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KATHRIN COHEN KADOSH[1,2], QIANG LUO[3,4], CALEM DE BURCA[2], MOSES SOKUNBI[5,7], JIANFENG FENG[3,4,6], DAVID E J LINDEN[5,7], & JENNIFER Y F LAU[1]

[1]*Psychology Department, Institute of Psychiatry, King's College London, London SE5 8AF, UK*

[2]*Department of Experimental Psychology, University of Oxford, South Parks Road, Oxford, OX1 3UD, UK*

[3]*Centre for Computational Systems Biology, Fudan University, Shanghai 200433, PR China*

[4]*Shanghai Center for Mathematical Sciences, Fudan University, Shanghai 200433, PR China*

[5]*MRC Centre for Neuropsychiatric Genetics and Genomics and National Centre for Mental Health, Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Cardiff, CF14 4XN, UK*

[6]*Department of Computer Science, University of Warwick, Coventry CV4 7AL, United Kingdom*

[7]*Cardiff University Brain Research Imaging Centre, School of Psychology, Cardiff University, Cardiff CF*

Corresponding author:
Kathrin Cohen Kadosh
Department of Experimental Psychology
University of Oxford
Oxford, UK
Phone: ++44(0) 1865 271 249
Email: kathrin.cohenkadosh@psy.ox.ac.uk

Abstract

For most people, adolescence is synonymous with emotional turmoil. Yet the current scientific evidence suggests that emotional reactivity per se does not change much in the transition from childhood to adulthood. In fact, most research up-to-date has shown that the observed change in emotional behaviour is due to continuous developmental improvement in the regulation of emotional responses, along with changes in its neural bases. Here, we used fMRI-based neurofeedback (NF) to investigate the suitability of NF to directly influence plasticity in the developing emotion regulation (ER) brain networks. We taught a group of 17 7-16 year-olds to up-regulate the bilateral insula, a key ER region and found that all participants learned to increase activation during the regulate trials in comparison to rest trials. Importantly, a subsequent Granger Causality Analyses of information flow within the wider ER network found that during regulation trials, bottom-up driven information flow increased from the amygdala to the bilateral insula and from the left insula to the mid-cingulate cortex, supplementary motor area and the inferior parietal lobe. This was reversed during rest trials, where we observed an increase in top-down driven information flow to the bilateral insula from mid-cingulate cortex, pre-central gyrus and intra-parietal lobule. This suggests that: 1) NF training had a differential effect on regulation and rest network connections, and specifically that 2) our training was not only superficially concentrated on surface effects but also relevant with regards to the underlying neurocognitive bases. Together these findings highlight the feasibility of using NF in paediatric populations and its possible use for shaping key social cognitive networks during development.

Highlights

Introduction

For most people, adolescence is synonymous with emotional turmoil (Guyer et al., 2012; Moor et al., 2010; Sebastian et al., 2011), which goes along with an increased risk for developing psychiatric disorders (Kessler et al., 2005; Paus et al., 2008). Yet the current scientific evidence suggests that emotional reactivity per se does not change much in the transition from childhood to adulthood (McRae et al., 2012). Rather, most research up to date has shown that the observed change in emotional behaviour is due to continuous developmental improvement in the control and regulation of emotional responses (McRae et al., 2012; Silvers et al., 2012). The improvements in emotion control abilities are only part of a general programme of development in that they go along with substantial cognitive and physiological maturation (Blakemore, 2008; Burnett et al., 2011). At the brain level, the ongoing development is reflected in both grey and white matter changes (Giedd et al., 1999; Harris et al., 2011; Lebel and Beaulieu, 2011; Petanjek et al., 2011; Tamnes et al., 2013), as well as increased functional connectivity in default and resting state brain networks (Fair et al., 2008; Fair et al., 2007). All these changes affect not only the brain structure, but also the functional responsiveness and processing abilities of the developing brain. It has been suggested that the timing of this transformational process, which coincides with a period of significant social cognitive change, could help explain the increased risk for developing a mental disorder (Haller et al., in press; Haller et al., in preparation; Paus et al., 2008).

With regards to emotion regulation, a handful of developmental functional magnetic resonance imaging (fMRI) studies have consistently found changes in anterior and lateral functional subdivisions of the prefrontal cortex (PFC) in response to emotional stimuli across childhood and adolescence (Guyer et al., 2012; Moor et al., 2010; Sebastian et al., 2011). These have been interpreted as improved recruitment of prefrontal regions in order to effectively down-regulate subcortical arousal (Nelson et al., 2005). Further support for this interpretation comes from data showing that functional regulatory connections between PFC and subcortical regions continue to mature throughout childhood and adolescence (Pitskel et

al., 2011) (Hare et al., 2008; Perlman and Pelphrey, 2011). For example, a recent study by Gee and colleagues (Gee et al., 2013) reported a shift towards negative connectivity in the amygdala-medial PFC network (with decreasing amygdala responsivity corresponding to an increase in medial PFC activity) during the viewing of negative faces from the age of 10 years onwards.

In view of these prolonged developmental trajectories of the neurocognitive bases of emotion regulation abilities, it seems plausible that neuro-behavioural plasticity – and hence the window for successful interventions- is also extended (Cohen Kadosh et al., 2013; Thompson-Schill et al., 2009). One such intervention approach is real-time fMRI-based neurofeedback (NF). NF is a newly emerging technique that utilizes the latest developments of real-time data processing and pattern analysis in order to train participants in the self-modulation of neural networks. As with some cognitive training techniques, such as modifications of attentional or interpretation biases (Bar-Haim, 2010; Lau, 2013; MacLeod and Holmes, 2011), it has been suggested that fMRI-based NF could be used to help influence brain responses at crucial developmental junctures (Cohen Kadosh et al., 2013; Haller et al., in preparation; Platt et al., 2013). Specifically, it could be used as a tool to explore response plasticity in the developing cortical networks for emotion regulation and, most importantly, to help shape these networks in the most optimal way (Cohen Kadosh et al., 2013). In fMRI-based NF studies, participants are presented with real-time brain activation in specific regions of interest (for example through a visually-presented thermometer) and they learn to reliably regulate their online brain response with high spatial precision (deCharms, 2007; deCharms et al., 2005; Johnston et al., 2010; Weiskopf et al., 2004a; Weiskopf et al., 2004b). NF has proven particularly useful for up- or down-regulating the brain regions involved in healthy adults' emotional responses (Johnston et al., 2010; Johnston et al., 2011; Paret et al., 2014; Zotev et al., 2011). In addition, it has been used to change brain responses in clinical populations, such as for example participants with schizophrenia (Ruiz et al., in press) or depression (Linden et al., 2012). One particular

