NeuroImage 89 (2014) 10–22

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Individual differences in the morphometry and activation of time perception networks are influenced by dopamine genotype

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ARTICLE INFO

Article history:
Accepted 11 November 2013
Available online 19 November 2013

ABSTRACT

Individual participants vary greatly in their ability to estimate and discriminate intervals of time. This heterogeneity of performance may be caused by reliance on different time perception networks as well as individual differences in the activation of brain structures utilized for timing within those networks. To address these possibilities we utilized event-related functional magnetic resonance imaging (fMRI) while human participants (n = 25) performed a temporal or color discrimination task. Additionally, based on our previous research, we genotyped participants for DRD2/ANKK1-Taq1a, a single-nucleotide polymorphism associated with a 30–40% reduction in striatal D2 density and associated with poorer timing performance. Similar to previous reports, a wide range of performance was found across our sample; crucially, better performance on the timing versus color task was associated with greater activation in prefrontal and sub-cortical regions previously associated with timing. Furthermore, better timing performance also correlated with increased volume of the right lateral cerebellum, as demonstrated by voxel-based morphometry. Our analysis also revealed that A1 carriers of the Taq1a polymorphism exhibited relatively worse performance on temporal, but not color discrimination, but greater activation in the striatum and right dorsolateral prefrontal cortex, as well as reduced volume in the cerebellar cluster. These results point to the neural bases for heterogeneous timing performance in humans, and suggest that differences in performance on a temporal discrimination task are, in part, attributable to the DRD2/ANKK1 genotype.

Introduction

Individuals vary greatly in their ability to estimate and discriminate intervals of time (Brown et al., 1995; Carlson and Feinberg, 1968). This variability may arise from multiple factors including memory and decision-making processes (Buhusi and Meck, 2005). Between-subject variance in time perception has been largely ignored until recently. Here we explore the neural and genetic factors that contribute to heterogeneous timing performance across individuals.

Human neuroimaging studies of timing demonstrate a wide degree of heterogeneity in the neural regions that become activated during a given timing task. Recently, we characterized this variability with a quantitative meta-analysis of the likelihood of activation of any given neural structure during different time perception tasks. Our results demonstrated that the likelihood of activation differed, depending on the temporal context (Wiener et al., 2010). Generally, subcortical structures, such as the basal ganglia and cerebellum, were more likely to be activated during sub-second intervals, whereas cortical regions, such as the prefrontal cortex, were more likely to be activated during supra-second intervals. Furthermore, the right inferior frontal gyrus (rIFG) and supplementary motor area (SMA) were highly likely to be active across all timing tasks. An additional finding from our meta-analysis was that the pattern of basal ganglia activation likelihood differed depending on the temporal context; given the proposed involvement of regions of the basal ganglia (i.e. caudate, putamen) in different cognitive functions (Grahn et al., 2008), and the central role of the basal ganglia in current models of timing (Matell and Meck, 2004), this differential pattern of activity may be particularly relevant.

Although the results of our meta-analysis provided some clarification of the heterogeneity of neuroimaging findings for timing, they are based on inferences from group performance. A shortcoming of group averaging of fMRI performance is that individual differences in activation patterns will not be detected (Fedorenko et al., 2011). For example, the SMA may be implicated across most timing studies, but this does not guarantee that every subject activates the SMA to the same extent, or, indeed, at all (Ferrandez et al., 2003). In a recent study combining transcranial magnetic stimulation (TMS) and electroencephalography (EEG) (Wiener et al., 2012), we found that the behavioral effect of TMS to the right supramarginal gyrus differed substantially between subjects, with respect to both the ability to alter timing performance and the polarity of contingent negative variation (CNV), a waveform

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http://dx.doi.org/10.1016/j.neuroimage.2013.11.019

that is in part mediated by the SMA (Nagai et al., 2004). Similar findings have been demonstrated within the working memory literature, where substantial differences between group and individual-based fMRI and EEG responses have been found (Feredoes and Postle, 2007; Vogel and Awh, 2008) with only individual-based regions predicting behavioral disruptions from TMS (Feredoes et al., 2007). As such, group differences in fMRI can tell us the regions most likely to be activated during time perception, but not whether those regions are differentially activated in individual subjects.

One explanation for individual differences in activation of timing networks is that different timing procedures may be employed as a function of task demands or subject strategy (Wiener et al., 2011b). One example of the effects of strategy comes from recent neuroimaging evidence demonstrating that networks of activated structures differ both within and between subjects as a function of whether subjects employ beat-based (Grahn and McAuley, 2009) or counting strategies (Hinton et al., 2004) during timing.

Another factor that may account, at least in part, for individual differences in temporal processing is basic personality profiles. Numerous studies have demonstrated differences between different personality indices and time perception abilities (see Rammsayer, 1997 for a brief review). Consistent among these differences is the notion that the rate of an internal pacemaker varies between individuals leading to a "faster" clock for some and "slower" clock for others.

