singular value decomposition (Friston, et al., 2006; Stephan, et al., 2010) and corrected for their low frequency drift, high frequency noise and spikes (Koush, et al., 2019; Koush, et al., 2012).

Effective connectivity analysis

To assess directional connectivity as a function of positive-social emotion upregulation, we used dynamic causal modeling (DCM)(Friston, et al., 2003). DCM is a Bayesian framework that can model a functional brain network as a set of differential equations describing not only the architecture of the network (i.e. the ROIs and their directional connections, matrix A), but also the dynamic influences between ROIs within the network due to external inputs to the ROIs (matrix C) and due to contextual modulations of connections between the ROIs (matrix B). For external and modulatory inputs in corresponding DCM analyses, we analyzed either conditions of (rapid) passive viewing or engaging in positive emotion upregulation for positive-social scenes. Note that external and modulatory inputs can reflect either the image presentation, the task, or both, being inherently linked to one another in our experimental design. By using Bayesian model comparison, DCM allows for quantitatively testing which model architecture and dynamics best explains the observed data (Penny, et al., 2004). DCM also allows for estimating the individual model parameters and can thus shed light on the strength and impact of connectivity changes during an experiment.

We performed a hierarchical DCM analysis, in that we first estimated all possible model alternatives and then applied family-level inference procedures to investigate which general model structure underlay the emotion upregulation condition. In order to generalize the results to the population, we used a random effect (RFX) approach for DCM analysis (Stephan, et al., 2009). We estimated the expected posterior model family probability and the model family exceedance probability, which indicate the probability how likely is that a specific model family generated the data of a randomly chosen subject and the probability that a model family explains the data better than any other model family, respectively (Stephan, et al., 2009; Stephan, et al., 2010).

Thus, to investigate which general model structure underlays effortful and passive viewing emotion regulation processes, we partitioned the model space in subsets of five model families that differed in the connectivity pattern between our 4 ROIs (**Figure 2A**). The first model family contained all models where there was a connection between the amygdala and the dmPFC as well as between the dmPFC and the sgACC (112 models); the second family contained all models where there was a

connection between the amygdala and the sgACC as well as between the sgACC and the dmPFC (112 models); the third family contained all models with direct connection between only the amygdala and the dmPFC (12 models); the fourth family contained all models with a direct connection between only the amygdala and the sgACC (12 models); and finally the fifth family contained all models with direct connections between all ROIs (448 models). Due to the large number of possible models within each family, we did not include direct connections between the left and right amygdala and took all possible combinations of modulatory inputs and external inputs for each model family into account. We assumed bilateral amygdala connections, and that external and modulatory inputs affect both hemispheres in the same way (Koush, et al., 2019). To investigate model parameters of the winning model family, we applied Bayesian model averaging (BMA). BMA computes a weighted average of each model parameter within the model family, where the weighting depends on the evidence for each of the contributing models, i.e. the posterior probability (Penny, et al., 2010). We used DCM as implemented in SPM12.

Correlations between psychometric scores and functional activity and connectivity

In addition to the first experiment data from established standardized psychometric questionnaires and inventories (Koush, et al., 2019), we collected similar data in the second experiment to explore differences in individual emotion upregulation habits and in psychometric scores that might characterize changes in brain activity and connectivity during emotion regulation. Specifically, participants were asked to complete the behavioral inhibition system (BIS) and behavioral activation system reward (BAS-R), drive (BAS-D), fun seeking (BAS-F) scales (Carver and White, 1994), the Emotion Regulation Questionnaire (ERQ, (Gross and John, 2003)), the White Bear Suppression Inventory (WBSI, (Wegner and Zanakos, 1994)) and the State-Trait Anxiety Inventory (STAI-T, (Spielberger, 1983)) after the experiment. We then correlated psychometric scores with percent signal changes between emotion regulation conditions and corresponding reference (baseline) conditions (**Figure 1A**) using two-tailed Spearman correlations. Percent signal changes were extracted separately for each ROI using GLM beta values as provided by SPM12. We also computed two-tailed Spearman correlations between psychometric scores and effective connectivity parameters, as well as cross-correlations between psychometric scores. The statistical significance was corrected for multiple comparisons using false-discovery-rate (FDR, $q < .05$) applied to the number of ROIs (four), number of effective connectivity parameters (fourteen given added matrices A and B), or questionnaires/inventories assessed (eight).

Results

We found complementary results in the first and second experiments that suggest engagement of the sgACC in positive-social emotion regulation. Below we report activation results between conditions within both experiments, while focusing primarily on the separate DCM analyses revealing model structure between the dmPFC, sgACC and amygdala.

Brain activation associated with emotion upregulation and passive viewing

For the first full factorial experiment, the interaction between task and stimuli was characterized by activation in the temporoparietal junction (TPJ), and the main effect of task (upregulation > viewing) was characterized by activation in the superior frontal gyrus (SFG) (**Table 1**, **Figure 1B**,**C**) (Koush, et al., 2019). The main effect of stimulus (positive > neutral) was additionally characterized by widespread activations, highlighting the TPJ, dmPFC, ventromedial PFC (vmPFC) and bilateral amygdala, among others. For the first experiment, we additionally contrasted the positive-social emotion upregulation condition (imagining the experience of those situations) to the positive-social passive viewing condition, which revealed activation in the SFG (**Table 1**, upregulate positive > viewing positive), and positive-social emotion upregulation condition in comparison to the neutral non-social passive viewing condition that revealed activation in the dmPFC (**Table 1**, upregulate positive > viewing neutral). The contrast of the positive-social passive viewing condition and the neutral non-social passive viewing condition mirrored the widespread activation associated with the main effect of stimuli, among others, in the dmPFC, sgACC and bilateral amygdala (**Table 1**, viewing positive > viewing neutral).

For the second experiment, we identified brain areas related to positive-social emotion upregulation in comparison to the neutral non-social passive viewing (baseline) condition (**Table 1**, upregulation positive > viewing neutral), and brain areas recruited during rapid passive viewing of images depicting positive-social situations in comparison to the neutral non-social rapid passive viewing (baseline) condition (**Table 1**, rapid viewing positive > rapid viewing neutral). During the positive-social emotion upregulation condition, activation was found in the left amygdala, superior temporal sulcus (STS), and most critically, in both the sgACC and dmPFC, as compared to the control baseline (**Table 1**, **Figure 1D**). During the positive-social rapid passive viewing condition, the bilateral amygdala was significantly active as compared to the control baseline. Significant dmPFC and sgACC activation was not observed during the rapid passive viewing condition as compared to the control baseline, which suggests a preferential involvement of both areas in effortful positive-

social emotion upregulation (**Table 1**, **Figure 1E**). Through laterality analyses during positive social emotion upregulation conditions, we observed higher activation in the left amygdala as compared to the right amygdala (peak at [-16 -2 -13], SVC FWE, p = .037) during this condition as compared to baseline.