advantage of fMRI-based (compared to EEG-based) NF lies in its high spatial resolution, which can be used to directly target and train the brain networks which are undergoing change – and which may be more responsive to external interventions. For example, in the study by Zotev and colleagues (2011), where typical adults learned to successfully up-regulate their left amygdala, they also observed significant increases in functional connectivity between different regions of the amygdala network comprising also the right medial frontal polar cortex, the bilateral dorsomedial prefrontal cortex, the left anterior cingulate cortex, and bilateral superior frontal gyri. This is important, as it shows that NF does not only affected brain responses within a specific brain region (i.e. the left amygdala), but also the processing flow within a larger network of regions. In turn, the network-based effect is important from a developmental perspective, as it would allow us to time interventive approaches to coincide with a period of substantial brain and cognitive development such as adolescence. In addition, it seems also likely that any changes to neurocognitive circuitry will have knock-on effect on behaviour that is stronger and more persistent than at other developmental stages (Cohen Kadosh et al., 2013).

However, up until now, all NF-based research on emotion regulation networks has been conducted with healthy adults (Caria et al., 2010; Johnston et al., 2010; Johnston et al., 2011; Paret et al., 2014; Zotev et al., 2011) or adult patients (Linden et al., 2012; Ruiz et al., in press). The current study aimed to establish the feasibility of using NF with paediatric populations. Our main aim was to teach children and adolescents to gain control over the insula region in a simple NF up-regulation task in comparison to a rest condition. We chose the right insula region, as it is a key region in the emotion regulation network (Kohn et al., 2014; Wager and Feldman-Barrett, 2004). It is also functionally well-connected with the amygdala and PFC regions, which are all relevant for improving emotion regulation abilities during development (Gee et al., 2013; Pitskel et al., 2011). In addition, previous studies have also shown that the insula responds reliably to modulation interventions (Pitskel et al., 2011), and particularly NF-based ones where the NF-intervention does have a more wide-spread effect on the emotion regulation network (Ruiz et al., in press). A second aim of the study

was therefore to assess the wider effect of NF training on the developing emotion regulation network, and particularly on changes in bottom-up and top-down information flow between the different brain regions for the two task conditions (regulate vs rest).

Methods

Participants. Nineteen children and adolescents (average age= 11.6 years, SD= 2.5, range 7-16 years, 8 females) were recruited from the local Cardiff community via word of mouth. We specifically chose to recruit across a large age-range which would cover the period right before puberty, as well as puberty itself. All participants had normal or corrected-to-normal vision and reported no history of neurological or psychological illness (as determined via self-report). Informed consent was obtained from the primary caregiver and informed assent was obtained from the child/adolescent prior to testing. Participants received an Amazon voucher (£20) for participating in the experiment. The study was approved by the local ethics committee (School of Psychology, Cardiff University).

Experimental task and stimuli.

Localiser task. We use a modified version of the Overlap task ((Bindemann et al., 2005; Cohen Kadosh et al., 2014) to localise the target region for the subsequent NF runs (**Figure 1**). The Overlap task consists of a stimulus set of 9 colour photographs of female faces (3 women x 3 emotional expressions (fearful, happy, neutral) that were selected from the NimStim set[1]. All pictures were cropped to show the face in frontal view and to exclude the neck and haircut of the person. For the face + target stimuli, a fixation cross was superimposed onto the face between the two eyes, and two black peripheral lines were presented on each side of the face. In total, 36 different stimuli (3 women x 3 expressions x

[1] Development of the NimStim Face Stimulus Set was overseen by Nim Tottenham and supported by the John D. and Catherine T. MacArthur Foundation Research Network on Early Experience and Brain Development.

target right or left of the face x green/red fixation cross (go/no-go trials)) were created. Note that we used only female faces in the current study in order to keep any task-irrelevant stimulus variation at a minimum. This approach was chosen, as it has been shown that facial identity serves a reference frame for interpreting emotional expressions (Cohen Kadosh, 2011; Ganel and Goshen-Gottstein, 2004) and that sex changes influence identity processing (Ganel and Goshen-Gottstein, 2002).

Procedure

We used a 3 Tesla 3T GE (General Electric) HDx MR system to acquire MRI and fMRI data at the Cardiff University Brain Research Imaging Centre, using a single shot echo-planar imaging sequence (TR = 2 s, TE = 30 ms, 27 slices, 3 mm slice thickness, inplane resolution 62 mm, soft tone mode). Each participant first underwent a localiser scan, which was followed by four NF runs. Following the functional scans, a T1-weighted structural image (1 mm^3 resolution) was acquired for co-registration and display of the functional data. Two participants, one female and one male did not continue on to participate in the NF runs and 1 male completed only 2 NF runs.

Localiser task

Each trial began with a central black fixation cross on a white background, being presented for 1500ms. The fixation cross was then replaced for 500ms by the face + target stimulus, with a red or green fixation cross super-imposed onto a face flanked by two peripheral black lines. The colour of the fixation cross indicated whether the trial was a go trial (green colour) or a no-go trial (red colour). During the go trials, the participant's task was to indicate which of the two lines on either side of the face was presented horizontally. Participants were instructed to indicate the location of the target stimulus via a button press on a response box, with the right button corresponding to a target on the right side of the face and the left button

corresponding to a target on the left side of the face. During no-go trials, participants were instructed not to respond and to wait for the next trial to begin. The face + target stimulus was followed by a white screen with black fixation cross, which was displayed for 2000-4000ms, or until a response was registered (**Figure 1**). Each session began with 12 practice trials (6 go trials, 6 no-go trials), with each emotional expression being shown 4 times. The practice was followed by 4 blocks of 36 trials with a ratio of 2:1 go (24) to no-go (12) trials, with each facial expression (fearful/neutral/happy) being shown an equal number of times in the trials. Additionally, we created three pseudo-randomised variations of the task to ensure that each emotional expression and trial type varied systematically throughout the blocks.

