Double Dissociation of Dopamine Genes and Timing in Humans

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Abstract

■ A number of lines of evidence implicate dopamine in timing [Rammsayer, T. H. Neuropharmacological approaches to human timing. In S. Grondin (Ed.), *Psychology of time* (pp. 295–320). Bingley, UK: Emerald, 2008; Meck, W. H. Neuropharmacology of timing and time perception. *Brain Research, Cognitive Brain Research, 3,* 227–242, 1996]. Two human genetic polymorphisms are known to modulate dopaminergic activity. DRD2/ANKK1-Taq1a is a D_2 receptor polymorphism associated with decreased D_2 density in the striatum [Jönsson, E. G., Nothen, M. M., Grunhage, F., Farde, L., Nakashima, Y., Propping, P., et al. Polymorphisms in the dopamine D_2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Molecular Psychiatry, 4,* 290–296, 1999]; COMT Val158Met is a functional polymorphism associated with increased activity of the COMT enzyme such that catabolism of synaptic dopamine is greater in pFC [Meyer-Lindenberg, A., Kohn, P. D., Kolachana, B., Kippenhan, S., McInerney-Leo, A., Nussbaum, R., et al. Midbrain dopamine and prefrontal function in humans: Interaction and modulation by COMT genotype. *Nature Neuroscience, 8,* 594–596, 2005]. To investigate the role of dopamine in timing, we genotyped 65 individuals for DRD2/ANKK1-Taq1a, COMT Val158Met, and a third polymorphism, BDNF Val66Met, a functional polymorphism affecting the expression of brain-derived neurotrophic factor [Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell, 112,* 257–269, 2003]. Subjects were tested on a temporal discrimination task with sub- and supra-second intervals (500- and 2000-msec standards) as well as a spontaneous motor tempo task. We found a double dissociation for temporal discrimination: the DRD2/ANKK1-Taq1a polymorphism (A1+ allele) was associated with significantly greater variability for the 500-msec duration only, whereas the COMT Val158Met polymorphism (Val/Val homozygotes) was associated with significantly greater variability for the 2000-msec duration only. No differences were detected for the BDNF Vall66Met variant. Additionally, the DRD2/ANKK1-Taq1a polymorphism was associated with a significantly slower preferred motor tempo. These data provide a potential biological basis for the distinctions between sub- and supra-second timing and suggest that BG are integral for the former whereas pFC is implicated in the latter. ■

INTRODUCTION

Although the ability to precisely mark the passage of time is crucial for perception and action, surprisingly little is known about the neurobiology of temporal processing. Additionally, processes underlying the perception of time from milliseconds to minutes may be of particular relevance to cognition as measures of temporal precision in humans have been found to correlate well with measures of general intelligence and working memory (Troche & Rammsayer, 2009). Furthermore, timing deficits are apparent in disorders such as schizophrenia, autism, and attention-deficit hyperactivity disorder (Meck, 2005), suggesting that timing may serve as an endophenotypic measure of psychiatric disease.

A large body of research has now demonstrated that time perception in both animals and humans can be disrupted by the administration of pharmacological agents affecting the dopamine system (Rammsayer, 2008; Meck, 1996), suggesting that this neurotransmitter system, which may underlie such crucial functions as working memory (Cools, 2008) learning (Klein et al., 2007) and reward value (Pierce & Kumaresan, 2006), is important for the perception of time. In an attempt to distinguish the roles of different dopamine receptor subtypes in interval timing, Meck (1986) administered a number of different neuroleptic drugs, including chlorpromazine, haloperidol, pimozide, promazine, and spiroperidol to animals performing an interval timing task. Drawing on evidence of the binding affinities to dopamine, norepinephrine, and serotonin receptors for each drug, Meck demonstrated that the ability of a drug to induce a 15–20% shift in the psychophysical function significantly correlated only with the binding affinity for dopamine receptor D_2.