Effective connectivity underlying positive-social emotion regulation

The key question investigated in our study concerned how positive-social emotion regulation modulated the functional interactions between the subgenual ACC, the prefrontal cortex and limbic brain areas. Using data of both experiments, analyzed separately, we determined which model architecture linking the sgACC with the amygdala and dmPFC could best explain the pattern of fMRI data during the upregulation of positive-social emotions, and how this may differ from passive viewing conditions with the same or more rapid stimuli display rate. To this aim, we partitioned the model space in subsets of five possible model families that differed in the connectivity pattern between the bilateral amygdala, the dmPFC, and the sgACC (**Figure 2A**). Each model corresponded to different structural and functional hypotheses about the underlying connectivity between these regions: model families assumed direct interactions of the amygdala with either dmPFC or sgACC or both (**Figure 2A**). Using a Bayesian approach, we then calculated for each model family the expected (P) and exceedance (Pe) probability, and estimated winning model family parameters using Bayesian model averaging (BMA, **Figure 2B-E**).

For the first experiment, we found that the fully connected 5th model family explained the data much better than other concurrent model families during emotion upregulation (**Figure 2C**, winning model family expected probability P = .86) and during passive viewing (**Figure 2B**, winning model family expected probability P = .82). For the second experiment, our results revealed the same 5th winning model family dominated during emotion upregulation (**Figure 2E**, winning model family expected probability P = .74) and during passive viewing with rapid stimuli presentation (**Figure 2D**, winning model family expected probability P = .74). All exceedance probabilities for winning model families where > .99.

The BMA anlysis revealed that during positive-social emotion upregulation condition of both experiments, the modelled network parameters were similar and driven by applied emotion upregulation as indicated by dmPFC response to the emotion upregulation, and positive connection strength from the dmPFC onto the sgACC and bilatel amygdala (**Figure 2C,E**). Conversely, during emotion upregulation, the sgACC displayed negative connections onto the dmPFC in both experiments and negative connections on bilateral amygdala in second experiment (**Figure 2E**). This

data may suggest that the sgACC is engaged in interactions with the bilateral amygdala and the dmPFC, and that the emotion upregulation condition induces distinct recruitment of the dmPFC, the sgACC and amygdala responses. Interestingly, the emotion upregulation network was more strongly driven by the experimental conditions of the second experiment as indicated by their stronger connection strengths (**Figure 2E**). In addition, the external input on the sgACC and connections between the sgACC and bilateral amydala showed a slightly different pattern of results when comparing emotion upregulation conditions of both experiments (**Figure 2C,E**). This could be attributed to the sign modulation, i.e., negative input onto the sgACC during emotion regulation of the first experiment was conveyed onto bilateral amygdala without changing the sign (**Figure 2C**), while positve external input on the sgACC was negatively conveyed onto the bilateral amgdala during emotion regulation of the second experiment (**Figure 2E**). The similar sign modulation was observed for the external input on the right amydala and its influence onto the sgACC during emotion upregulation of both experiments (**Figure 2C,E**, emotion upregulation). During the passive viewing condition in the first experiment (**Figure 2B**), we did not observe a substantial modulation of model network parameters by external passive viewing inputs, but rather a positve interaction between network nodes and negative modulation of the dmPFC by the sgACC. Interestingly, during rapid passive viewing within the second experiment (**Figure 2D**), the connection strengths substantially increased, with the sgACC exerting positive modulation on the bilateral amygdala, and negative modulation on the dmPFC, in addition to bilateral amygdala exerting positive modulaton on the dmPFC. These results suggest that the emotion upregulation condition induced distinct interactions between the dmPFC, sgACC and amygdala as compared to passive viewing when effortful engagement is attenuated, and that these distinct interactions are more evident when effortful engagement is limited due to shortened stimuli duration, i.e. the network upregulation is more automated.

Correlations between psychometric scores and functional activity and connectivity

In the first experiment, we found that emotion suppression scores (ERQ-S) correlated negatively to percent signal change between positive emotion upregulation and neutral passive viewing conditions in the dmPFC (**Figure 3A**, rho = -.52, adjusted p = .045, FDR correction across ROIs, q < .05) (Koush, et al., 2019). Interestingly, in the first experiment, we also found that intrusive thought suppression scores (WBSI) correlated positively with the connectivity strengths from the left amygdala onto the sgACC during upregulation condition (**Figure 3B**, rho = .69, adjusted p = .004; FDR correction across connectivity parameters, q < .05).

In the second experiment, we found that intrusive thought suppression scores (WBSI) correlated negatively with percent signal changes between positive emotion upregulation and neutral passive viewing conditions in all four ROIs (**Figure 3C**, **Table S1**; dmPFC: rho = -.64, adjusted p = .030; sgACC: rho = -.62, adjusted p = .030; left amygdala: rho = -.60, adjusted p = .030; right amygdala: rho = -.56, adjusted p = .039; FDR correction across ROIs, q < .05). Thus, individuals with higher tendency to suppress emotions (ERQ-S) and intrusive thoughts (WBSI) exhibited weaker upregulation effects within dmPFC and all these brain regions, respectively, yet exhibited higher modulation of the sgACC by the left amygdala. Higher WBSI scores also suggest worse emotion regulation capabilities (Wegner and Zanakos, 1994). During positive-social emotion upregulation in the second experiment, we also found a positive correlation between fun-seeking scores (BAS-F) and external connectivity strengths on the dmPFC (**Figure 3D**, rho = .86, adjusted p = .001; FDR correction across connectivity parameters, q < .05), which implies that individuals with a higher desire for new rewards and rewarding events exhibited higher external modulation of the dmPFC.

In the first experiment, we did not find significant correlations between psychometric scores and activity levels and connectivity strengths during positive-social passive viewing conditions. However, in the second experiment, we found that fun seeking (BAS-F) scores positively correlated with the sgACC percent signal changes between rapid positive-social and rapid neutral passive viewing conditions (**Figure 3E**, rho = .65, adjusted p = .044, FDR correction across ROIs, q < .05), as well as anxiety scores (STAI-T) negatively correlated with the connectivity strength from the left amygdala onto the sgACC (**Figure 3F**, rho = -.73, adjusted p = .042; FDR correction across connectivity parameters, q < .05).

Cross-correlations between questionnaires in the first experimental group revealed a significant positive correlation between reward responsiveness (BAS-R) and fun seeking (BAS-F) scores (rho = .64, adjusted p = .025, FDR corrected across questionnaires, q < .05). In the second experimental group, the same analysis revealed a significant positive correlation between trait anxiety (STAI-T) and intrusive thought suppression (WBSI) scores (rho = .88, adjusted p < .001, FDR corrected across questionnaires, q < .05). No effects were found in other cross correlations of the questionnaires.