Neurofeedback task

The localiser task was followed by four NF runs. We used TurboBrainvoyager (BrainInnovations, Maastricht, Netherlands) for the online analysis during the NF runs. Each run consisted of 5 20 second rest blocks and 4 20 second regulate blocks (**Figure 1**). Each participants target area (right anterior insula) was identified based on an average effect contrast across all conditions in the preceding localiser task. The participant's task was to increase activity in the insula region during the regulation blocks and to keep activation low during the rest blocks. During the runs, a continuous signal from the target area (updated every TR and thus every 2 seconds) was displayed using the picture of a thermometer whose dial indicated the amplitude of the fMRI signal in the target area (**Figure 1**). Changes in the amplitude were indicated as the percent of signal change, calculated using the current signal intensity value and comparing it with the average value determined from the rest period immediately preceding each upregulate block. The scaling of the thermometer was in steps of 0.05%, with a maximum value of 0.5%. A change of background colour every 20 sec indicated to participants whether their task was to regulate (green background) or rest (yellow background). The online GLM was computed with one predictor for the regulate state,

convolved with a haemodynamic reference function. The top one-third (defined by the t value for the contrast between the regulate predictor and baseline) of the voxels from the target region was used to compute the feedback signal. Participants were also instructed to keep head movement to a minimum and fixate the middle of the display during both, the localiser and the NF in order to avoid eye movements.

---------- *Insert Figure 1 about here* ----------

FMRI analyses

Data were analyzed using SPM8 (Wellcome Department of Imaging Neuroscience; http://www.fil.ion.ucl.ac.uk/spm). The pre-processing analysis was identical for the localiser and NF runs. First, a slice-scan time correction was applied to all runs. Then, EPI volumes were spatially realigned to correct for movement artifacts, normalized to the Montreal Neurological Institute (MNI) standard space (Ashburner and Friston, 2003a, 2003b) and smoothed using an 8-mm Gaussian kernel.

For the localiser run, a general linear model was computed with 6 regressors, one for each condition in the design (2 trial types x 3 emotional expressions). In addition, a covariate was included with the mean accuracy rates for each participant (collapsed across emotional expressions, as the main effect of expression or the interaction between trial type x expression was not significant) to prevent the possibility of proficiency-dependent differences affecting the fMRI results. To account for (linear) residual movement artifacts, the model also included 6 further regressors representing the rigid-body parameters estimated during realignment (note that none of the participants included in this data set exhibited greater than 3-mm deviation in the centre of mass in any direction).Voxelwise parameter estimates for these regressors were obtained by restricted maximum-likelihood estimation

using a temporal high-pass filter (cutoff = 128 sec) to remove low frequency drifts, and modeling temporal autocorrelation across scans with an AR(1) process. Images of these parameter estimates comprised the data for a second GLM that treated participants as the only random effect. This GLM included the 12 conditions of interest, using a single pooled error estimate, whose nonsphericity was estimated using restricted maximumlikelihood estimation as described in Friston et al. (2002). Note that apart from the region of interest (ROI) analyses, the results from the localiser task will not be reported here.

For the NF runs, each block was modelled as an epoch of 20 seconds and convolved with a canonical hemodynamic response function. Voxel-wise parameter estimates for these regressors were obtained by restricted maximum likelihood estimation (ReML), using a temporal high-pass filter (cut-off 128 seconds) to remove low-frequency drifts, and modelling temporal autocorrelation across scans with an Auto-regression (1) process. Finally, to obtain the areas for the ROI analyses and the subsequent Granger causality analyses, eight 10-mm ROIs were localized based on group local maxima for an average effect contrast in the localiser task, as well as two 10-mm ROIs based on the individual local maxima in the bilateral insula, using the same contrast. This independent analysis approach was chosen to avoid the issue of double dipping (Kriegeskorte et al., 2009; Vul et al., 2009). For the NF ROI analyses, we first extracted the BOLD time series in the bilateral insula (mean and standard deviation of the coordinates are for peak voxel location, x, y, and z, in MNI space): left insula (lINS): -37(6), 9(7), 4(3); right insula (rINS): 39(4), 8(8), 1(4) in each participant individually. In addition, for the Granger causality analysis, we extracted the time-series of BOLD activations in 8 core emotion regulation network regions. The selection of these 8 regions was based on a recent meta-analysis of 23 studies (Kohn et al., 2014), which used fMRI or PET to investigate cognitive emotion regulation in adults, as well as a recent fMRI-based-NF study on emotion regulation in patients with schizophrenia (Ruiz et al., in press), who were taught to gain control over the bilateral insula regions. The following ROIs were selected for the Granger Causality Analysis: left amygdala (lAMY): -21, -3, -7; lINS: -39, 14, 3; rINS: 36,

15, 3; left mid-cingulate cortex (MCC): -6, 18, 39; left middle frontal gyrus (lMFG): -38, 34, 27; left medial frontal gyrus/supplementary motor area (lSMA): -2, 16, 50; left intra-parietal lobule (lIPL): -60, -48, 35; left precentral gyrus (lPreG): -48, 2, 32.

Granger causality analysis

Following the ROI of our NF target regions, we conducted a Granger causality analysis (GCA) to assess the extended effect of NF-induced changes on the extended emotion regulation network. GCA is a widely used research approach that allows us to investigate how changes in brain activation over time in different brain regions relate to each other (Palaniyappan et al., 2013; Wen et al., 2012) (Hamilton et al., 2011) (Ge et al., 2012; Guo et al., 2008) (Luo et al., 2011; Luo et al., 2013a; Luo et al., 2013b). Crucially, GCA also can provide insights into the directional information flow between brain regions, also known as effective connectivity, which is currently impossible to explore experimentally (Park and Friston, 2013).

For the current fMRI study, we adopted a previously successful GCA analysis approach (Wen et al., 2013), which included several important pre-processing steps (Smith et al., 2012), such as outlier removal, baseline correction and an analysis of the percent signal change within blocks. For the outlier analysis, we used the Grubbs test to remove movement-induced outliers in the data (Barnett and Lewis, 1994). To this end, the data points in regulate blocks were aligned according to the block onset-time. At each post block onset-time, the corresponding data points in all regulate blocks were treated as repeated observation from the same random distribution, and thereby the Grubbs test could be applied to detect outliers. In case an outlier was detected, the mean signal at the corresponding post block onset-time was used to replace the raw data.

