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Temporal unpredictability of a stimulus sequence and the processing of neutral and emotional stimuli

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Most experimental settings in cognitive neuroscience present a temporally structured stimulus sequence, i.e., stimuli may occur at either constant and predictable or variable and less predictable inter-stimulus intervals (ISIs). This experimental feature has been shown to affect behavior and activation of various cerebral structures such as the parietal cortex and the amygdala. Studies employing explicit or implicit cues to manipulate predictability of events have shown that unpredictability particularly accentuates the response to events of negative valence. The present study investigates whether the effects of unpredictability are similarly affected by the emotional content of stimuli when unpredictability is induced simply by the temporal structure of a stimulus sequence, i.e., by variable as compared to constant ISIs.

In an fMRI study, we applied three choice–reaction–time tasks with stimuli of different social–emotional content. Subjects (N = 30) were asked to identify the gender in angry and happy faces, or the shape of geometric figures. Tasks were performed with variable and constant ISIs.

During the identification of shapes, variable ISIs increased activation in widespread areas comprising the amygdala and fronto-parietal regions. Conversely, variable ISIs during gender identification resulted in a decrease of activation in a small region near the intraparietal sulcus.

Our findings reveal that variability in the temporal stimulus structure of an experimental setting affects cerebral activation depending on task demands. They suggest that the processing of emotional stimuli of different valence is not much affected by the decision of employing a constant or a variable temporal stimulus structure, at least in the context of implicit emotion processing tasks. In contrast, temporal structure diversely affects the processing of neutral non-social compared to emotional stimuli, emphasizing the relevance of considering this experimental feature in studies which aim at differentiating social–emotional from cognitive processing in general, and more particularly, aim at identifying circumscribed alterations of social cognition in mental disorders.

Introduction

An extensive amount of neuroscience studies has focused on disentangling the contribution of various brain areas to social cognition and emotion processing (e.g., Adolphs and Tranel, 1999; Garvert et al., 2014; Hariri et al., 2002, 2003), and, in the context of mental disorders, has related alterations within associated areas with specific deficits in these domains (e.g., Domes et al., 2009; Evans et al., 2008; Meyer-Lindenberg et al., 2005). To this end, the neuronal response towards social–emotional stimulus material needs to be contrasted to non-social and/or non-emotional (control) stimulation. However, a clear dissociation between these processes is only warranted if all properties of the experimental design affect stimulus categories in an equal manner. Stimulus timing for instance, is one experimental feature which may represent a potential confound. In functional magnetic resonance imaging (fMRI), stimulus timing is partly associated to the improvement of design efficiency (Dale, 1999; Friston et al., 1999; Liu and Frank, 2004; Liu et al., 2001), as variable interstimulus intervals (ISIs) are more efficient, and necessary in rapid event-related designs (Burock et al., 1998; Dale, 1999). However, besides improving efficiency, variable stimulus timing is also less predictable and affects behavior and activation in social and emotionally relevant brain areas (Koppe et al., 2014; Ryan et al., 2010; Wodka et al., 2009). The question that arises is whether unpredictability in the temporal stimulus structure has different consequences on the processing of social–emotional vs. neutral information.

It is well established that unpredictability in respect to the temporal onset of an aversive event, promotes anxiety-like behavior in rodents (e.g., Abott, 1985; Fanselow, 1980; Imada and Nageishi, 1982 for

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review; Seligman, 1968; Seligman and Meyer, 1970), as well as in humans (e.g., Grillon et al., 2004; Katz and Wykes, 1985; McClure et al., 2003; Price and Geer, 1972), as measured by an increase in avoidance behavior, preference for predictable environments, more disturbed physiological responding, or a potentiated startle reflex. In these studies, temporal cues, sometimes in the form of a conditioned stimulus, are typically employed to signal the occurrence or non-occurrence, the duration, and/or the temporal window of an aversive, unconditioned stimulus (UCS), rendering this event more predictable. It has been proposed that cued, that is, predictable aversive events, are preferred to non-cued, unpredictable events, since they signal reliable periods of safety, allowing the agent to reduce vigilance and relax (Seligman and Binik, 1977).

However, in contrast to the employment of temporal cues which signal the onset of an aversive event, temporal unpredictability may also be conceptualized as an inherent property of the stimulus structure, i.e., with the UCS itself occurring at unpredictable, variable as compared to predictable, constant ISIs (Coull and Nobre, 2008; Imada and Nageishi, 1982). When stimuli are presented at variable or constant ISIs, temporal predictions are exogenously triggered and assumed to emerge as a byproduct of the temporal regularity at which they are presented (see Coull and Nobre, 2008 for reviews; Coull et al., 2011). The timing processes underlying these predictions are assumed to differ from implicit timing mechanisms that are triggered by temporal cues (Coull and Nobre, 2008; Coull et al., 2011).