Discussion

Using fMRI and DCM with Bayesian model selection procedures, we investigated the engagement of the sgACC within the dmPFC-amygdala affective circuit during positive-social self-referential emotion regulation. With both experiments, we found that positive-social emotion upregulation was associated with activation in the dmPFC, sgACC and bilateral amygdala, and with an increase of direct and indirect top-down connections from the dmPFC on bilateral amygdala via the sgACC. During rapid passive viewing runs where the stimuli were presented briefly as to limit the effortful engagement in the self-referential emotion upregulation task, the sgACC and dmPFC were not significantly activated as compared to baseline conditions, yet were characterized by distinct connectivity patterns. We also explored correlations between neuroimaging measures and individual psychometric scores.

dmPFC-sgACC-amygdala circuit activity

Our results revealed that engaging oneself in upregulation of self-referential positive-social emotions activated target brain regions similar to those that are recruited when regulating negative and positive emotions reported elsewhere (Beauregard, et al., 2001; Herwig, et al., 2007; Kim and Hamann, 2007; Koush, et al., 2019; Ochsner, et al., 2012; Vrticka, et al., 2012; Zotev, et al., 2018; Zotev, et al., 2013; Zotev, et al., 2014), particularly the dmPFC, sgACC, and the bilateral amygdala (**Table 1**, **Figure 1**). This is well in line with the suggested role of the sgACC in transferring emotional feedback from the limbic system to higher-order cognitive structures (Azab and Hayden, 2018; Banks, et al., 2007; Disner, et al., 2011; Greicius, et al., 2007; Lockwood and Wittmann, 2018; Rudebeck, et al., 2014; Stevens, et al., 2011; Wager, et al., 2008a; Wager, et al., 2008b). For instance, the sgACC has been found to be activated when participants were asked to modulate negative emotional responses (Banks, et al., 2007; Wager, et al., 2008b) and attend and rate core affective feelings (Lindquist, et al., 2012). Indeed, positive emotion upregulation via real-time fMRI neurofeedback of the amygdala has previously been found to be associated with increased activation in the rostral ACC and dmPFC (Koush, et al., 2017c; Zotev, et al., 2013). Also on balance with previous findings, in both experiments, we found that the dmPFC displayed increased activation when participants cognitively upregulated emotions associated with positive-social situations. In particular, dmPFC has been shown to be implicated in upregulation of negative (Ochsner, et al., 2004) and positive (Ochsner and Gross, 2005) emotions (for review, see (Ochsner and Gross, 2005; Ochsner, et al., 2012)).

Interestingly, activation within the sgACC did not always mirror that of the dmPFC, which was prominently involved in effortful emotion upregulation processes of both experiments. The dmPFC

and sgACC co-activations were observed (a) in the main effect of stimuli in the first experiment, (b) during passive viewing of the positive-social stimuli condition as compared to the passive viewing of neutral non-social stimuli condition in the first experiment, and (c) during the positive-social emotion upregulation condition as compared to the passive viewing of neutral non-social stimuli condition in the second experiment. However, we did not observe sgACC activation during the positive-social emotion upregulation condition as compared to passive viewing of neutral non-social stimuli condition in the first experiment, and the sgACC and dmPFC activations during rapid passive viewing of positive-social emotion stimuli in comparison to the rapid passive viewing of neutral non-social scenes. These results support previous findings that link the sgACC with engagement of effortful positive-social emotion upregulation, and together with other findings, suggests a potential role of the sgACC as a gatekeeper between cognitive control areas (involving dmPFC) and bilateral amygdala (Disner, et al., 2011; Greicius, et al., 2007; Palomero-Gallagher, et al., 2015). Overall, brain areas that we found to be associated with positive emotion regulation largely overlap with those involved in the regulation of negative emotions in previous studies (Herwig, et al., 2007; Kim and Hamann, 2007; Ochsner, et al., 2012; Vrticka, et al., 2012).

Identified activity in dmPFC, sgACC and bilateral amygdala is also consistent with their relevance to social cognition. For instance, it has been suggested (a) that amygdala activation is independent on valence for social images but is dependent on valence of nonsocial images, and (b) that the amygdala is more strongly activated for neutral social than non-social stimuli (Vrticka, et al., 2012). Similarly, dmPFC has been shown to be more active in social as compared to non-social conditions regardless of the emotional content (Vrticka, et al., 2012), and has an integral role in emotion regulation and social cognition (Bzdok, et al., 2013; Ochsner, et al., 2012; Reeck, et al., 2016). Finally, the sgACC has also been shown to be implicated in both emotion regulation (Banks, et al., 2007; Wager, et al., 2008a; Wager, et al., 2008b), and social cognition (Lockwood and Wittmann, 2018; Palomero-Gallagher, et al., 2015).

dmPFC-sgACC-amygdala circuit connectivity

Further evidence supporting the gatekeeping role of the sgACC was provided by our analysis of connectivity and dynamic causal interactions between the ROIs, where a network hierarchy including the sgACC as a relay between bilateral amygdala and dmPFC was found to be the most likely architecture during the upregulation condition (**Figure 2**, model family 5). The brain network architecture that emerged during the emotion upregulation condition involved the dmPFC as the predominant entry point for external inputs into the network, which then was conveyed to the

bilateral amygdala in a top-down fashion via direct dmPFC-amygdala connections and indirectly via the sgACC. Although passive viewing and rapid passive viewing conditions of positive-social stimuli as compared to corresponding (rapid) passive viewing of neutral non-social stimuli conditions revealed distinct dmPFC and sgACC activations (**Table 1**), these areas were characterized with strong intra-network connections (**Figure 2B,D**). In particular, during rapid passive viewing, the sgACC exerted strong positive modulation on the bilateral amygdala, and strong negative modulation on the dmPFC, in addition to the bilateral amygdala exerting strong modulaton on the dmPFC (**Figure 2D**), which suggests more prominent enagement of the sgACC and amygdala into the automated network upregulation processes.

Indeed, the sgACC appears to constitute a key station relaying bottom-up emotion information from low-level areas to the dmPFC, and vice versa conveying top-down signals from the latter to the amygdala. Previous studies are consistent with a major role of the sgACC during emotion regulation, where this area is associated with the top-down control of amygdala reactivity (Banks, et al., 2007; Ghashghaei, et al., 2007; Wager, 2008), and is further implicated in negative mood and depressive symptoms (George, et al., 1995). Importantly, previous studies have found that the up-regulation of emotions has been shown to increase effective coupling between the amygdala, ACC and dmPFC, which was correlated to individual success of regulation (Morawetz, et al., 2017).

The sgACC has been shown to be hyperactive in patients with depression and anxiety disorders (Drevets and Savitz, 2008; Gotlib, et al., 2005; Laxton, et al., 2013; Ressler and Mayberg, 2007b), where successful treatment and recovery of mood disorders has been associated with a normalization of this hyperactivity (Escolano, et al., 2014; Mayberg, et al., 2005; Nobler, et al., 2001; Ressler and Mayberg, 2007b; Zotev, et al., 2011). Furthermore, normalization of this neural architecture involving hyperactive limbic regions (including the amygdala) and hypoactive emotion regulation areas (including the dmPFC) is also a key target for interventions in trauma-related disorders (Doll, et al., 2016; Koch, et al., 2016; Nicholson, et al., 2017b; Nicholson, et al., 2018; Zotev, et al., 2018). Interestingly, the sgACC is intimately connected to regions involved in emotion processing and interoception, such as the amygdala, the hypothalamus (Beckmann, et al., 2009; Freedman, et al., 2000; Johansen-Berg, et al., 2008), as well as the hippocampus, insula, orbitofrontal cortex, and both the dorsolateral and dorsomedial PFC (Beckmann, et al., 2009; Carmichael and Price, 1996; Craig, 2011; Johansen-Berg, et al., 2008; Vogt and Pandya, 1987). This pattern of connectivity is compatible with a role of the sgACC as a gatekeeper between cognitive

control areas in the dmPFC and lower-level areas of the limbic system responsible for the elicitation of emotional responses (Disner, et al., 2011; Greicius, et al., 2007; Palomero-Gallagher, et al., 2015).