Specifically, if we denote the data for regulate blocks as $x_t^{s,b}$, where $t = 0,2,\ldots,9$ indicates the post block onset-time, $s = 1,2,3,4$ denotes the session number, and $b = 1,2,3,4$ gives the block order, we aligned the data according to the post block onset-time as follows:

$$\begin{matrix} x_1^{1,1} & x_2^{1,1} & \cdots & x_{10}^{1,1} \\ \vdots & \vdots & \ddots & \vdots \\ x_1^{1,4} & x_2^{1,4} & \cdots & x_{10}^{1,4} \\ x_1^{2,1} & x_2^{2,1} & \cdots & x_{10}^{2,1} \\ \vdots & \vdots & \ddots & \vdots \\ \vdots & \vdots & \ddots & \vdots \\ x_1^{4,4} & x_2^{4,4} & \cdots & x_{10}^{4,4} \end{matrix}$$

Therefore, the outliers were detected for each column of the aligned data matrix which contains all the measurements at the same post block onset-time t , i.e., $\{x_t^{s,b}\}_{s=1,2,3,4;b=1,2,3,4}$. Let O denote the indexes (s,b) of the detected outliers at post block onset-time t , and the outliers were replaced with the mean signal of $\{x_t^{s,b}\}_{s=1,2,3,4;b=1,2,3,4} \setminus \{x_t^{s,b}\}_{s,b\in O}$, where $\setminus$ denotes the set difference. Similarly, the outliers were removed for the rest blocks.

We also transformed the raw data into the percentage of change. While this is not a requirement of GCA, it nevertheless provides a better understanding of the signal. The percentage of change was calculated by the relative difference between the actual measurement and the baseline. The mean signal time series during all rest blocks, $\bar{y}_s = \overline{\{y_t^{s,b}\}}_{b=1,2,3,4,5} (s = 1,2,3,4),$ where $y_t^{s,b}$ is the measurement at post block onset-time t in rest block b session $s,$ was used as the baseline of each session and subtracted from the raw signal time series $r_t^{s,b}$ ($s = 1,2,3,4$ and $t = 0,1,\cdots,9$; for the signal in rest blocks $r = y$ and $b = 1,2,3,4,5$; for the signal in regulate blocks $r = x$ and $b = 1,2,3,4$) in the same session, *i.e.*, $\tilde{r}_t^{s,b} = \frac{r_t^{s,b} - \bar{y}_s}{\bar{y}_s} \times 100.$

To minimize the task-induced variance in the signal (Wen et al., 2013), we subtracted the block-mean from the regulate blocks. In session s the block-mean was calculated at each

post block onset-time $t(=0,1,\cdots,9)$ as $\overline{\tilde{r}}_t^{\,s} = \overline{\{\tilde{r}_t^{s,b}\}}_{b=1,\cdots,5\ for\ rest,\ b=1,\cdots,4\ for\ task}$, and the subtracted from the signal time series to have the our input signal $\{\tilde{\tilde{r}}_t^{s,b}\}$ to the GCA as $\tilde{\tilde{r}}_t^{s,b} = \tilde{r}_t^{s,b} - \overline{\tilde{r}}_t^{\,s}$. Further, at each regulate block, the time series data was de-trended and its temporal mean was removed to satisfy the preconditions required by GCA. Before each run of the GCA, the Dickey-Fuller test was employed to test if each pair signal time series as input to the GCA were covariance-stationary (Seth, 2005), which was confirmed for the majority of signal time series pairs (99% during regulate and 98% during rest).

However, the assumption that the time series models during the regulate blocks in different sessions would stay the same is likely to be an oversimplification, as fluctuations in the model coefficients are almost as certain as the physiological oscillations in the BOLD signal. As discussed in detail previously (Luo et al., 2013b), assuming a static model to a time-varying casual structure usually leads to misleading estimation of Granger causality. We proposed and demonstrated the reliability of an averaged Granger causality (avGC), which was a new framework to tackle the time-varying causal structure (Luo et al., 2013b). Basically, the Granger causality for a pair of brain regions was estimated at each regulate/rest block, and then the avGC was established by averaging the estimated Granger causality during regulate/rest blocks across different sessions. Here, we used the avGC to measure the directed information flow between brain regions.

To detect significant differences in the directed information flow as a function of the two task conditions (regulate vs rest), the avGC during regulate/rest were tested against the null hypothesis of non-causality by the distribution of sum of many independent F statistics (Luo et al., 2013b). The results that survived the false discovery rate correction (FDR, $q < 0.03$) were reported for the different conditions at the group level. After the information flow (i.e., the avGC) estimated at each direction between brain regions for each subject during rest and during regulate separately, the paired t test was applied to compare the avGC during

regulate with that during rest at each direction. The resulting p-values were FDR ($q < 0.05$) corrected for multiple comparisons.

Last, in order to understand the functional meaning of the directed information flow detected by the avGC, we computed Pearson's correlation coefficients across subjects between the two experimental conditions (defined by contrast map given by SPM8) in the bilateral insula. The avGC in the bilateral insula was estimated for the in- and out- flow of information as a function of age and sex in each subject.

Results

Successful insular cortex self-regulation during NF

To assess the effect of the NF training on the BOLD signal increase in the lINS and rINS in each NF session, we computed a Fisher score (FS) (Ruiz et al., in press), which measures the discriminability between BOLD signals of two conditions (in this case ''rest" and ''regulate" blocks). A FS-based analysis allows us to take into account both the variance and the mean BOLD signal change between two conditions, rather than just the mean difference between the two conditions, as is done conventionally (Ruiz et al., in press). The FS is defined as the ratio of the square of the difference between the mean BOLD values in each time-series to the sum of the variance in the time-series. In the current study, we were able to confirm that our children and adolescents learned to successfully increase insula activity during the regulate blocks in the 4 training sessions (**Figure 2a/b**).

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GCA reveals differential NF effect on information flow within the emotion regulation networks

We then used GCA to assess the effect of the NF training on the differential effect of the two task conditions on information in- and out- flow in the 8 emotion regulation network regions. For the regulate condition, we found a significant information in-flow from the lAMY, MCC, lMFG, lIPL, and lSMA to the bilateral insula, as well as from the lPreG to the lINS (see **Figure 3b** for all directed information flow during regulate). In contrast, during the rest blocks, we found a directed information in-flow from the lMFG to the bilateral INS, and from the lMCC to the lINS, but importantly no bottom-up in-flow from the lAMY (see **Figure 3c** for all directed information flow during rest).

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NF-dependent changes information flow to and from the bilateral insula

We then assessed whether the in- and out- flow of information in the bilateral INS regions correlated with the INS percent signal change activation (**Figure 4a,b, Table 1**).

Right insula. A significant positive correlation (r=0.25, p=0.045) was found between the directed information flow from the lAMY to the rINS, $GC^{task}_{lMAY \rightarrow rINS}$, and the brain activity in the rINS in the regulate condition, but not for the rest condition. Interestingly, during the rest blocks, we observed a reversal in the information flow from the rINS to the lAMY, $GC^{rest}_{rINS \rightarrow lMAY}$, which was also positively correlated with the brain activity at rINS (r=0.30, p=0.015). That is, the stronger the bottom-up information flow from the lAMY to the rINS, the stronger the activity in the rINS in the regulate condition, a finding which suggests an effective bottom-up control during these blocks. Crucially, this effect was reversed for the rest condition, with a more directed information flow from the rINS to the lAMY predicting stronger activity of the rINS.