Rammsayer and colleagues have conducted a number of experiments over the past two decades investigating the effects of dopamine antagonists on interval timing in humans. Rammsayer (1989a) first demonstrated that administration of 3 mg of the D_2 receptor antagonist haloperidol to humans increased variability on an auditory temporal

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discrimination task, in which subjects were required to judge whether a comparison stimulus was longer or shorter than a standard stimulus. The effect of haloperidol on interval timing in humans has been replicated across numerous experiments at different interval ranges (Rammsayer, 1989b, 1993, 1997a, 1997b, 1999). However, the effects of other dopaminergic drugs on humans have not elicited similar effects. Rammsayer (1989a) found no effect of the indirect dopamine agonist L-Dopa on interval timing; furthermore, Rammsayer and Vogel (1992) demonstrated that alpha-methyl-*p*-tyrosine, an indirect dopamine antagonist, did not alter interval timing. Rammsayer concluded that dopaminergic modulation of time perception depended on selective effects on dopamine receptors rather than dopamine synthesis. However, Rammsayer (1997a) also found no effect of the atypical neuroleptic sulpiride, a D_2/D_3 receptor antagonist, on time perception abilities.

Additional work on the role of dopamine in time perception has come from studies involving patients with Parkinson disease (PD). Several experiments revealed that patients with PD exhibit deficits on temporal reproduction tasks; notably, the administration of L-Dopa attenuated these deficits (Malapani & Rakitin, 2003; Malapani, Deweer, & Gibbon, 2002; Malapani et al., 1998). A further study demonstrated that administration of a higher dosage of L-Dopa than that used by Rammsayer (1989a) to older and younger adults induced a subjective lengthening of duration on a reproduction task (Rakitin, Scarmeas, Li, Malapani, & Stern, 2006). These findings culminated in a quantitative model of timing, suggesting that dopamine levels could alter the firing rate of neurons acting as a temporal accumulator (Shea-Brown, Rinzel, Rakitin, & Malapani, 2006).

A consideration of the role that dopamine plays in interval timing is further complicated by the existence of three different dopamine pathways in the brain, the nigrostriatal, mesocortical, and mesolimbic pathways. The nigrostriatal pathway projects from the substantia nigra pars compacta to the dorsal striatum and is thought to underlie motor programming and responses as well as attentional set-shifting and error prediction (Dreher & Grafman, 2002; Middleton & Strick, 2000). The mesolimbic and mesocortical pathways both project from the ventral tegmental area, with mesolimbic neurons targeting the nucleus accumbens of the ventral striatum, and mesocortical neurons primarily targeting pFC. The mesolimbic pathway is thought to underlie motivation and reward (Pierce & Kumaresan, 2006), whereas the mesocortical pathway underlies working memory (Cools, 2008; Aalto, Bruck, Laine, Nagren, & Rinne, 2005; Kimberg, D'Esposito, & Farah, 1997).

To dissociate between the dopamine pathways in humans, Rammsayer (1993, 1997a) tested for differential effects between the D_2 antagonists haloperidol (3 mg) and remoxipride (150 mg) in humans. Remoxipride blocks D_2 receptors in the mesolimbic and mesocortical pathways (Gerlach & Casey, 1990), whereas haloperidol blocks D_2 receptors in all dopamine pathways (Lidow & Goldman-Rakic, 1994). Haloperidol disrupted performance stimuli that were greater and less than 500 msec, but remoxipride disrupted performance exclusively for the longer durations. Rammsayer concluded that different neural circuits are recruited for the processing of short- and long-duration ranges.

Although these studies argue for the role of dopamine in temporal processing, several confounds diminish their conclusiveness. First, medications such as haloperidol reduce alertness and arousal. Second, methamphetamine and haloperidol—the most commonly used drugs in studies of interval timing—tend to alter temperature (Sandoval, Hanson, & Fleckenstein, 2000; Lin, Wang, Wang, & Chern, 1979), a parameter that is known to influence timing (Wearden & Penton-Voak, 1995). Furthermore, haloperidol has also been shown to antagonize serotonergic and stimulate α_1-adrenergic receptors (Schotte, Janssen, Megens, & Leysen, 1993; Pazo, De Stein, Tumilasci, Medina, & De Robertis, 1985), limiting the specificity of behavioral results to alterations of the dopamine system. Finally, although a substantial number of studies demonstrate deficits in performance associated with methamphetamine administration in animals (Meck, 1996), a growing number of studies report a failure to replicate this effect (for a review, see Balci et al., 2008).

The case for a distinction between mesocortical and nigrostriatal dopamine pathways may not be as robust as previously claimed. The conclusion of Rammsayer's (1993, 1997a) earlier work was based on pharmacological evidence for differential effects of haloperidol and remoxipride, with remoxipride primarily acting on D_2 receptors in the mesolimbic and mesocortical pathways. However, the evidence that remoxipride acts exclusively on mesolimbic and mesocortical pathways is currently inconclusive, as numerous studies using autoradiographic techniques have demonstrated alterations at striatal binding sites following remoxipride administration (Nadal, 2001; Eaton, Tian, Lookingland, & Moore, 1992). Thus, the differential effects of haloperidol and remoxipride at different interval ranges may not be sufficiently explained by preferred action on the nigrostriatal system.