Overall, our results suggest that the dmPFC and sgACC are important hubs for cognitively engaging in positive-social emotions in a self-relevant, first-person perspective, which substantially extends recent findings in positive-social emotion regulation (Kim and Hamann, 2007; Koush, et al., 2019; Ochsner, et al., 2012; Vrticka, et al., 2012). This is in line with the proposal that the dmPFC may be crucially involved in evaluating social information (Amodio and Frith, 2006; Bzdok, et al., 2013; Gallagher and Frith, 2003; Kampe, et al., 2003; Lieberman, 2007; Vrticka, et al., 2012) and situating oneself in social contexts (Amodio and Frith, 2006; Gallagher and Frith, 2003; Kampe, et al., 2003; Lieberman, 2007; Northoff and Bermpohl, 2004). However, prefrontal regions implicated in emotion upregulation and reappraisal are also commonly involved in other non-emotional tasks and may subserve more general cognitive control processes (Braunstein, et al., 2017; Etkin, et al., 2011; Ochsner, et al., 2012).

Amygdala activity and connectivity

In our study, the bilateral amygdala was active during positive-social passive viewing and emotion upregulation conditions (i.e., the main effect of stimulus), but did not show a functional lateralization within this main effect (Koush, et al., 2019). However, during the emotion upregulation condition in the second experiment, activity in the bilateral amygdala shifted predominantly towards the left side, as indicated by our laterality analysis. This laterality might reflect a putative hemispheric difference in encoding the valence of emotional experiences, with a principle role of the left amygdala in positive emotions (Kim and Hamann, 2007; Lanteaume, et al., 2007; Sergerie, et al., 2006; Vrticka, et al., 2012). This result also adds to the recent findings that suggest that cognitive reappraisal of social emotions might recruit the left amygdala more than the right (Vrticka, et al., 2012; Young, et al., 2014). This would in turn be consistent with models proposing that the left amygdala is involved in elaborated cognitive information processing and the manipulation of affective representations with linguistic content (Glascher and Adolphs, 2003; Phelps, et al., 2001). We therefore hypothesize that the observed shift in activity towards the left amygdala may represent increased cognitive evaluation of the social scene stimuli due to positive upregulation, however, further research is needed to test more directly these speculations. Our results also showed that during positive-social emotion upregulation conditions in both experiments, the amygdala received top-down modulating inputs directly from the dmPFC, as well as indirectly via the sgACC (**Figure 2**). This is generally in accordance with previous work showing

that the amygdala plays a major role in the detection and encoding of emotional information, in which the amygdala is modulated by cognitive reappraisal strategies (Banks, et al., 2007; Goldin, et al., 2008; Ochsner and Gross, 2005; Vrticka, et al., 2012; Wager, et al., 2008b).

Linking psychometric scores with observed activity and connectivity patterns

The modulation of functional activity within the dmPFC-sgACC-amygdala circuit was mediated by individual characteristics, as indexed by standard psychometric scores which may influence emotion regulation capacities (**Figure 3**). In the first experiment, the higher emotion suppression scores were found to predict lower activity in the dmPFC during positive-social emotion upregulation conditions (ERQ-S, (Koush, et al., 2019)) and higher positive connectivity strengths from the left amygdala onto the sgACC (WBSI). In the second experiment, the higher tendency to suppress intrusive thoughts (WBSI) was found to predict the lower activity in bilateral amygdala, the sgACC and dmPFC during positive-social emotion upregulation conditions. This indicates that individuals with higher tendencies to suppress emotions and intrusive thoughts achieve less effective recruitment of these areas in positive-social emotion upregulation. During rapid passive viewing conditions in the second experiment, we found that trait anxiety was negatively correlated with connectivity strength from the left amygdala onto the sgACC. Taken together with a positive correlation between intrusive thought suppression and anxiety scores in the second experiment, these findings suggest that more anxious individuals, with a greater tendency to suppress emotions and intrusive thoughts, were likely to display decreased amygdala, dmPFC, sgACC activity, and stronger modulation of the sgACC by the left amygdala during effortful emotion upregulation. In addition, individuals with lower anxiety scores were likely to display higher modulation of the sgACC by the left amygdala during more automated emotion regulation processes. In the second experiment, we also found that individuals with a higher desire for new rewards and rewarding events exhibited higher positive external modulation of the dmPFC during positive-social emotion upregulation condition, and higher sgACC activity during the rapid passive viewing condition, although the sgACC did not reach the whole-brain group-level significance in this condition (**Table 1**, rapid viewing positive > rapid viewing neutral). These findings are consistent with an important role of the sgACC in emotion processing and mood (Drevets and Savitz, 2008; Gotlib and Hamilton, 2008; Wager, et al., 2008b) as well as self-referential representations (Lockwood and Wittmann, 2018). Furthermore, these result add to the view that neural correlates of cognitive control and emotion regulation are reduced in anxiety disorders (Etkin, et al., 2010).

Experimental design implications

We applied experimental design settings which could be useful for designing the future emotion regulation experiments. In the first experiment, we used emotion regulation conditions with conventional stimuli display duration (6s) and number of stimuli per block (4 images, 24s block duration) (**Figure S1A**). However, in the second experiment, we tested the feasibility of two functional run designs with reduced stimuli display duration. Here, in positive-social emotion upregulation runs, we reduced image display duration to 4s and the number of images per block to 3, which resulted in a twofold decrease in condition block duration as compared to the first experiment (24s vs. 12s) (**Figure S1B**). This shortening was done to check the feasibility of the periodic functional run design with relatively short experimental blocks. Our results validated the feasibility of such periodic functional runs with reduced valence and arousal of positive-social stimuli, which could be of specific benefit for real-time fMRI and neurofeedback paradigms targeting effortful positive-social emotion upregulation with the dmPFC, bilateral amygdala and sgACC engagement (Koush, et al., 2017c).

