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Temporal unpredictability of a stimulus sequence affects brain activation differently depending on cognitive task demands

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ABSTRACT

Within cognitive neuroscience, in nearly every experimental setting, subjects are presented with stimuli that appear at either constant or variable points in time, referred to as interstimulus intervals (ISIs). These temporal patterns differ in the degree to which an exact stimulus onset may be predicted. We investigated whether this experimental feature affects brain and behavior, and whether the impact is modulated by the cognitive demands of a task. Subjects (N = 26) were assessed via fMRI while solving three different tasks under either temporally predictable (constant ISI) or unpredictable (variable ISI) conditions. The tasks differed with regard to demands on working memory and response uncertainty. Compared to constant ISIs, variable (i.e., less predictable) ISIs led to a general increase in reaction time and in right amygdala activation. Depending on the cognitive demands required by the specific task, the left amygdala, the parietal cortex, the supplementary motor area, and the dorsolateral prefrontal cortex were engaged as well. The results indicate that the temporal structure in a stimulus sequence affects both overt and covert behaviors. Implicit temporal uncertainty increases activation in several brain regions depending on cognitive demands. Thus, an often-overlooked basic design feature, the application of constant or variable ISIs, may contribute to heterogeneity in cognitive neuroscience findings.

Introduction

Nearly every experimental setting in cognitive neuroscience involves the presentation of stimuli that serve as input for various cognitive processes determined by the specific task. These stimuli form an event sequence, and it is well known that the properties of this sequence affect the induced cognitive processes. Phenomena such as exhaustion, training, and implicit or explicit expectations about the type of future stimuli all modulate cognitive processing (e.g., Fecteau and Munoz, 2003; Hermanutz et al., 1981; Polich and Bondurant, 1997; Squires et al., 1976). Unless these phenomena are being explicitly investigated, such as in studies on learning, anticipation, and preparatory processes (e.g., Niemi and Näätänen, 1981), sequential stimulus effects are generally controlled for by experimental methods, such as randomizing the stimulus type, or balancing the frequency of individual stimulus arrays. Less attention has been directed to experimental control of temporal features of a stimulus sequence: specifically, the choice between constant and variable interstimulus intervals (ISIs). In fMRI studies, this choice is at least partially associated with methodological considerations regarding the optimization of design efficiency. Rapid event-related designs require variable ISIs to improve statistical efficiency, while blocked designs do not (Dale, 1999; Friston et al., 1999; Liu and Frank, 2004; Liu et al., 2001). Although the question on the application of constant or variable ISIs arises every time an experimental setting is configured, studies that have investigated the specific impacts of this choice on cognitive processing and its neuronal substrates are lacking.

Therefore, the present study investigated how the application of variable or constant ISIs affects behavior and brain activation during cognitive tasks that present distinct processing demands.

Constant and variable ISIs differ in the degree of uncertainty regarding when an event is likely to occur. In contrast to constant ISIs, which allow for a precise prediction of the onset of an upcoming stimulus, stimulus onsets with variable intervals are less predictable, leading to uncertainty in the formation of temporal expectations. This uncertainty depends on ISI duration; as intervals become longer, the conditional probability that an expected event will occur, given it has not yet occurred, increases. This phenomenon is known as the ‘hazard function’ (Cui et al., 2009; Nobre et al., 2007), and describes how over time, temporal expectations increase while uncertainty decreases. In humans, hazard rate computation has been identified within the supplementary motor area (SMA) and the superior temporal gyrus as an immediate burst of activity towards stimulus onset, with its amplitude being

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proportional to the cumulative hazard function (Cui et al., 2009). Other studies have associated monitoring of the hazard function specifically to the right dorsolateral prefrontal cortex (dlPFC) (Vallesi et al., 2009).

Studies that have examined the effects of the temporal structure of stimulus sequences during cognitive processing typically investigate mechanisms of timing (Coull and Nobre, 2008; Coull et al., 2011). Timing is essential here, since precise predictions of stimulus onsets rely on a metrical representation of time. Within the functional taxonomy of timing, the implicit processing of ISIs is ascribed to the domain of 'exogenous temporal expectations' (EXTEs) (Coull and Nobre, 2008).

EXTEs are established subconsciously and incidentally via temporal features of the stimulus structure. They may be distinguished from endogenous temporal expectations, i.e., those formed deliberately via informative pre-cues that signal the temporal onset of an event such as in the foreperiod paradigm and the temporal-cueing paradigm (Jepma et al., 2012). Exogenous and endogenous temporal expectations are summarized as 'perceptual implicit timing' (Coull and Nobre, 2008), which is characterized as a by-product of cognitive processing by temporal properties of a perceptual input or motor output, and is distinguished from explicit timing, in which tasks more directly require the perceptual discrimination or a motor production of a timed duration.