In light of the uncertainties involved in pharmacological studies, we sought to assess the role of dopamine for short and long interval timing with behavioral genetic paradigms. To elucidate the effects of dopamine on time perception in humans, we investigated two well-known single-nucleotide polymorphisms known to modulate human dopamine function. The first, DRD2/ANKK1-Taq1a, is a C/T substitution located in the ANKK1 gene that is in linkage disequilibrium with the dopamine D_2 receptor gene (Hirvonen et al., 2009; Duan et al., 2003). The presence of a single allele of the Taq1a polymorphism (A1+) has been demonstrated to reduce the density of D_2 receptors in the striatum by 30–40% (Jönsson et al., 1999). The Taq1a polymorphism has been behaviorally associated with deficits in reversal learning and attention (Klein et al.,

2007; Fossella, Green, & Fan, 2006). The second, COMT Val158Met, is a valine-to-methionine conversion that occurs within the COMT gene, affecting the enzymatic activity of catechol-*O*-methyltransferase. The COMT enzyme is responsible for catabolism of synaptic dopamine and is known to be preferentially active within pFC (Egan et al., 2001). The Val158Met polymorphism results in differential activity of the COMT enzyme; homozygous carriers of the Val allele have an increase in COMT activity, resulting in decreased dopamine availability in pFC. Consistent with this finding, the Val158Met polymorphism has been associated with disruptions in working memory and frontal executive tasks (Meyer-Lindenberg et al., 2005; Egan et al., 2001).

We also investigated a third polymorphism, BDNF Val66Met, a valine-to-methionine conversion affecting the expression of brain-derived neurotrophic factor. Although BDNF has not been hypothesized to be involved in timing functions previously, we chose to include this gene because of its involvement in episodic memory and hippocampal activity (Egan et al., 2003), which may ostensibly be involved in timing abilities.

METHODS

Participants

Sixty-five right-handed volunteers (mean age = 23; range, 18–35; 38 women) participated in the study. Subjects included 51 white participants, 8 black participants, and 6 Asian participants. All subjects gave informed consent to the procedures and the collection of saliva samples. Subjects were screened for personal and familial neurologic, psychiatric, and other medical conditions as well as drug use and abuse; female subjects were screened for premenstrual tension. Saliva samples were collected with an OG-100 Oragene collection kit (DNA Genotek, Ontario, Canada), and DNA was extracted using standard methodology.

Temporal Discrimination

Behavioral effects resulting from changes in genotype may be subtle, so rigorous psychometric procedures are necessary to elucidate any differences (Green et al., 2008). Therefore, subjects were tested on a visual temporal discrimination task utilizing a maximum-likelihood adaptive procedure, the Parameter Estimation by Sequential Testing (PEST) algorithm (Pentland, 1980). Temporal discrimination requires subjects to judge whether a comparison duration is longer or shorter than a standard duration presented on every trial. The PEST algorithm provides a continuously updated maximum-likelihood estimate of the threshold for detecting a difference between the comparison and standard durations (Lieberman & Pentland, 1982). As such, the current upper or lower threshold value is presented as the comparison duration for each trial. Furthermore, the range and frequency of comparison stimuli is different for each subject, thus allowing task difficulty to be scaled to individual performance. We set the initial lower and upper thresholds to equal 50% and 150% of the standard interval duration, respectively. For the purpose of our study, two standard durations were tested, 500 or 2000 msec, in separate, 60-trial blocks. The initial stepsize for adjustments in the comparison duration were set to 15% of the standard duration for the first 20 trials, then for 5% for the remaining 40 trials. A 30-trial practice block with a 1000-msec standard was administered before testing. Stimulus presentation and the PEST algorithm were carried out using Matlab with the Psychophysics Toolbox extensions (Brainard, 1997). Visual stimuli demarcating the standard and comparison durations consisted of a 4 × 4 cm red square presented for each duration; a 1000-msec interstimulus interval separated standard and comparison durations. Subjects indicated on a keyboard whether the comparison duration was longer by pressing L or shorter by pressing S. Subjects were not told the durations tested and were not given feedback regarding accuracy. Subjects were instructed not to count or use subvocal strategies when timing.