It is yet unclear, whether temporal unpredictability induced implicitly by application of variable as compared to constant ISIs may similarly modulate the response to aversive stimulation, and whether this modulation deviates from effects in neutral stimulation. With respect to neutral stimuli, Herry et al. (2007) were the first to show that presenting variable background sound pulses of high frequency (in the range of 200 ms) induces sustained amygdala activation, which is accompanied by increased avoidance behavior in rodents, as well as an increased spatial attention bias towards threatening information in humans. On a time scale of a few seconds, Koppe et al. (2014) observed a similar increase in amygdala activation to neutral visual stimuli presented at variable ISIs, and thus in a time frame relevant to fMRI. Beside activation within the amygdala, variable ISIs additionally engaged prefrontal and parietal areas during a choice reaction task. The increase of activation during this condition could at least partially be attributed to the formation of temporal expectations over time. The BOLD response within these regions co-varied with the cumulative conditional probability that a stimulus would occur, given it had not already occurred, i.e., the cumulative hazard function, an index of temporal expectancy (Cui et al., 2009; see Nobre et al., 2007 for a review). Regarding aversive stimuli, studies which investigate effects of variable and constant ISIs on this time scale are lacking. However, rodent studies employing fixed or variable time schedules of shock application provide first evidence that variably timed shock increases anxiety-like behavior (Bassett et al., 1973; Guile, 1987; Orsini et al., 2002), albeit the interval duration applied in these studies exceed durations customary in fMRI (i.e., >30 s).

In the present study, we investigated how constant and variable ISIs in the seconds range affect processing of emotional and neutral stimuli. To this end, we employed angry facial expressions serving as aversive stimuli since they signal potential threat, and are furthermore well known to induce amygdala activation (Boll et al., 2011). Studies which have employed temporal cues to investigate the relationship of unpredictability and threat, demonstrate that combining unpredictability with aversive stimulation results in a potentiated fear response. This effect has been measured by the fear potentiated startle reflex, with the amygdala representing one underlying neuronal substrate (Grillon, 2008; Vaidyanathan et al., 2009 for reviews). Based on these observations, we hypothesized that effects of temporal unpredictability in the stimulus structure would be potentiated during aversive stimulation, and thus result in a non-additive effect when compared to neutral stimuli or events of positive valence, i.e., happy facial expressions.

We focused on brain areas which have previously been linked to the differential effects of constant and variable ISIs in the processing of neutrally valent stimuli, investigated in a design similar to that used in the present study: the amygdala, and the parietal cortex, the supplementary motor area (SMA), and the dorsolateral prefrontal cortex (DLPFC). These areas are more strongly engaged in variable compared to constant ISI conditions (Koppe et al., 2014). The amygdala is of particular interest in the present study since it has been linked to the processing of threat and fear in general (Phelps and LeDoux, 2005), as well as in the context of uncertainty and unpredictability in particular (Bar and Neta, 2008; Herry et al., 2007; Whalen, 2007). Both the inferior and the superior parietal cortices have been associated with temporal orienting and adjustment processes (Cotti et al., 2011; Coull, 2004; Nobre, 2001; Sakai et al., 2000), and are modulated by predictability linked to cueing (Coull, 2004; Sakai et al., 2000), while the DLPFC and the SMA have been implicated in monitoring and updating of the hazard function when the temporal interval between events varies between trials (Coull and Nobre, 2008; Cui et al., 2009; Vallesi et al., 2007a, 2007b, 2009).

Materials and methods

Subjects

Thirty healthy subjects (15 male, 15 female; age: 24.2 ± 2.5 years) participated in the study. All subjects were right-handed (Annett, 1967), and had normal or corrected-to-normal vision. All of them were undergraduate students at the Justus-Liebig-University, Giessen, with no history of psychiatric or neurological disorders. They were either awarded credits for research participation or received 15 Euros for participating in the study. All participants gave their written informed consent prior to participating in the study. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the local ethics committee of the University of Giessen, School of Medicine.

Stimulus material

Stimulus material consisted of stimuli conveying emotional information (happy and angry faces), as well as emotionally neutral, non-social stimuli. Face stimuli were obtained from the Karolinska Directed Emotional Faces set (Lundqvist et al., 1998). From this set, pictures Q4 from 18 male and 18 female identities posing frontally for angry and happy emotional facial expressions were chosen. As non-social, non-emotional control stimuli, we applied geometric shapes, consisting of triangles and squares according to a previous study (Koppe et al., 2014). To reduce differences between shapes and faces in regard to low level visual characteristics, shapes were presented on a background picture of scrambled facial stimuli.

Within each task, stimuli were presented in pseudo-random order on a computer screen (stimulus duration 100 ms, see Figure S1). Throughout the tasks, a resting button and two target buttons were displayed and labeled with ‘male’ and ‘female’, or ‘triangle’ and ‘square’, respectively. The subjects were instructed to respond as fast as possible, while avoiding errors. Subjects signaled their choice by releasing a resting button and pressing the appropriate target button with the index finger of the right hand. The currently pressed button was indicated by a cursor on the screen. Responses had to be initiated within 2 s after stimulus onset, slower reactions were processed as errors.

Experimental paradigm

All subjects were asked to solve choice reaction tasks with three types of stimuli under two conditions of temporal stimulus structure, varying in regard to predictability (see Figure S1).

The first experimental factor was thus the temporal structure of the applied stimuli. The temporal structure, i.e., the occurrence of stimuli in

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