In contrast to implicit endogenous timing or explicit timing, few studies have examined the effects of EXTEs (for review, see Coull and Nobre, 2008; Coull et al., 2011; Nobre et al., 2007). Those studies that have directly compared effects of variable and constant ISIs on cognitive processing have investigated effects on elementary cognitive processes. In the most basic paradigm, Herry et al. (2007) studied the effects of the mere listening to a sequence of temporally variable, task-irrelevant sound pulses, and found that temporally unpredictable tones evoked an increased bilateral amygdala response compared to temporally regular tones. Choice reaction tasks and Go/NoGo tasks designed to minimize the perceptual and cognitive demands have shown that variable ISIs result in slower processing times (Li et al., 2003; Sakai et al., 2000; Wodka et al., 2009). Variable ISIs have been associated with increased activation of the parietal cortex and the left premotor cortex, which have been linked to the modification and integration of temporal adjustment processes (Dreher and Grafman, 2002; Sakai et al., 2000).

A number of findings suggest that effects of temporal expectations may be modulated by the specific cognitive processes involved in a task, i.e., that their effects are context-dependent. The lateral premotor cortex shows a more pronounced activation towards variable ISIs in case of higher demands on response selection processes (Sakai et al., 2000). Context-specific effects are also suggested by studies investigating effects of foreperiod duration on temporal expectations: during the foreperiod, neural firing rates have been shown to vary dynamically as a function of the hazard rate, with the specific cerebral region depending on the specific cognitive demands of the applied task (Ghose and Maunsell, 2002; Janssen and Shadlen, 2005; Riehle et al., 1997).

In sum, several studies suggest that the decision to use constant or variable timing of stimuli in an experimental setting affects both overt and covert behaviors, and that these effects might depend on the cognitive demands of a task. However, the few existing studies have applied simple cognitive tasks, and have varied ISIs up to a maximum of only 1100 ms, which can be assumed to be linked to mechanisms of timing other than those typically involved when ISIs are jittered in fMRI designs. Thus, the aim of the present study was to address whether uncertainty in the formation of EXTEs by ISI variability in a range typically applied in fMRI designs exerts an impact on behavior and brain activation during more complex cognitive tasks, and whether this effect is modulated by cognitive task demands.

We chose working memory (WM) and response selection processes as the cognitive functions of interest. WM is defined as a system that allows information that is no longer present in the environment to be maintained for future manipulation to ensure goal-directed behavior (Baddeley, 1986; Fuster, 2002). This characterizes WM as crucial in a variety of different task settings. Beyond that, the WM network overlaps with prefrontal areas employed in timing, which suggests that WM and the processing of temporal uncertainty may particularly influence each other (e.g., Lewis and Miall, 2006). To induce WM processes, we used n-back tasks, since these allow the manipulation of demands on WM and response selection processes within a comparable experimental setting (Owen et al., 2005; Plichta et al., 2012; Redick and Lindsey, 2013). In a delayed-matching-to-sample n-back task, subjects were required to decide 'when to do what', while in a delayed-response n-back task, they already knew 'what' to do, but had to predict 'when' to do it (Lis et al., 2011). Together with a 0-back control task, this experimental setting allows separation of the processing of temporal uncertainty ('when') and response uncertainty ('what to do') within the context of more complex cognitive functions such as WM. We hypothesized that uncertainty in the building of EXTEs during variable ISIs would: 1) result in reduced performance compared to constant ISIs, and 2) result in an engagement of the amygdala and cerebral structures that have been shown to be involved in timing, such as the parietal cortices, the SMA, and the dlPFC. Furthermore, 3) as we were interested in whether the effects of unpredictability are modulated by cognitive demands of the task, we hypothesized that effects of temporal unpredictability would accentuate when the task required more complex cognitive functions (i.e., WM), and that this effect would be more pronounced under conditions of response uncertainty (i.e., when a delayed-matching-to-sample n-back task is performed during variable ISIs). The effects were expected to be less pronounced when WM is combined with response certainty, such as in the delayed-response n-back task, and when no WM is involved in task solving, such as in the 0-back control task.

Materials and methods

Subjects

A total of 26 healthy subjects (13 male, 13 female; mean age 25 ± 3.5 years) participated in the study. Entry criteria included being right-handed (Annett, 1967), having normal or corrected-to-normal vision, and reporting no history of psychiatric or neurological disorders. All subjects were students at the Justus-Liebig-University, Giessen, and received credits for participating in this research. The study was approved by the local ethics committee of the University of Giessen, School of Medicine, and written informed consent was obtained from each participant prior to enrollment.

Experimental paradigm

Subjects solved three types of tasks under two conditions of temporal unpredictability while undergoing fMRI.

Temporal unpredictability was varied experimentally by manipulation of the ISI duration. In the predictable condition (constant ISI), the stimuli were presented at constant intervals of 4 s, while in the unpredictable condition (variable ISI), ISIs varied between 2.5 and 5.5 s (mean 4 s, step-width 0.375 ms).

The tasks, which served to vary the demands on WM and response selection processes, consisted of a continuous matching 1-back task (CMT), a continuous delayed response 1-back task (CDRT), and a 0-back control task. See Table 1. In each task, one of two visual stimuli (square or triangle) was presented in pseudorandom order (50% probability, duration 50 ms). The subjects had to respond as fast as possible while avoiding errors. Responses had to be initiated within 2 s after stimulus onset; slower reactions were processed as errors (for further task description, see Fig. S1).

In the CMT, subjects had to compare the present stimulus with the one occurring 1 step back in the sequence and indicate whether these were the same or different (Gevins et al., 1990). Since response selection is based on the results of the matching process, the subjects do not know 'what' to do after the WM delay before the next stimulus is