The probability of the subject making a "longer" response choice was plotted as a function of the comparison interval. These data were then fit with a sigmoidal, psychometric curve using the psignifit version 2.5.6 software package (see bootstrap-software.org/psignifit/) for Matlab, which implements the maximum-likelihood method described by Wichmann and Hill (2001a). Upper and lower thresholds, the approximate points at which the subject is 25% or 75% likely to judge the stimulus as longer, were calculated using the bias-corrected bootstrap method implemented by psignifit based on 4999 simulations (Wichmann & Hill, 2001b). The results of this analysis yield point of subjective equality (PSE; the time value at which subjects were equally likely to judge the stimulus as longer or shorter), difference limen (DL; upper–lower thresholds), and coefficient of variation (CV; DL/PSE). For each duration, groups defined by gene status were compared with respect to accuracy (PSE) and variability (CV).

Spontaneous Motor Tempo

The spontaneous motor tempo (SMT) task is a sensitive measure of individual differences in timing (McAuley, Jones, Holub, Johnston, & Miller, 2006). All subjects were told to tap a response key at a comfortable rate; that is, subjects were asked to tap consistently at their "natural," comfortable rhythm. Subjects performed four separate runs of 31 taps. The first tap was removed from each run, and the remaining 30 intertap intervals (ITI) were measured for mean response rate and variability (*SD*/mean ITI).

Genotyping

Genotyping for the DRD2/ANKK1-Taq1a (rs1800497), COMT Val158Met (rs4680), and BDNF Val66Met

(rs6265) polymorphism was performed using Applied Biosystems "Assays-on-demand" (Applied Biosystems, Inc., Foster City, CA) SNP genotyping assays as per manufacturers protocol.

RESULTS

Screening

We identified seven female subjects that self-identified as experiencing high premenstrual tension at the time of testing. These subjects were removed from the analysis because of concerns regarding fluctuations in both dopamine (Dreher et al., 2007) and timing (Farjampour & Hellström, 2000) during premenstrual tension. One additional female subject was removed because of a reported family history of schizophrenia.

Genotypes

The results of our genotyping analysis identified 21 subjects with the DRD2/ANKK1-Taq1a polymorphism (A1 allele carriers), 34 subjects who lacked the polymorphism (A2 homozygotes), and 2 subjects for whom the samples failed to amplify because of poor DNA quality. Consistent with earlier studies (Noble, 2003), we detected a very low frequency of A1/A1 homozygotes ($n = 3$); therefore, in accordance with other studies, we combined A1/A1 homozygotes and A1/A2 heterozygotes as A1+ carriers. For the COMT Val158Met polymorphism, we identified 12 subjects homozygous for the Val allele, 35 Val/Met heterozygotes, and 9 Met homozygotes. For the purposes of the present experiment and statistical analysis, we combined Val/Met and Met/Met groups as Met+ carriers (see Frank, Doll, Oas-Terpstra, & Moreno, 2009; Stelzel, Basten, Montag, Reuter, & Fiebach, 2009; Frank, Moustafa, Haughey, Curran, & Hutchison, 2007). For the BDNF Val66Met polymorphism, we identified 8 subjects heterozygous for the Met allele, 5 subjects homozygous for the Met allele, and 42 subjects homozygous for the Val allele with two failures; Val/Met heterozygotes and Met/Met homozygotes were combined as Met+. We note that we were unable to explore possible epistatic interactions between COMT Val158Met and DRD2/ANKK1-Taq1a polymorphisms because of a low number of subjects with both polymorphisms of interest ($n = 4$); that is, we were unable to examine the within-subject interaction of one gene on another. Additionally, the data files for temporal discrimination at 500 msec for one subject and 2000 msec for another subject were corrupt; as such, these subjects are missing PSE and CV values for these durations.

