



Resting-state functional connectivity remains unaffected by preceding exposure to aversive visual stimuli



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ABSTRACT

While much is known about immediate brain activity changes induced by the confrontation with emotional stimuli, the subsequent temporal unfolding of emotions has yet to be explored. To investigate whether exposure to emotionally aversive pictures affects subsequent resting-state networks differently from exposure to neutral pictures, a resting-state fMRI study implementing a two-group repeated-measures design in healthy young adults ($N = 34$) was conducted. We focused on investigating (i) patterns of amygdala whole-brain and hippocampus connectivity in both a seed-to-voxel and seed-to-seed approach, (ii) whole-brain resting-state networks with an independent component analysis coupled with dual regression, and (iii) the amygdala's fractional amplitude of low frequency fluctuations, all while EEG recording potential fluctuations in vigilance. In spite of the successful emotion induction, as demonstrated by stimuli rating and a memory-facilitating effect of negative emotionality, none of the resting-state measures was differentially affected by picture valence. In conclusion, resting-state networks connectivity as well as the amygdala's low frequency oscillations appear to be unaffected by preceding exposure to widely used emotionally aversive visual stimuli in healthy young adults.

Introduction

Emotions are closely tied to cognitive, attentional and motivational processes. The amygdala strongly reacts to emotional stimuli and there is ample evidence that functional interactions of the amygdala with other brain regions are critically implicated in emotion processing upon acute emotional stimuli (Banks et al., 2007; Eippert et al., 2007; Erk et al., 2010; Townsend et al., 2013). The amygdala receives input from all sensory systems and polymodal cortices. Behavioral responses are generated primarily through amygdala projections to hypothalamic and brainstem centers involved in autonomic control. Among these is the locus coeruleus (LC), a major norepinephrine synthesis site. Norepinephrine pathways are important in maintaining arousal and level-setting for gathering sensory information and storing emotional memories (Venkatraman et al., 2017). Connections between the amygdala and the hippocampal complex contribute to the memory-enhancing effect of

emotional arousal (Fastenrath et al., 2014; Richardson et al., 2004; Roozendaal et al., 2009), while the prefrontal cortex (PFC) plays a role in cognitively and emotionally interpreting affectively valenced stimuli, and in controlling the subsequent behavioral responses (Höistad and Barbas, 2008). In humans, top-down and bottom-up mechanisms orchestrated by interactions between the amygdala and medial PFC have been discussed extensively in the context of anxiety and emotion regulation (Kim et al., 2011).

Whereas much is known about the immediate effects of emotions on brain activations measured with blood-oxygen-level dependent contrast (BOLD) functional imaging during the acute emotional state (Murty et al., 2010; Verduyn et al., 2015; Waugh and Schirillo, 2012), little is known about the further temporal unfolding of emotions and their long-term neural consequences. On the behavioral level, there is ample evidence for such long-term consequences. For example, pathological anxiety may be expressed in excessive apprehension subsequent to immediate

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emotion processing (Calhoun and Tye, 2015). Moreover, in animals it has been shown that the amygdala plays a key role in enhancing memory consolidation processes and, thereby, long-term memory of emotionally arousing information (Phelps and LeDoux, 2005; Roozendaal et al., 2009).

One possibility to investigate delayed neural consequences of emotional stimuli is to analyze functional connectivity (FC) in a resting-state period after an emotional task. The resting-state is defined as a state of nonattendance in an active task and absence of external stimulation (Barkhof et al., 2014), while FC reflects the temporal dependence of neural activity patterns of separated brain regions (van den Heuvel et al., 2010). The repertoire of functional networks utilized by the brain in action may persist in the resting-state, where they can be mapped as overlapping resting-state networks (RSN) (Biswal et al., 2010; Damoiseaux et al., 2006; Laird et al., 2011; Smith et al., 2009) using resting-state functional magnetic resonance imaging (rs-fMRI). Among the most commonly used approaches for identifying functionally interacting brain regions from rs-fMRI data are independent component analysis (ICA), seed-to-voxel, and seed-to-seed approaches (Smith et al., 2014; Whitfield-Gabrieli and Nieto-Castanon, 2012). Besides network measures, BOLD signal changes in regional spontaneous activity are valuable complements for characterizing resting-state low frequency oscillations (LFO), e.g. fractional amplitude of low frequency fluctuations (fALFF) (Zou et al., 2008).

Whereas initial cognitive theories have regarded the resting-state as a “default state of mind”, it is becoming clearer now that cognitive activity also affects later rs-FC. Studies in healthy subjects have already indicated that the time following acute stressors is characterized by particular patterns of amygdala-FC, e.g. increased amygdala-FC after watching highly aversive video clips (van Marle et al., 2010). More precisely, female subjects not used to violent media watched a movie of 1.5 min duration while inside the MRI scanner. Directly afterwards, enhanced amygdala-FC with a set of predefined regions was observed (van Marle et al., 2010). Among those was the dorsal anterior cingulate cortex (dorsal ACC) and anterior insula (AI), which are implicated in the subjective experience of emotion, and the LC, which contributes to arousal by noradrenergic innervations to the amygdala. In another study, as much as 1 h after a well-established psychosocial stress task, increased amygdala-FC with cortical midline structures, pertaining to the default mode network (DMN), and the medial PFC was found (Veer et al., 2011). The authors discuss the increased amygdala-FC with DMN regions as reflecting stress-induced facilitation of self-evaluative processes under emotionally salient experiences. The enhancements in amygdala-medial PFC coupling may be an indicator of top-down processes (Kim et al., 2011; Veer et al., 2011).