As compared to effortful upregulation condition with the same image display duration, the positive-social passive viewing condition could be considered an attenuated emotion upregulation condition which does not exclude activation of the dmPFC and sgACC. Therefore, in rapid passive viewing runs in the second experiment, we further reduced stimuli duration to limit the participants' engagement with the content of presented scenes (0.5s image display duration, 24 images per block, 12s block duration) (**Figure S1B**). We showed that sgACC and dmPFC were not significantly activated in rapid passive viewing runs as compared to positive-social emotion upregulation runs (**Table 1**). However, rapid passive viewing of positive-social stimuli was still associated with activations in bilateral amygdala, suggesting that the role of self-referential engagement with the context of presented scenes in emotion regulation processes could be reduced and that automatic emotion regulation processes could be stimulated (Braunstein, et al., 2017; Diano, et al., 2016). Thus, rapid passive viewing runs with minimized participant engagement in the content of presented scenes could be recommended for checking the feasibility and sensitivity of MR sequences vulnerable to gradient dropouts in bilateral amygdala (Weiskopf, et al., 2006). The rapid passive viewing condition could be further studied in different emotion regulation domains and clinical populations.

Clinical implications

The brain circuits identified in our study might particularly be important for the mechanisms of projecting oneself in emotional scenarios with a self-relevant, first-person perspective. Such first-

person projections are important in constituting an effective strategy within therapeutic settings (Holmes, et al., 2008; Philippot and Segal, 2009; van der Velden, et al., 2015). Appraisals of self-relevance also constitute a key ingredient of emotional experiences that determine their intensity irrespective of valence and emotion type (Sander, et al., 2005; Scherer, 1982). Moreover, self-referential processing also recruits medial prefrontal, sgACC and amygdala regions that partly overlap with those associated with emotion regulation (Buckner and Carroll, 2007; Koush, et al., 2019; Reeck, et al., 2016; Zaki and Ochsner, 2012), and is implicated in mood and trauma-related disorders (Disner, et al., 2011; Drevets, 2001; Drevets and Savitz, 2008; Wagner, et al., 2015; Wu, et al., 2016; Yehuda, et al., 2015; Zaki and Ochsner, 2012).

Critically, the current study informs neurobiological treatment interventions for psychiatric disorders, for example, real-time fMRI neurofeedback studies in PTSD and depression that aim to regulate the amygdala activity (Nicholson, et al., 2017a; Nicholson, et al., 2017b; Nicholson, et al., 2018; Young, et al., 2017; Young, et al., 2014; Zotev, et al., 2018; Zotev, et al., 2013). Results from the current study suggest that optimal upregulation may be achieved by modulating the amygdala from both the dmPFC and the sgACC, when using effective connectivity as a feedback signal. Indeed, Young and colleagues has previously shown therapeutic effects in depressed patients by upregulating the amygdala during positive emotion regulation in a randomized clinical trial, which also specifically recruited areas of the ACC. Future studies might extend our work to patients suffering from anxiety, mood and trauma-related disorders, thereby helping to identify the brain dynamics that prevent positive emotions and affect dysregulation in these patients. Brain-based measures of these functional interactions might also serve to evaluate the success or failure of specific treatments in patients with abnormal network dynamics, and be used as targets for neurofeedback training (Sitaram, et al., 2017) to recover the impaired network dynamics (Bruhl, et al., 2014; Keynan, et al., 2019; Koush, et al., 2017a; Koush, et al., 2019; Linden, et al., 2012; Misaki, et al., 2018; Nicholson, et al., 2018; Sulzer, et al., 2013; Young, et al., 2018; Young, et al., 2014; Zotev, et al., 2018).

Limitations

In the current study we focused on engaging oneself in positive-social emotion upregulation. While this is a realistic scenario of therapeutic relevance, our study design does not allow for separating self-referential, affective, and social aspects in applied emotion regulation. Nevertheless, as discussed above, identified dmPFC, sgACC and bilateral amygdala activity is highly relevant to both social cognition and emotion regulation. Also, affective (positive/neutral/negative) and social/non-

social content relevance to emotion regulation processes in bilateral amygdala has been previously characterized (Vrticka, et al., 2012). In particular, the amygdala is engaged in both social and emotion regulation (Vrticka, et al., 2012). Future research could further delineate social aspect from applied positive-social emotion regulation paradigms when contrasting positive social and positive non-social conditions. An interesting extension of our study would be the direct comparison of the sgACC role in positive-social and negative-social emotion regulation conditions. Although our study does not allow for directly contrasting these two conditions, it revealed that positive-social emotion upregulation recruited a distributed cortico-limbic network that overlaps with areas involved in regulating negative emotions (Kim and Hamann, 2007; Ochsner, et al., 2012; Vrticka, et al., 2012).

Future studies might also include more diverse participant populations to assess if the present results generalize beyond the population included in this study (which consisted predominantly of young students and researchers). Here, the purpose of our study was to examine dynamic mechanisms underlying positive-social emotion upregulation in a healthy population, where future studies are warranted in aforementioned clinical populations hypothesized to exhibit disrupted emotion regulation networks.

Conclusion

In sum, the present study complements and extends previous research with the sgACC engagement in positive-social emotion regulation processes and dmPFC-amygdala interactions. We provide evidence that the sgACC is involved in effortful positive-social emotion upregulation and more automated positive-social passive viewing and rapid passive viewing conditions. These findings support a potential role of the sgACC as a gatekeeper between cognitive control areas and emotional limbic areas, which interactions within prefrontal-limbic network increase in more automated emotion regulation processes as compared to effortful emotion upregulation. We found that more anxious individuals with a greater tendency to suppress emotions and intrusive thoughts, were likely to display decreased amygdala, dmPFC, sgACC activity, and stronger modulation of the sgACC by the left amygdala during effortful emotion upregulation. During more automated emotion regulation, less anxious individuals were also likely to display higher modulation of the sgACC by the left amygdala. Our findings may have significant therapeutic relevance for those suffering from psychiatric illnesses, in which disrupted emotion regulation network capacities are a key mechanism contributing to many forms of psychopathology. Finally, our study informs neurobiological treatment interventions, such as neurofeedback, in how optimal emotion regulation of target neural network

may be achieved when using effective connectivity as a feedback signal by providing insights on specific prefrontal-limbic neural network interactions.

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Figure captions

(a)

Experiment 1	condition block	
	emotion upregulation	passive viewing
positive-social stimuli	**4** *images per block,* **6s** *display duration*	**4** *images per block,* **6s** *display duration*
neutral nonsocial stimuli	**4** *images per block,* **6s** *display duration*	**4** *images per block,* **6s** *display duration*

Experiment 2	emotion upregulation / passive viewing run	rapid passive viewing run
positive-social condition	**3** *images per block,* **4s** *display duration*	**24** *images per block,* **0.5s** *display duration*
neutral nonsocial baseline	**3** *images per block,* **4s** *display duration*	**24** *images per block,* **0.5s** *display duration*