Temporal Discrimination

We sought to investigate both between-genotype and within-genotype differences for our analysis. To interrogate differences across genotypes, temporal discrimination data were analyzed using a mixed-model ANOVA, with standard duration (500 and 2000 msec) as a within-subject factor and genotype [DRD2/ANKK1-Taq1a (A1−, A1+), COMT Val158Met (Val/Val, Met+), BDNF Val66Met (Val/Val, Met+)] as independent between-subject factors. Separate ANOVAs were run for PSE and CV data. For differences within genotype, a series of independent planned t tests were conducted examining differences between group means for each genotype. Plotted values for the CV scores for each genotype are displayed in Figure 1. For CV data, the results of a mixed-model ANOVA revealed a significant group level between-genotype interaction for DRD2/ANKK1-Taq1a and COMT Val158Met genotypes [$F(1, 44) = 5.006, p = .03$]. Within genotype analyses demonstrated that A1 allele carriers of the Taq1a polymorphism (A1+) were significantly more variable than subjects lacking this polymorphism at 500 msec [$t(52) = -1.694, p = .048$], but not at 2000 msec [$t(52) = 0.018, p = .493$]. The opposite pattern was observed for homozygous carriers of the COMT Val allele (Val/Val) as compared with carriers of the COMT Met allele (Met+); the former group exhibited greater variability at 2000 msec [$t(53) = -2.311, p = .012$] but did not differ at 500 msec [$t(53) = 0.529, p = .299$]. No differences in performance were found for Met allele carriers of the BDNF polymorphism (Met+) at either 500 msec [$t(52) = 1.258, p = .107$] or 2000 msec [$t(52) = -.134, p = .447$]. To further elucidate differences across duration between DRD2/ANKK1-Taq1a and COMT Val158Met genotypes, we conducted a post hoc mixed-model ANOVA on the CV values with duration as a within-subject factor and polymorphisms of interest (A1+ for Taq1a, Val/Val for Val158Met); because of the low number of subjects with both polymorphisms of interest, we removed these subjects from this secondary analysis. The results of this follow-up analysis demonstrated a significant duration by genotype interaction [$F(1, 22) = 4.490, p = .046$]. For PSE data, we detected no significant differences either between or within genotype (all $p > .05$).

Spontaneous Motor Tempo

For SMT data, separate univariate ANOVAs were conducted for mean tapping rate and variability to examine between-genotype differences for DRD2/ANKK1-Taq1a (A1−, A1+), COMT Val158Met (Val/Val, Met+), and BDNF Val66Met (Val/Val, Met+)] genotypes (Figure 2). No interactions between genotypes were detected for either mean tapping rate or variability (all $p > .05$); however, a significant main effect of the DRD2/ANKK1-Taq1a genotype was detected for tapping rate [$F(1, 45) = 4.172, p = .047$]. Within-genotype analysis further demonstrated that A1+ subjects tapped at a significantly slower rate than subjects lacking this polymorphism [A1+: 814 msec, A1−: 497 msec, $t(53) = -2.409, p = .0095$]. No effect on tapping rates was found for either Val/Val homozygotes of the COMT Val158Met polymorphism [$t(55) = -0.565, p = .287$] or Met allele carriers of the BDNF Val66Met [$t(53) = -0.898,$