The positive correlation between the brain activity of the rINS and the directed information flow was observed for several other directions, including MCC→rINS and lSMA→rINS in the

regulate condition, and the MCC→rINS and lPreG→rINS in the rest condition. The bottom-up information flow from lAMY to lINS was also found to increase the activity of lINS (r=0.28,p=0.024) during the regulate condition but not during the rest condition.

Left insula. For the lINS, a few out-flows of lINS, including those from lINS to MCC, lSMA, and lIPL, positively correlated with the activity at lINS in the regulate condition, while a few in-flows, including those from MCC and lPreG to lINS were positively correlated with the activity.

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NF training significantly increases amygdala-insula connectivity in the regulate condition

We compared the magnitudes of the directed information flow for the two experimental conditions, the difference between the Granger causality during the regulate condition and that during the rest condition at each direction.

Right insula. We found that the directed information flow from the lAMY to the rINS as measured by Granger causality was significantly increased (t= 3.97, p = 0.001) for the regulate condition in comparison to the rest condition (**Figure 5a**), whereas the out- flow from bilateral insula to the other regions of interest did not differ for the two task conditions.

---------- *Insert Figure 5 about here* ----------

We then assessed the functional meaning of the change in the directed information flow from rest condition to regulate condition, by looking at task performance, i.e. the successful upregulation of the insula region. To this end, we computed the partial correlation coefficient between the change in the directed information flow and the brain activity at insula as a function of age and sex in each subject. The significantly change in the bottom-up

information flow from the lAMY to the rINS, $GC^{task}_{lMAY \rightarrow rINS} - GC^{rest}_{lMAY \rightarrow rINS}$, was found to be positively correlated (r=0.26, p =0.035) with the brain activity in the rINS.

Left insula. The change in the directed information flow from the lAMY to the lINS from the regulate to the rest condition was also positively correlated (r=0.27, p=0.028) with the brain activity in the lINS (**Figure 5**). That is, the stronger the increase in directed information flow from the lINS to the rINS, the less activity was observed at lINS in the regulate condition. Moreover, a significant negative correlation (r=-0.32, p=0.009) was observed between the causality change in this direction from rest to regulate and the brain activity of the lINS.

Discussion

The current study had two main aims: 1) to show the feasibility of using fMRI-based neurofeedback (NF) with paediatric populations and 2) to assess the differential effect of NF training on the wider emotion regulation network. Our results allowed us to fulfil both aims.

NF training enhances insula activation in children and adolescents

We found that all participants were able to up-regulate activation in the bilateral insula during the regulate blocks in comparison to rest blocks, which supports the feasibility of using fMRI-based NF with paediatric populations. The important role of the right insula in self-relevant affect has been repeatedly shown in previous research (Craig, 2003; Wager and Feldman-Barrett, 2004) and this result is particularly striking given our simple task instruction to “think happy thoughts”. The NF success in the current study opens up possibilities for new, brain-based intervention approaches, which take into account the developmental changes in the developing brain (Cohen Kadosh et al., 2013). For example, within the context of emotion regulation abilities, NF could be used to both increase or decrease the responsiveness of

age-appropriate brain networks at critical developmental stages e.g. (Paret et al., 2014). Similarly, such an approach could be useful for enhancing helpful brain network connections in at-risk populations, such as for example high socially-anxious children and adolescents (Haller et al., in preparation). However in order to identify these network connections, a better understanding of the wider effects of insula regulation on the emotion regulation network is necessary.

NF training increase bottom-up driven information flow in the emotion regulation network

In the present study, we also found that NF training had a differential effect on the information flow within the emotion regulation network. That is the bottom-up driven information flow from the amygdala to the bilateral insula and from the left insula to the MCC, SMA and the IPL during the regulation blocks contrasted with more top-down driven information flow to the bilateral insula from MCC and PreG and IPL during the rest blocks. This finding validates the effectiveness of our 'increase' instruction to affect brain regions beyond the NF target region. It also shows that the two task conditions had a qualitatively different effect on the brain network. More specifically, by using a simple task instruction, we were able to change information flow along previously established emotion regulation routes in the brain e.g.(Ruiz et al., in press). The more wide-spread effect of NF training has been previously shown in both healthy adults (Rota et al., 2011; Zotev et al., 2011), as well as patients with schizophrenia (Ruiz et al., in press), but this is, to the best of our knowledge, the first study to document NF-induced regulation effects in the developing emotion regulation network. We also note that our participants, despite the relatively wide age range of our sample, did all activate the same regions of the emotion regulation network and the general NF success was not affected by age or gender. What we cannot predict however, based on the current sample of 17 participants, whether directional information flow also

varied as a function of age, which is a critical question for the development of future intervention approaches – especially those aimed to particular developmental junctures.

Increased bottom-up information flow from amygdala to insula correlates with NF success

We also found that increased bottom-up information flow from the left amygdala to the right insula correlated with NF success in the regulate blocks This effects runs in line with the research reported in a recent review, which highlighted the role of the left amygdala in increasing positive affect (see (Silvers et al., 2014). There is also evidence of amygdala-insula co-activation in humans, albeit more within the context of negatively-valenced emotions (Carlson et al., 2011; Phelps et al., 2001). Similarly, within the context of anxiety, a recent study found effective connectivity in a resting state analysis, as well as structural connectivity (Baur et al., 2013). In the current study, we did not find any evidence for top-down emotion regulation in the insula from ventromedial prefrontal cortex regions, as shown in previous studies e.g. (Hare et al., 2008; Perlman and Pelphrey, 2011; Pitskel et al., 2011). There are two possible explanations as to why this may be the case. The first has to do with the task itself and the fact that all observed effects are based on significant differences in Granger connectivity between the two conditions. Namely, our participants were not asked to control their emotions during rest, but rather to not increase insula response in these blocks. This would also reduce any top-down regulation effects during these blocks. Another possible explanation might be the considerable age range in our sample, which, given the prolonged maturational trajectory of the prefrontal cortex (Gogtay et al., 2004; Tamnes et al., 2013), is likely to have introduced considerable variance amongst our participants, which prevented us from finding a significant effect.

