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Disentangling reward anticipation with simultaneous pupillometry / fMRI

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ABSTRACT

The reward system may provide an interesting intermediate phenotype for anhedonia in affective disorders. Reward anticipation is characterized by an increase in arousal, and previous studies have linked the anterior cingulate cortex (ACC) to arousal responses such as dilation of the pupil. Here, we examined pupil dynamics during a reward anticipation task in forty-six healthy human subjects and evaluated its neural correlates using functional magnetic resonance imaging (fMRI). Pupil size showed a strong increase during monetary reward anticipation, a moderate increase during verbal reward anticipation and a decrease during control trials. For fMRI analyses, average pupil size and pupil change were computed in 1-s time bins during the anticipation phase. Activity in the ventral striatum was inversely related to the pupil size time course, indicating an early onset of activation and a role in reward prediction processing. Pupil dilations were linked to increased activity in the salience network (dorsal ACC and bilateral insula), which likely triggers an increase in arousal to enhance task performance. Finally, increased pupil size preceding the required motor response was associated with activity in the ventral attention network. In sum, pupillometry provides an effective tool for disentangling different phases of reward anticipation, with relevance for affective symptomatology.

Introduction

Abnormalities in the processing of rewarding stimuli constitute a core symptom in various psychiatric disorders, including major depressive disorder (MDD), bipolar disorder and schizophrenia (American Psychiatric Association, 2013). For instance, reduced reward responsiveness (also referred to as anhedonia) in MDD has been linked to symptom severity (Vrieze et al., 2014), longer time to remission (McMakin et al., 2012) and poorer treatment outcome (Spijker et al., 2001). Previous studies employing reward learning paradigms have revealed that in comparison to healthy controls, MDD patients show reduced reward learning that was associated with self-reported anhedonic symptoms (Pizzagalli et al., 2008; Vrieze et al., 2013).

Reward processing involves two distinct temporal components: the anticipation of a positive stimulus and its pleasure-related consummation (Berridge, 1999). The reward anticipation phase has been suggested to involve a positive arousal response that is related to approach behavior (Knutson and Greer, 2008) and has been linked to motivation, attention and motor-preparation processes as well as goal-directed activity (Berridge et al., 2009; Klein, 1987; Sherdell et al., 2012; Whitton et al., 2015). Also, these processes are not necessarily bound solely to hedonic stimuli, but can become associated with reward-*predicting* cues as well, for example through a Pavlovian or instructed conditioning procedure (Sherdell et al., 2012). Interestingly, there is initial evidence that deficits in reward anticipation rather than reward consummation drive the reward-related abnormalities observed in depressive patients (Dichter, 2010; Sherdell et al., 2012) and individuals at risk for MDD (Olino et al., 2014).

Although the two reward processing components are strongly coupled, functional magnetic resonance imaging (fMRI) studies in humans have revealed that reward anticipation and consummation are in fact associated with the activity of distinct brain regions. For instance, previous studies have shown that reward anticipation involves increased activity in the ventral striatum (VS), ACC, bilateral anterior insula, inferior parietal lobule and brainstem, whereas the medial prefrontal cortex (mPFC), medial orbitofrontal cortex, and amygdala are more strongly activated during reward consummation (Knutson et al., 2001, 2003; Liu et al., 2011; Samanez-Larkin et al., 2007).

A recent study employing pupil size recordings in macaque monkeys by Rudebeck et al. (2014) could show that the reward anticipation phase is characterized by a sustained increase in pupil size, reflecting an increase in autonomic arousal. After lesions in the subgenual (and in some animals more dorsal) parts of the ACC, the macaque monkeys showed a failure to sustain this increased arousal during reward anticipation

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(Rudebeck et al., 2014). The initial pupil dilation at onset of the reward cue was not affected, which would suggest that the actual prediction update was not affected by the lesion – and that pupillometry may be helpful to dissect different processes during the reward anticipation phase. Furthermore, its use in macaque monkeys and human subjects makes it a promising translational tool, which can be readily employed as a readout during simultaneous fMRI.

To date, relatively few fMRI studies have incorporated pupillometry during reward tasks (Bijleveld et al., 2009; Chiew and Braver, 2013, 2014; O'Doherty et al., 2003; Takarada and Nozaki, 2017), even though it provides a sensitive readout in addition to behavioral responses and an objective experimental control. To our best knowledge, the neural correlates of pupil dilations during reward anticipation are unknown. In previous fMRI/pupillometry studies, we were able to show that pupil dilations are strongly linked to activity in dorsal ACC (dACC) and bilateral insula (also referred to as the salience network) during both resting state and fear learning (Leuchs et al., 2016; Schneider et al., 2016).