Finally, several investigators have reported data that genetic factors influence temporal processing. We demonstrated that timing performance differs between individuals with single-nucleotide polymorphisms of genes affecting dopamine function on temporal perception (Wiener et al., 2011a) and production (Balci et al., 2013). Such differences have also been found for dopamine genes in different cognitive domains, such as working memory (Berryhill et al., 2013), learning (Klein et al., 2007) and task switching (Stelzel et al., 2010). Additionally, differences as a function of genotype have been found in fMRI responses to a variety of cognitive tasks (Green et al., 2008). These differences may be used as intermediate phenotypes between genetic differences and the behavioral manifestation of different psychiatric disorders (Winterer and Weinberger, 2004).

Within the neuroimaging literature, two recent studies have focused specifically on individual differences in the brain mechanisms recruited for time perception. Tipples et al. (2013) utilized fMRI while subjects performed a sub-second temporal bisection task with face stimuli or an orthogonal gender identification task in a blocked design. The bisection point, a measure of accuracy, when regressed against activation, revealed a correlation with activity in the SMA and rIFG, with greater activity associated with overestimation of durations. A second study by Gilaie-Dotan, Kanai and Rees (2011) examined differences in structural morphometry associated with performance on supra-second discrimination tasks. Significant positive correlations were found between discriminability and gray matter differences in the right primary auditory and secondary somatosensory cortices for longer (12 s) durations; negative correlations were also found between discriminability and bilateral parahippocampal volume. Shorter (2 s) durations did not correlate with any region when correcting for whole-brain significance levels, although primary visual cortices (positively) and SMA volume (negatively) did correlate at uncorrected thresholds.

Additional studies, not focusing directly on individual differences, have also noted correlations between subject performance and activation. Wencil et al. (2010), utilizing a between-subject covariate for accuracy on a sub- to supra-second temporal discrimination task noted positive correlations between performance and activation within bilateral inferior frontal gyrus. In contrast, Coull et al. (2008) noted that activity within the left putamen positively correlated with sub- to supra-second temporal discrimination accuracy; notably this correlation was only found for encoding, as opposed to retrieval. As a further difference, Harrington et al. (2004a) noted a positive correlation between supra-second bisection points and right parahippocampal activation. Notably, some of these studies only examined correlational activity post-hoc, in regions that had already been activated in group-level contrasts.

In order to elucidate the neural mechanisms associated with differences *across* individuals, we conducted a study using event-related fMRI to measure activity within brain regions correlating with inter-individual differences in behavior. Additionally, we used voxel-based morphometry (VBM) to address the question of morphological, as well as functional differences. Finally, in order to investigate the contribution of genetic predisposition on individual differences in brain network recruitment during temporal perception, we separated subjects on the basis of a well-known genetic polymorphism (DRD2/ANKK1-Taq1a) previously implicated in temporal perception. We hypothesized that individual differences in timing ability would be associated with differential activation of frontostriatal circuitry commonly activated in studies of temporal perception (Wiener et al., 2010). Additionally, we expected to find that A1 allele carriers of the DRD2/ANKK1-Taq1a polymorphism would demonstrate impaired timing performance, but only with durations in the sub-second range (Wiener et al., 2011a, 2011b), and not on a control task. We further hypothesized that this difference in performance would also be associated with a difference in activation within the brain regions we identified. However, we note that we were agnostic as to the direction (over- or under-activation) of this effect, as alterations in the dopamine system may lead to either increased (Jahanshahi et al., 2010) or decreased (Coull et al., 2012) levels of activity during timing along with decreases in performance.

A common and vexing issue in neuroimaging studies of time perception is the choice of an appropriate control task. In any timing paradigm, the duration of the stimulus cannot be known until the interval is over; thus, unlike many other stimulus features (i.e. size, pitch, intensity, etc.) that may be classified with very brief presentation, processing of a temporal interval necessarily extends for the duration of the stimulus. For our analysis of individual differences in brain activation, we therefore chose to use the well-known time-color behavioral paradigm (Coull et al., 2004). This task, utilized by a number of fMRI researchers (Coull et al., 2004, 2008, 2012; Livesey et al., 2007; Morillon et al., 2009), surmounts the above issue by presenting subjects with two sequentially presented, rapidly flickering colored stimuli; in the timing condition, subjects must judge the relative duration of both stimuli, whereas in the color condition they must judge the overall color of both stimuli by integrating information from the entire exposure. In this way, subjects cannot make a judgment regarding the colored stimulus until it has extinguished. The use of this task has been previously demonstrated to provide adequate control of the attentional and working memory demands in temporal discrimination, as both tasks use identical stimulus conditions (Coull et al., 2004).

In order to investigate the role of individual differences in time processes, we chose to use the relative difference in performance between time and color tasks within subjects, rather than raw accuracy on each task. This decision was motivated by the fact that the time and color tasks share many of the same task requirements (e.g., sustained attention, visual processing). Thus, although performances on the color and time tasks are not correlated (Gilaie-Dotan et al., 2011), the signed difference between them is likely to reflect the relative differences in task-specific ability. As such, a large difference indicates that an individual is better at leveraging timing (or color) related circuitry than color (or timing) circuitry. Support for this approach is provided by pharmacological studies (Coull et al., 2011, 2012) utilizing the time-color paradigm that demonstrated impairments in timing with preserved color processing. We believe that raw accuracy scores would be less informative for regressing against hemodynamic responses, as differences in performance may reflect discrepancies in non task-related processing. We hypothesized that subjects who are better at leveraging timing-related regions than color-related regions will also show greater activation in timing-related regions than those with little or no difference.