While the results from this study are certainly encouraging, many open questions remain concerning for example the longevity of the observed effect, and particularly the specificity and sustainability of any changes to the functional architecture of the emotion

regulation network. Similarly, it remains to be determined how NF relates to overt behaviour changes. Previous research in clinical populations has made some progress into this question by showing a reduction in chronic pain symptoms after 6 months (deCharms et al., 2005) or improved motor fluency in Parkinson's disease (Subramanian et al., 2011). A better understanding of the underlying mechanisms of the translational effects of NF would go a long way towards developing effective interventions during development. Finally, while our simple task instruction proved effective for the current study, it is not difficult to imagine how much more effective NF training could be in combination with a more established cognitive training programme, such as attention/ or cognitive bias modification (Bar-Haim, 2010; MacLeod and Holmes, 2011).

Conclusions

The current study provided proof-of-concept for using fMRI-based neurofeedback with children and adolescents. Within the context of an emotion regulation network, we were also able to show that NF training had a differential effect of regulation and rest connections within the network, suggesting that our training was not only superficially concentrated on surface effects but actually relevant with regards to the underlying neurocognitive bases of a key social cognitive ability. More research is now needed to investigated the longevity of the effects and to explore the possible combination of NF with cognitive training programmes, in particular with view of future intervention in clinical populations.

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Figures

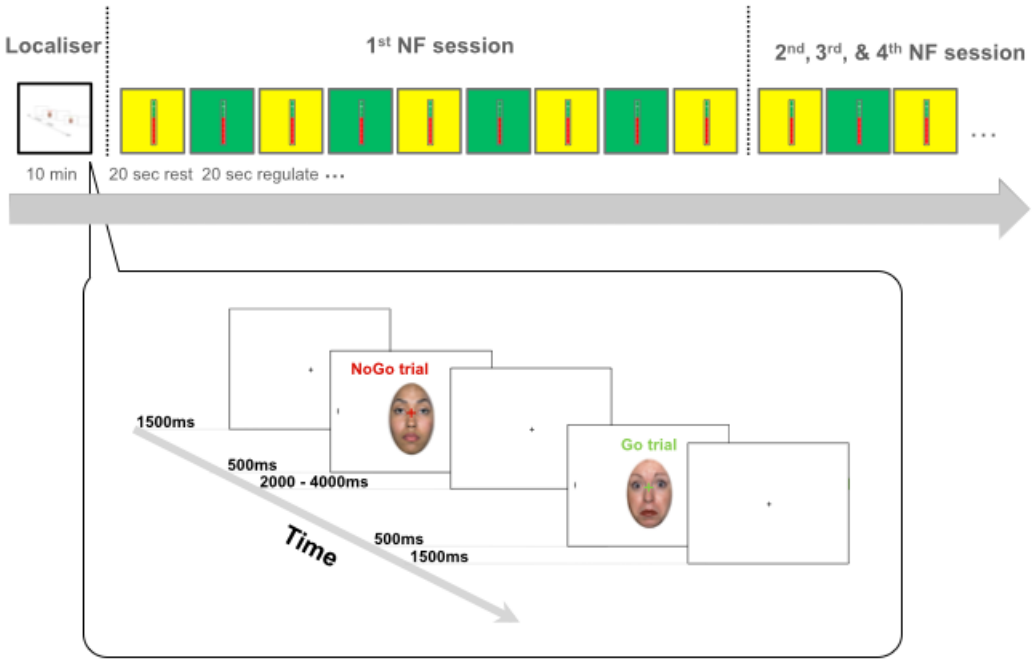


Figure 1. Top: Experimental procedure. During the neurofeedback runs (4 in each of the 4 sessions), participants alternated between 20 s periods of rest and 20 s periods where they had to upregulate activity in the target area. The level of activation was fed back in real time (updated for each TR of 2 s) through the thermometer display. **Bottom:** Two sample trials in the localiser task. A fixation cross was replaced by an emotional face + fixation cross flanked by two bars. A red fixation cross indicated a NoGo trial, where no action was required. A green fixation cross indicated a Go trial, where participants had to disengage from the face as quickly as possible in order to detect the horizontal target bar.