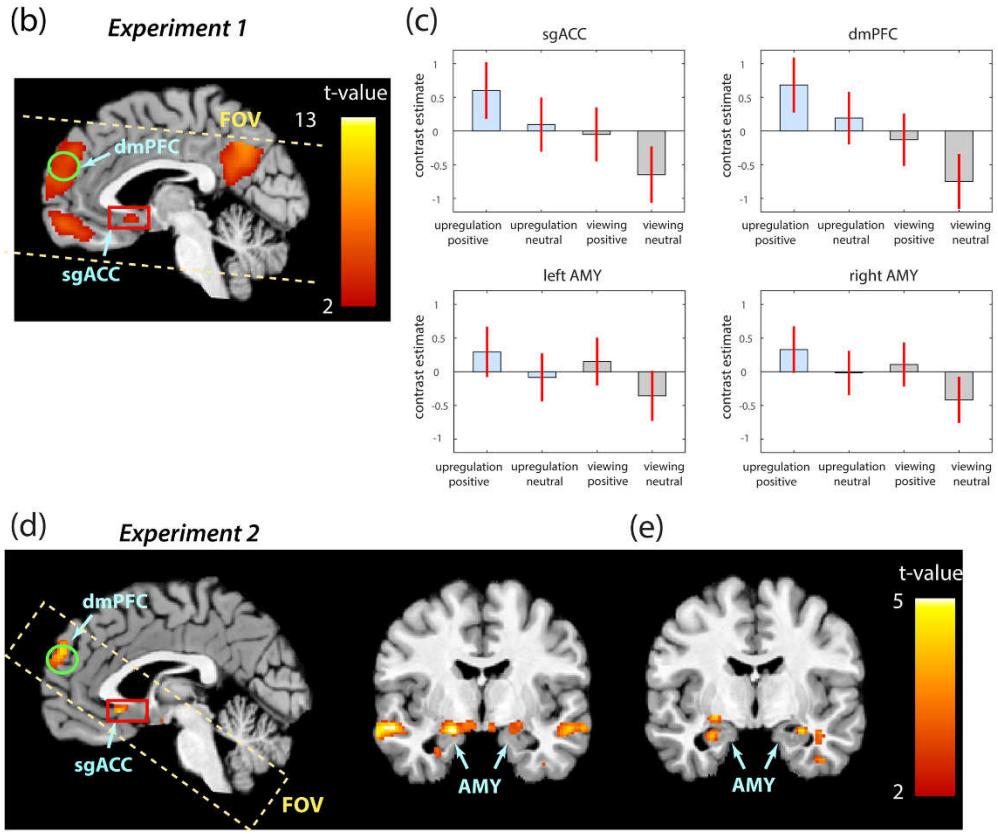

Figure 1. Brain activity related to positive-social emotion upregulation and passive viewing conditions. (A) In both experiments, Tables resume the number and duration of displayed images per condition block. Blue boxes indicate conditions by which participants were instructed to effortfully upregulate. (B) For the first experiment (Koush, et al., 2019), the dmPFC and sgACC activations are illustrated (the main effect of stimuli, positive > neutral), and (C) the bar plots for target ROIs showcase contrast estimates of modelled conditions with their 90% confidence intervals (CI, red error bars). Shaded blue color denotes emotion upregulation conditions. (D) For the second experiment, positive-social emotion upregulation was associated with increased activity in the left amygdala, the dmPFC, and the sgACC, as compared to baseline. Passive or rapid passive viewing of neutral non-social stimuli conditions were selected as control (denoted baseline) conditions in the experimental runs. (B,D) The sgACC and dmPFC ROIs are highlighted as red rectangular box and green circle, respectively. (E) Rapid passive viewing of the depicted positive-social situations was associated with bilateral amygdala activation, as compared to baseline. For illustration purposes, activation maps were thresholded ($p < .005$ unc., 10 voxels extent) and overlaid onto the structural template using Mango software (ric.uthscsa.edu/mango). AMY – amygdala, dmPFC – dorsomedial prefrontal cortex, sgACC – subgenual anterior cingulate cortex, FOV - field of view.