Here we investigated if emotionally arousing pictures similar to stressful events can also induce changes in rs-FC. We chose a picture task because such tasks are widely used in human brain activation studies, and because viewing emotional pictures acutely increases activation in several brain regions, including the amygdala and hippocampus (Fasstenrath et al., 2014; Murty et al., 2010; Rasch et al., 2009). Since emotional arousal is known to enhance not only memory encoding but also memory consolidation processes (Roozendaal et al., 2009), we hypothesized that such long-term effects may be reflected in increased amygdala rs-FC with brain regions like the hippocampus.

Implementing a repeated-measures mixed design with two experimental groups of equal size (total $N = 34$), a neutral-picture and a negative-picture group, we focused on the between-groups comparison in terms of changes in rs-FC from baseline (pre-intervention) to post-intervention (time point*group interaction). In a first step, we investigated FC of the amygdala with the whole brain in a seed-to-voxel approach, as well as with the hippocampus only in a ROI-to-ROI analysis. In a second step, we used ICA coupled with dual regression to assess functional connectivity changes in the brain in a more explorative way to address the diversity of networks potentially involved in emotion regulation. To get a complementary view on the amygdala's regional resting-

state activity, we additionally extracted its mean fALFF. For validation purposes, the seed-based analyses done with amygdala masks were conducted with two segmentation procedures. Upon a more explorative background, we secondarily investigated FC of the hippocampus with the whole brain. Due to the uncontrolled nature of vigilance in rs-fMRI (Tagliazucchi and Laufs, 2014), we utilized simultaneous electroencephalography (EEG)-fMRI recordings to take into account in a post-hoc manner potential fluctuations in vigilance.

Materials and methods

Subjects

Thirty-four healthy, normal-weight (BMI 19 to 25) subjects aged 18 to 25 participated in this study ($M = 22.5$, $SD = 2.06$, range = 18.4 to 25.8). Male ($N_{\text{male}} = 14$) and female ($N_{\text{female}} = 20$) subjects did not significantly differ in age ($t(31.3) = 0.94$, $p = 0.35$). Participation was not possible if one or more of the following applied: regular intake of medical drugs with the exception of oral contraceptives, currently pregnant or breastfeeding, known or suspected non-compliance, drug or alcohol abuse, inability to follow the procedures of the study (e.g. due to language problems), present diagnosis of acute or chronic mental and/or somatic disorder, presently doing psychotherapy, not fulfilling MRI eligibility criteria. Previous participation in another study of the Transcultural Research Platform Molecular and Cognitive Neurosciences (MCN), University of Basel, Switzerland (<2 years ago), if concordant visual stimuli employed, was also an exclusion criterion. For eligibility clarification, a psychologist screened subjects by telephone. When in doubt, assertion was obtained through medical counseling. Written informed consent was given at the study visit day. The study was conducted in approval with the local Ethics Committee, Ethikkommission Nordwest-und Zentralschweiz (EKNZ), Switzerland. The study took place between March and June 2015.

The method of allocating participants to a picture valence group (negative-group vs. neutral-group) was quasi-random: there was an alternation per participant in the order they were included in the study. Indispensably, towards the end of the study, three exceptions had to be made in order to equalize the ratio of experimental group within the factor sex. Subjects were instructed to refrain from caffeine intake and cigarette smoking at least 2 h, cannabis intake at least 2 weeks, alcohol and medical drug intake at least 24 h prior to commencement of the experiment, and to adhere to their personal sleeping habits the night before the examination.

Depression scores were measured with a screening questionnaire, the long version of the Allgemeine Depressionsskala (ADS) (Hautzinger and Bailer, 1993) (supplementary Table A1). Generally, there were no scores indicative for presence of depression (Table 1). However, two female subjects and one male subject met or surpassed the clinical threshold of 23 points. As exclusion of these subjects did not alter the results of the main brain imaging analyses (section “Seed-to-voxel and seed-to-seed analysis with bivariate correlation”), we retained them in the analyses while controlling for depression score by including it as a covariate (section “Brain imaging analysis”).

Experimental procedure

The experimental procedure is illustrated in Fig. 1. Upon arrival, written informed consent was acquired and the participant was made familiar with the MRI environment. After this, about 50 min were spent filling out questionnaires while the investigator was attaching the EEG electrodes. Participants wore the EEG cap during the entire experiment. EEG was recorded in five sessions: shortly before the first MRI as a brief quality check, during both MRI sessions, during the pictorial rating task and throughout the free recall task. After satisfactory quality check of the EEG signal (impedances well below 20 k Ω ; for reference and ground electrodes below 10 k Ω), the first MRI session followed, which took

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