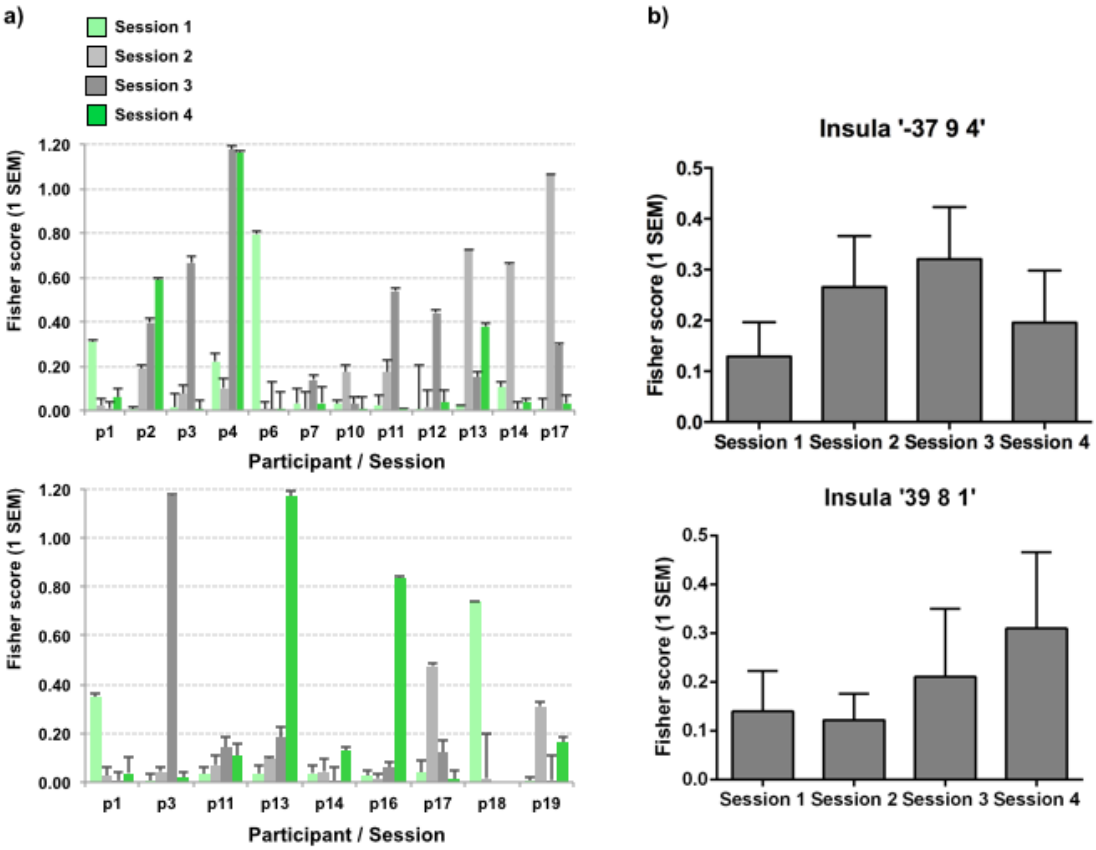


Figure 2. Results from the fMRI-based neurofeedback training: **a).** Mean BOLD-signal change (Fisher score + 1 standard error of the mean (SEM)) in the individually localised left (top) and right (bottom) insula in the regulate vs rest blocks for each participant in the 4 neurofeedback sessions. Note that only those participants were included in this analysis whose insula activation survived p= .005 uncorrected. **b).** Mean Fisher score (+ 1 SEM) indicating the group BOLD-signal change in the left (top) and right (bottom) insula in the regulate vs rest blocks in the 4 neurofeedback sessions.

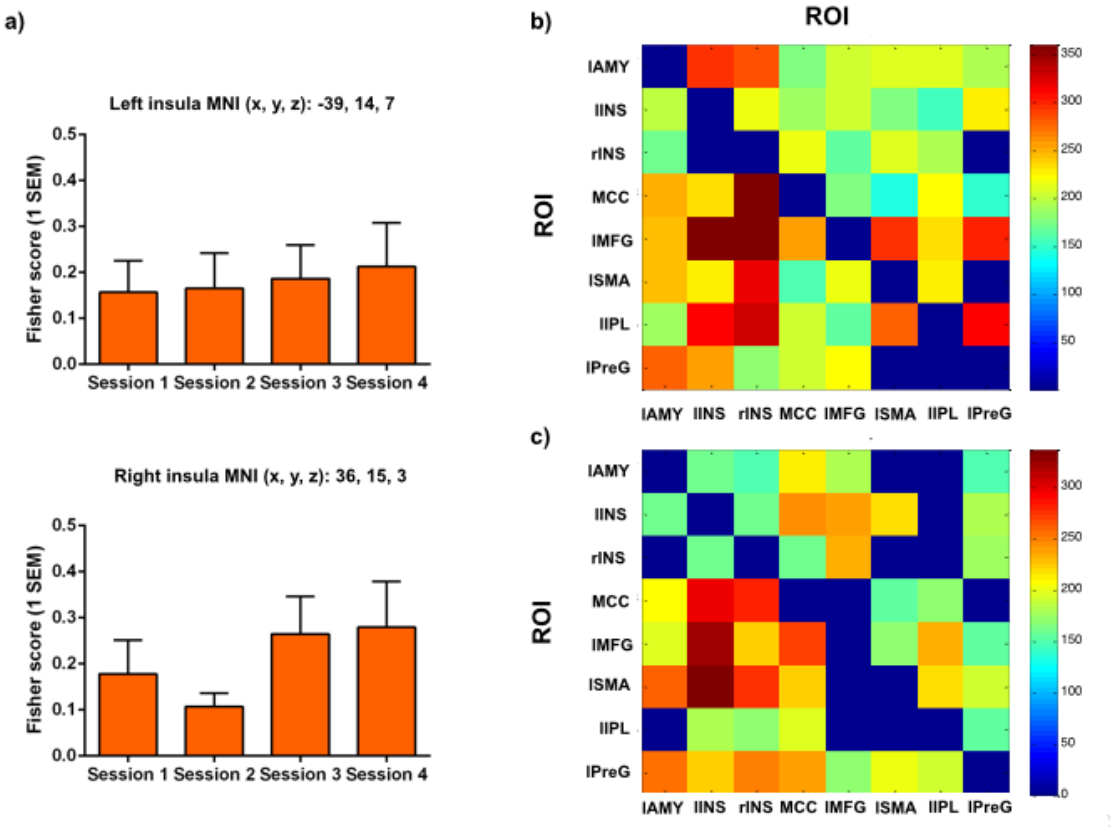
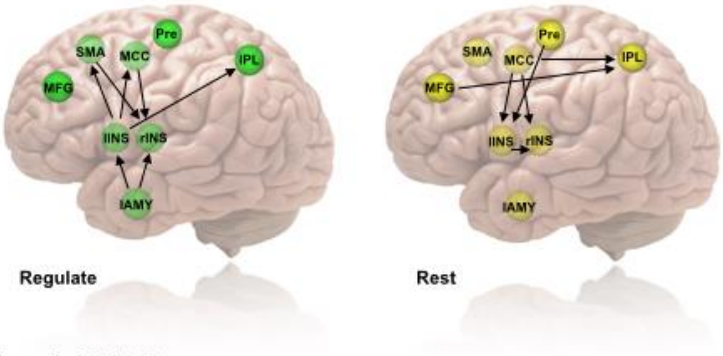


Figure 3. Results from the fMRI-based neurofeedback training: **a).** Fisher score (+ 1 standard error of the mean (SEM)) indicating the group BOLD-signal change in the left (top) and right (bottom) insula in the regulate vs rest blocks in the 4 neurofeedback sessions. **b-c).** Granger causality analysis of the directed information flow in the emotion regulation network insula during the regulate condition **(b)** and the rest condition **(c)**. Abbreviations: lAMY= amygdala; lINS= left insula; rINS= right insula; lIPL= left inferior parietal lobule; MCC= mid cingulate cortex; lMFG= left middle frontal gyrus; MNI= Montreal Neurological Institute template; lPreG= left precentral sulcus; lSMA= left supplementary motor area.

a) Left insula MNI ((x, y, z): -39, 14, 7)



b) Right insula MNI ((x, y, z): 36, 15, 3)

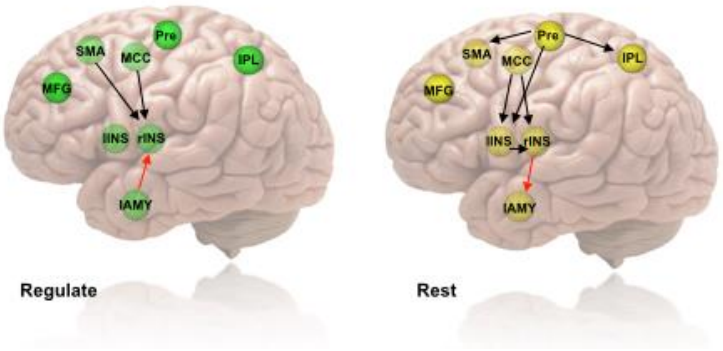


Figure 4. Granger causality analysis of the effective connectivity in the emotion regulation network as a function of percent signal change in the bilateral insula during the regulate condition **a)** and the rest condition **b)**. Abbreviations: lAMY= amygdala; lINS= left insula; rINS= right insula; lIPL= left inferior parietal lobule; MCC= mid cingulate cortex; lMFG= left middle frontal gyrus; lPreG= left precentral sulcus; lSMA= left supplementary motor area.