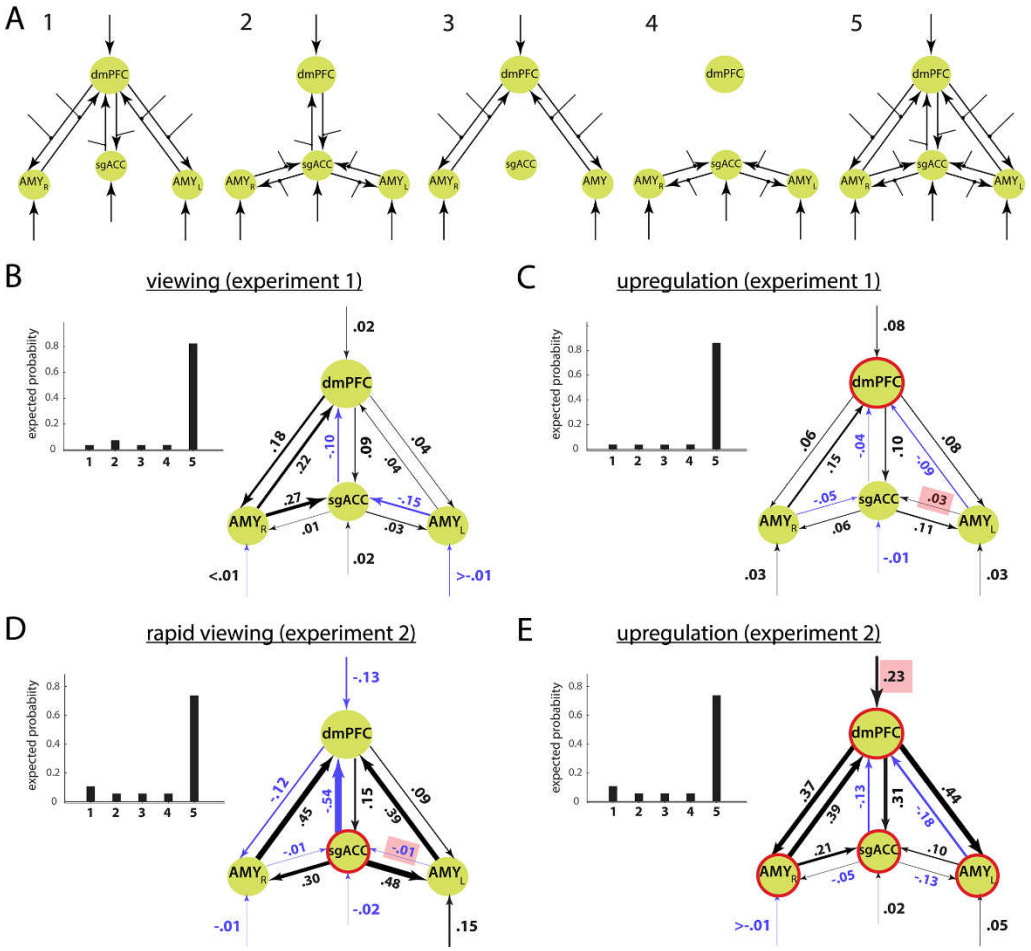

Figure 2. Estimation of general network structures. (A) All models consisted of four ROIs, reciprocal connections between the ROIs (arrows between nodes), modulatory inputs (lines with dotted end points), and external inputs into the ROIs (arrows). For family-level inference, the model space was partitioned into 5 subsets with different connectivity patterns between the bilateral amygdala, the dmPFC, and the sgACC. For the first experiment, expected and exceedance family probabilities revealed that the fully connected model dominated during positive-social (B) passive viewing and (C) emotion upregulation (6 s stimuli display duration) conditions. For the second experiment, expected and exceedance family probabilities showed the same dominance of the fully connected model family during positive-social (D) rapid passive viewing (0.5 s stimuli display duration) and (E) emotion upregulation (4 s stimuli display duration) conditions. (B-E) Blue arrows highlight negative values. (C-E) Red circles around network nodes highlight corresponding experiment and condition brain areas that showed a significant correlation with psychometric scores, as well as red rectangles highlight the connectivity parameters that showed a significant correlation with psychometric scores (**Figure 3**). For simplicity, the reciprocal connections (matrix A in DCM) and the modulatory inputs (matrix B in DCM) between the ROIs are added and depicted as arrows between the ROIs. The BMA parameters are indicated next to the corresponding connections and illustrated by the proportional arrow thickness. The external input can reflect either the image presentation, the task, or both, being inherently linked to one another in our experimental designs. AMY – amygdala, dmPFC – dorsomedial prefrontal cortex, sgACC – subgenual anterior cingulate cortex, L – left, R – right.

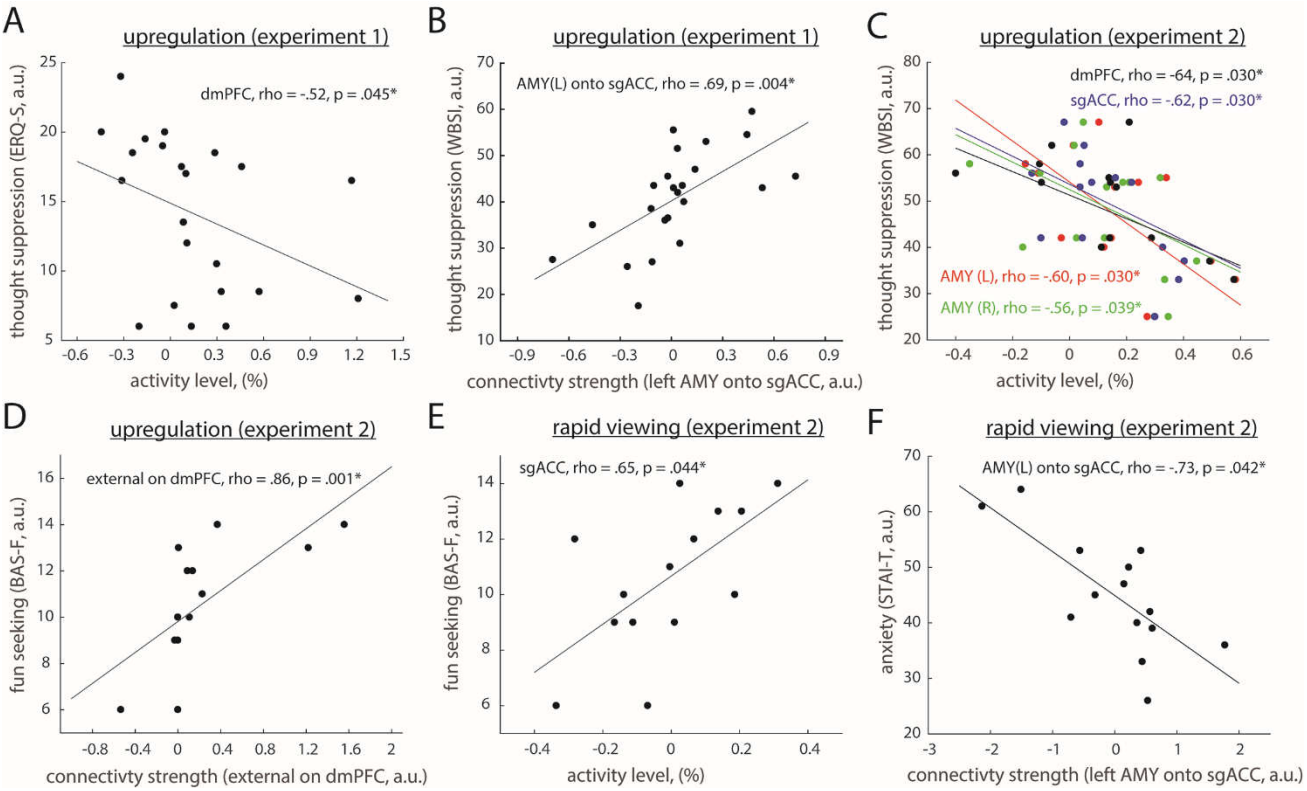

Figure 3. Correlation between the psychometric scores and observed activity and connectivity patterns. In the first experiment, during positive-social emotion upregulation condition, we observed (A) that the tendency to suppress emotions (ERQ-S) was negatively correlated with activity levels in the dmPFC (Koush, et al., 2019) and (B) that the tendency to suppress intrusive thoughts (WBSI) was positively correlated with the connectivity strengths from the left amygdala onto the sgACC. In the second experiment, during positive-social emotion upregulation condition, we observed (C) that the tendency to suppress intrusive thoughts correlated negatively with the activity levels in the dmPFC, the sgACC and bilateral amygdala, and (D) that fun seeking scores (BAS-F) correlated positively with the external connectivity strengths on the dmPFC. In the second experiment, during positive-social emotion rapid passive viewing condition, we observed (E) that the fun seeking scores correlated positively with the activity levels in the sgACC, and (F) the negative correlation between the anxiety scores and the connectivity strengths from the left amygdala onto the sgACC. In the first experiment, we did not observe significant correlations between psychometric scores and activity levels and connectivity strengths during positive-social passive viewing conditions. ***** survived FDR correction for multiple comparisons.

Tables

Table 1: Brain areas related to experimental conditions.