This coupling of the salience network, particularly dACC, with spontaneous and fear-induced pupil dilations is in line with the observation that the dACC, as well as the lateral orbitofrontal cortex, are major input regions to the locus coerueleus (LC), the brainstem's noradrenergic arousal center (Aston-Jones and Cohen, 2005). In one human pupillometry/fMRI study employing neuromelanin-sensitive imaging, the LC and dACC were found to correlate with pupil size fluctuations during rest (Murphy et al., 2014). Moreover, spontaneous pupil fluctuations increase with increasing sleepiness (referred to as “pupillary unrest”; Lowenstein et al., 1963; Wilhelm et al., 1998), which in mildly sleep deprived subjects resulted in more pronounced correlations to the thalamus in addition to the dACC and insula (Schneider et al., 2016). Among others, activity in the dACC has been associated with the occurrence of sympathetic arousal reactions (e.g. skin conductance responses and increases in heart rate) and the insular cortices have been suggested to track changes in arousal states (Critchley, 2005; Critchley et al., 2000; Fredrikson et al., 1998). Based on this, we proposed that the pupil/salience network correlation observed in our previous studies may reflect fluctuations in arousal levels, and specifically in emotional arousal. This would make pupil dilation a primary readout for reward anticipation, akin to fear learning (Leuchs et al., 2016).

Here, we recorded the pupil size of healthy subjects while they performed a reward anticipation task inside the MRI scanner. We hypothesized that the reward-predicting stimuli would be associated with an increase in pupil size. Furthermore, in order to investigate the blood oxygen level dependent (BOLD) correlates of reward anticipation- (and consummation-) related pupil dynamics, we determined the pupil size and pupil change (first order derivative of pupil size) time course within the reward anticipation phase. We hypothesized that reward anticipation-related *changes* in pupil size would be associated with activity of the salience network.

Methods

Subjects

Forty-six healthy subjects (range: 20–41 years, mean [M] age = 28.02, standard deviation [SD] = 4.17, 25 female) participated in the study, as part of a larger in-house study (Biological Classification of Mental Disorders). All subjects were right-handed, non-smokers and had normal or contact lens corrected vision. Prior to participation, a general medical interview and an anatomical MRI screening were conducted to exclude subjects with present or past psychiatric and neurological disorders, structural brain abnormalities, as well as current use of psychotropic medication. The study protocol was in accordance with the Declaration of Helsinki and was approved by a local ethics committee. Subjects provided their written informed consent after the study protocol had been fully explained and were reimbursed for their participation.

Reward task

The reward task was largely adopted from Knutson et al. (2001) and modified for pupillometric recordings by using isoluminant stimuli. All stimuli were presented using Presentation Software (Neurobehavioral Systems Inc., Berkeley, California, USA) in a central position on a monitor located at the end of the scanner bore, and could be seen by the subjects through a first surface reflecting mirror that was attached to the head coil. The Shine toolbox (Willenbockel et al., 2010) was used in order to edit the three reward-predicting stimuli such that their mean luminance matched to the grey background (RGB-code: 153, 153, 153) on which all stimuli were presented (mean luminance across stimuli: M = 152.90, SD = 0.025).

At the beginning of each trial, a fixation cross was presented for a variable interval between 3 and 10 s. Next, one of three quadratic gabor patch stimuli featuring different stripe orientations (see Fig. 1) appeared for 6 s (reward anticipation phase). The presented stimulus either signaled the possibility to gain money (tilted stripes), to receive a non-monetary/“verbal” reward (vertical stripes), or no response requirement (control stimulus; horizontal stripes). In both reward conditions, the reward anticipation phase was followed by a brief flash of light (target stimulus; duration of 100 ms), to which subjects had to respond as fast as possible by pressing a button. In monetary reward trials, participants won 1 € if they pressed the button fast enough. This was indicated by a green euro symbol that was subsequently presented for 1.5 s. In the non-monetary reward trials, subjects could not win money for fast responding, but were nevertheless instructed to react as fast as possible in order to receive a green checkmark symbol (serving as a form of non-monetary/verbal reward). In both conditions, a red cross served as feedback for responses that were too slow. An adaptive algorithm ensured that participant would succeed on approximately 50% of his or her responses across the session, typically resulting in a total monetary reward of around 5 to 6 € (M = 5.67 €, SD = 1.24 €). The algorithm automatically adjusted the width of the response time window: For instance, if subjects responded fast enough, the response time window that defined button presses as sufficiently fast (vs. too slow) would get narrower, such that subjects would have to respond comparably faster in the next trial to continue getting rewards.

Compared to previous reward anticipation paradigms which involved a text-based feedback (e.g. “fast response!” vs. “slow response!”), we decided to use single digits/symbols (“€”, “✓”,“X”) as feedback stimuli in order to avoid saccades caused by reading, thus minimizing artifacts related to eye movement in the pupil data. The red and green color used for the feedback stimuli were matched to the luminance of the grey background (RGB-codes: 112, 176, 142 [green], 248, 111, 120 [red]). The respective feedback stimulus was then followed by a number indicating the subject's cumulative total at that point (e.g. “3€” following the third successful monetary reward trial), which was presented for 1.5 s. The control trials did not involve any light flash, therefore no response was required and neither a feedback stimulus nor a number indicating the cumulative total was presented.

The duration of a single trial was on average 14.41 s (SD = 3.25 s). The task involved 10 trials for each condition (i.e. 30 trials in total), lasting approximately 7.5 min. The three conditions were presented in a pseudo-randomized order, with no more than two subsequent trials of the same condition.

Procedure

Before performing the task inside the scanner, subjects received an instruction about the reward task in front of a computer outside the scanner. For this purpose, subjects were first familiarized with the three different gabor patch stimuli and informed about the corresponding conditions (i.e., tilted stripes = monetary reward trial, vertical stripes = non-monetary reward trial, and horizontal stripes = no reward trial), as well as the light flash/button press and feedback procedure. To