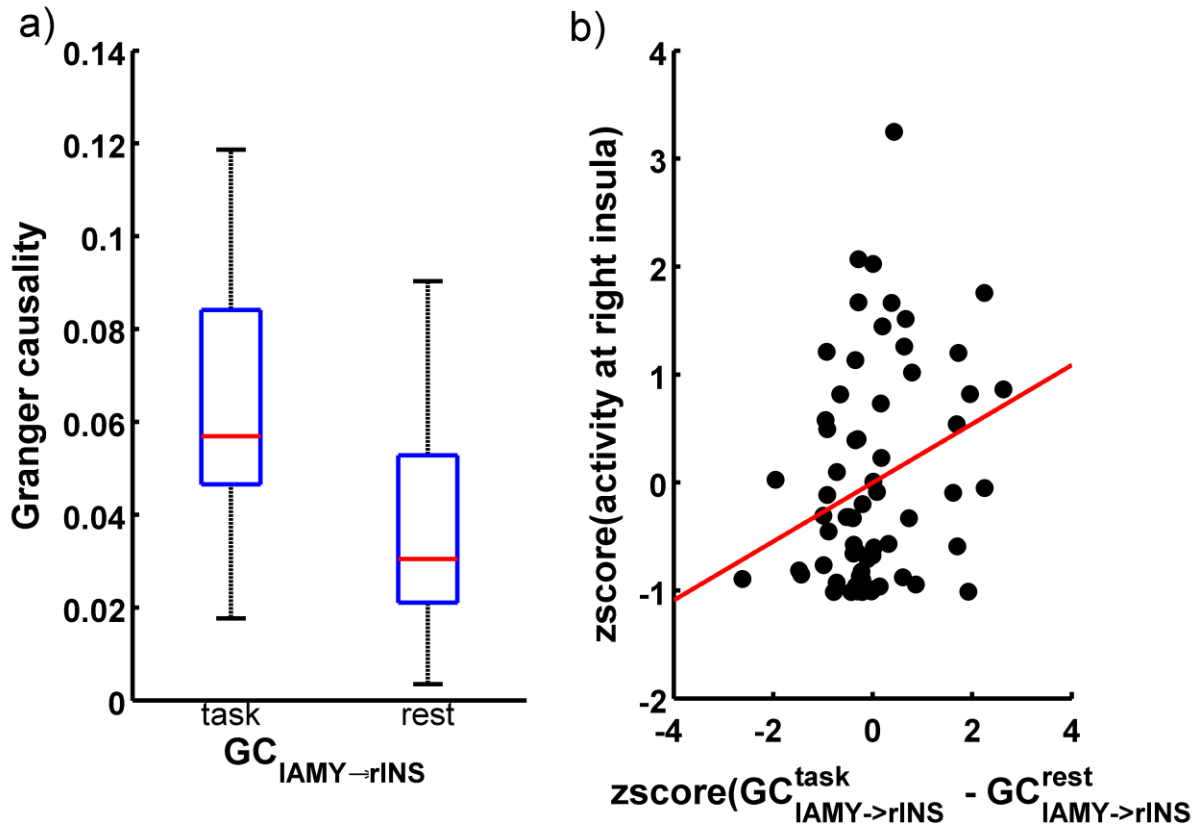


Figure 5. Change in bottom-up information flow and its correlation with brain activity of rINS. **a)** Comparison of Granger causality between the regulate condition and the rest condition. **b)** The correlation between the change in the directed information flow from lAMY to rINS and the brain activity at rINS. For each session, the brain activity was plotted against the change in the Granger causality at lAMY→rINS. The red line is the linear fitting. See also **Figure 3b**.

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Table 1. Comparison of correlations between directed information flow and brain activity at insula for the two conditions. Only significant (p<0.05, uncorrected) correlation were listed between the brain activities at bilateral insula and the directed information flows in different directions among the brain regions of interest (i.e., $GC^{(condition)}_{ROI1\rightarrow ROI2}$). The correlation was calculated by conditioning on both age and sex of each subject. In the brackets, we listed the correlation between the brain activity and the change in directed information flow from rest condition to regulate condition (i.e., $GC^{(task)}_{ROI1\rightarrow ROI2} - GC^{(rest)}_{ROI1\rightarrow ROI2}$) . Abbreviation: l= left; r= right; SMA= supplementary motor area.

Regulate condition			**Rest condition**		
Left Insula	***r=***	***p=***	***Left Insula***	***r=***	***p=***
Amygdala → l Insula	**0.28 (0.27)**	**0.02 (0.03)**	**l Insula → r Insula**	**0.31 (-0.32)**	**0.01 (0.01)**
Amygdala → r Insula	**0.34 (0.38)**	**0.01 (0.01)**	Mid Cingulate Cortex → l Insula	0.32	0.01
l Insula → Mid Cingulate Cortex	0.27	0.03	Mid Cingulate Cortex → r Insula	0.25	0.05
l Insula → l SMA	0.26	0.04	Mid Cingulate Cortex → Inferior parietal lobe	0.34	0.01
l Insula → Inferior parietal lobe	0.26	0.03	Middle frontal gyrus → Inferior parietal lobe	0.30	0.02
Mid Cingulate Cortex → r Insula	**0.26 (-0.26)**	**0.04 (0.04)**	Precentral gyrus → l Insula	0.32	0.01
l SMA → r Insula	0.31	0.01			
Right Insula	***r=***	***p=***	***Right Insula***	***r=***	***p=***
Amygdala → r Insula	**0.25 (0.26)**	**0.05 (0.04)**	r Insula → Amygdala	0.31	0.01
Mid Cingulate Cortex → r Insula	0.31	0.01	Mid Cingulate Cortex → l Insula	0.32	0.01
l SMA → r Insula	0.28	0.03	Mid Cingulate Cortex → r Insula	0.25	0.05
			Mid Cingulate Cortex → Inferior parietal sulcus	0.34	0.01
			Precentral gyrus → l Insula	0.35	0.01

			Precentral gyrus → SMA	0.27	0.03
			Precentral gyrus → Inferior parietal lobe	0.30	0.02