condition / contrast	area	MNI coordinates			t-value	p-value
		x	*y*	*z*		
Experiment 1						
interaction task × stimuli	**TPJ**	-58	-56	26	4.00	.014^{+}
main effect of task (upregulation > viewing)	**SFG**	-14	56	36	3.91	.018^{+}
main effect of stimuli (positive > neutral)	**AMY**	-18/18	-8/-6	-14/-14	6.28 / 6.94	.002 / <.001
	dmPFC	6	50	34	5.48	.025
	sgACC	2	12	-8	4.70	.002^{+}
	TPJ	-42/44	-54/-56	24/18	3.76 / 10.28	.025^{+} / <.001
	vmPFC	4	58	-12	6.29	.002
	PVC	-22/28	-102/-96	-2/-6	9.37 / 10.11	<.001 / <.001
	FFA	-42/42	-52/-52	-20/-18	9.52 / 13.43	<.001 / <.001
	Precuneus	2	-58	40	8.42	<.001
	STS	-68/54	-12/-10	-12/-12	5.64 / 6.44	.016 / .001
	V5/MT	-48/48	-72/-74	12/4	10.93 / 16.96	<.001 / <.001
	IFG	36	16	26	5.33	.041
upregulate positive > viewing positive	**SFG**	-8	50	40	3.82	.023^{+}
upregulate positive > viewing neutral	**dmPFC**	-2/6	56/50	24/36	4.06 / 4.64	.002^{+}/.002^{+}
viewing positive > viewing neutral	**AMY**	-18/20	-4/-4	-14/-14	4.91 / 6.43	.001^{+} / .001
	dmPFC	6	50	32	4.83	.001^{+}
	sgACC	0	12	-8	3.80	.030
	TPJ	42	-56	18	9.35	<.001
	vmPFC	4	58	-12	4.60	.002^{+}
	PVC	-24/28	-100/-96	-2/-6	6.61/ 7.86	.001 / <.001
	FFA	-42/42	-50/-54	-20/-18	9.43 / 12.40	<.001 / <.001
	Precuneus	4	-56	40	5.59	.019
	STS	54	-6	-12	5.48	.027
	V5/MT	-50/50	-74/-74	12/4	10.21 / 14.82	<.001 / <.001
	IFG	38	12	26	5.50	.025
Experiment 2						
upregulation positive > viewing neutral (baseline)	**AMY**	-18	-7	-16	6.10	.008
	dmPFC	-4/2	63/58	27/29	5.41 / 4.67	.001^{+} / .008^{+}
	sgACC	2	22	-9	4.49	.016^{+}

	STS	-54	-9	-14	5.66	.027
rapid viewing positive > rapid viewing neutral (baseline)	**AMY**	-23/18	-9/0	-9/-16	5.46 / 3.81	.045 / .038^{+}

Reported are the main peak coordinates of areas that survived whole-brain FWE correction ($p < .05$, voxel-level inference). $^{+}$ Plus denotes activity peaks that survived SVC statistics ($p < .05$, peak-level FWE). Note that the sgACC activity peak also survived the whole-brain FDR correction (Experiment 1, main effect of stimuli) (Koush, et al., 2019). TPJ – temporoparietal junction, AMY – amygdala, dmPFC – dorsomedial prefrontal cortex, vmPFC – ventromedial prefrontal cortex, MT – middle temporal gyrus, PVC – primary visual cortex, FFA – fusiform face area, STS – superior temporal sulcus, IFG – inferior frontal gyrus, SFG – superior frontal gyrus.

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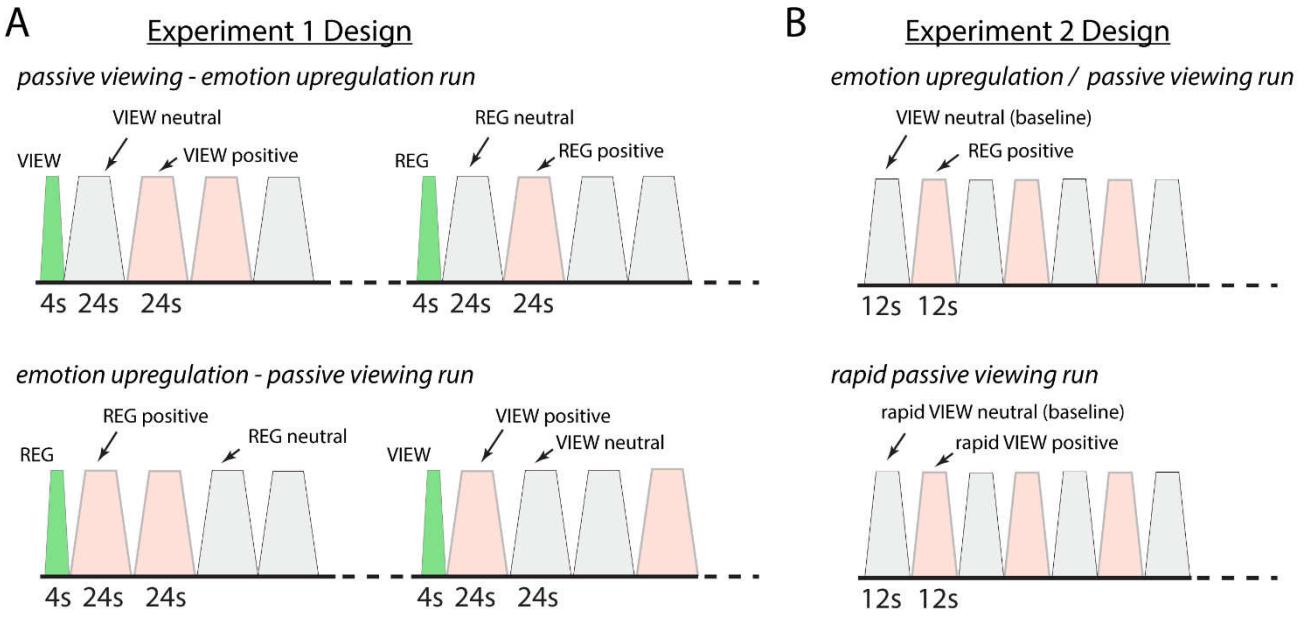

Figure S1. Designs of two alternating functional runs per subject for both experiments. (A) For the first experiment, emotion upregulation and passive viewing blocks were randomized and organized in two alternating epochs per functional run (2 upregulation / passive viewing epochs, 14 blocks of positive-social / neutral nonsocial conditions per epoch). Emotion upregulation and passive viewing conditions lasted 24s each (7 blocks per each stimuli category per epoch, 4 images per block, 6s image display duration, 11.3 min total run duration). The instruction word, i.e. upregulate (REG) or view (VIEW), was displayed prior to each epoch (4s display duration, green blocks). (B) For the second experiment, emotion upregulation and rapid passive viewing runs were performed separately, i.e. passive or rapid passive viewing conditions were selected as control (denoted baseline) conditions. Each run had periodically alternating baseline (passive viewing of nonsocial stimuli) and corresponding condition blocks, i.e. upregulation or rapid passive viewing of positive-social scenes (4s image display duration, 10 blocks of positive-social stimuli, interleaved with 11 blocks of neutral stimuli, 3 images per block, 4.2 min total run duration). For both experiments, red color denotes blocks where positive-social stimuli were presented, and grey color denotes blocks were neutral nonsocial stimuli were presented. VIEW positive – passive viewing condition for positive-social scenes, VIEW neutral – passive viewing condition for neutral nonsocial scenes, REG positive – emotion upregulation condition for positive-social scenes, REG neutral – emotion upregulation condition for neutral nonsocial scenes.

Table S1: Average psychometric scores.

Test	mean ± sem
upregulation (ERQ-R)	27.5±1.4
suppression (ERQ-S)	16.6±1.6
suppression (WBSI)	48.4±3.2
trait anxiety (STAI-T)	45.0±2.8
inhibition (BIS)	19.1±.6
activation (BAS-R)	15.4±.9
activation (BAS-D)	9.9±.7
activation (BAS-F)	10.6±.7