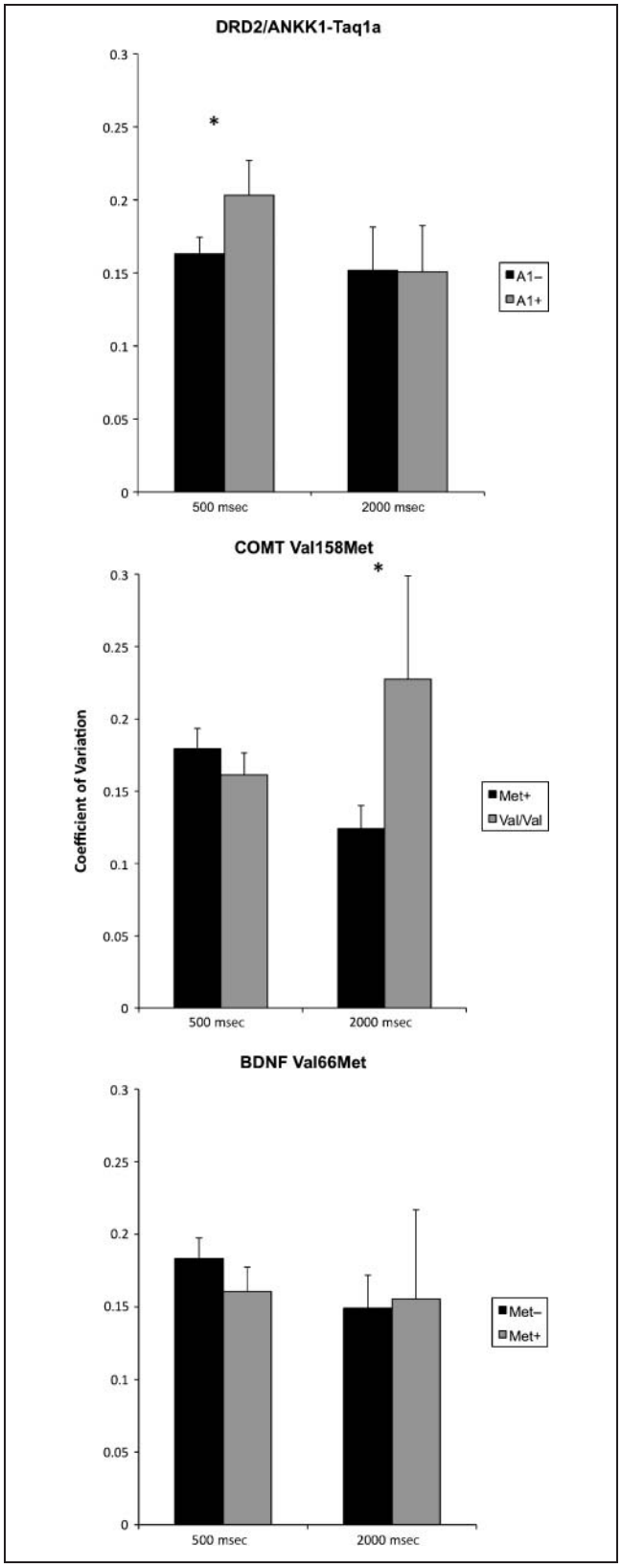

Figure 1. Mean CV values (+*SEM*) for temporal discrimination at 500- and 2000-msec duration standards. A1+ allele carriers demonstrated increased variability only for 500 msec, but not for 2000 msec. In contrast, Val/Val homozygotes of the COMT Val158Met polymorphism exhibited increased variability for 2000 msec, but not 500 msec. No effects on variability were observed for BDNF Val66Met polymorphisms.

$p = .373$]. No significant differences for variability scores between or within genotype were detected on either the univariate ANOVA or planned t tests (all $p > .05$).

DISCUSSION

The present study demonstrates a functional dichotomy between genes that regulate dopamine and sub- and supra-second interval timing. Distinctions between sub- and supra-second processing have been suggested as far back as 100 years (Musterberg, 1889). Although the hypothesis has received support from neuroimaging (Wiener, Turkeltaub, & Coslett, 2010), lesion (Mangels, Ivry, & Shimizu, 1998), and neural stimulation studies in humans (Jones, Rosenkranz, Rothwell, & Jahanshahi, 2004), the validity of the distinction remains controversial (Macar et al., 2002). The present results provide support for the utility of the distinction between sub- and supra-second timing and offer insight into the neural basis for this distinction.

Anatomical and Physiological Effects of Genotype

Subjects with the DRD2/ANKK1-Taq1a polymorphism (A1+), characterized by a reduction in striatal D_2 receptor density, exhibited an increased CV during temporal discrimination of a 500-msec, but not a 2000-msec, standard. Recent work suggests that the effect of the DRD2/ANKK1-Taq1a polymorphism is restricted to BG; as research utilizing the high-affinity D_2 radioligand [^{11}C] FLB457 has demonstrated in vivo that A1 allele carriers of the Taq1a polymorphism exhibit no significant differences in D_2 receptor binding at sites outside the striatum compared with non-A1 allele carriers (Hirvonen et al., 2009). Additionally, it should be noted that the density of D_2 receptors in the cortex is approximately 0.3% that of the striatum (Hurd & Hall, 2005). In light of these findings, we suggest the effect of the Taq1a polymorphism on sub-second timing is a BG-mediated phenomenon.

In recent years, BG have emerged as a strong candidate region for interval timing (Matell & Meck, 2004). Patients with PD and Huntington's disease exhibit timing impairments (Beste et al., 2007; Malapani & Rakitin, 2003; Malapani et al., 1998, 2002); furthermore, dorsal striatal lesions in rats lead to substantial timing impairments (Meck, 2006). Neuroimaging studies of timing also demonstrate BG activation during timing tasks; consistent with the findings reported here, in a recent meta-analysis of functional imaging studies of timing, BG activation was observed primarily in studies employing sub-second stimuli (Wiener, Turkeltaub, & Coslett, 2010).

In a double dissociation with the Taq1a results, subjects with the COMT Val158Met polymorphism (Val/Val homozygotes) exhibited a significantly increased CV for the supra-second standard duration (2000 msec) only. The Val allele of the Val158Met polymorphism has been

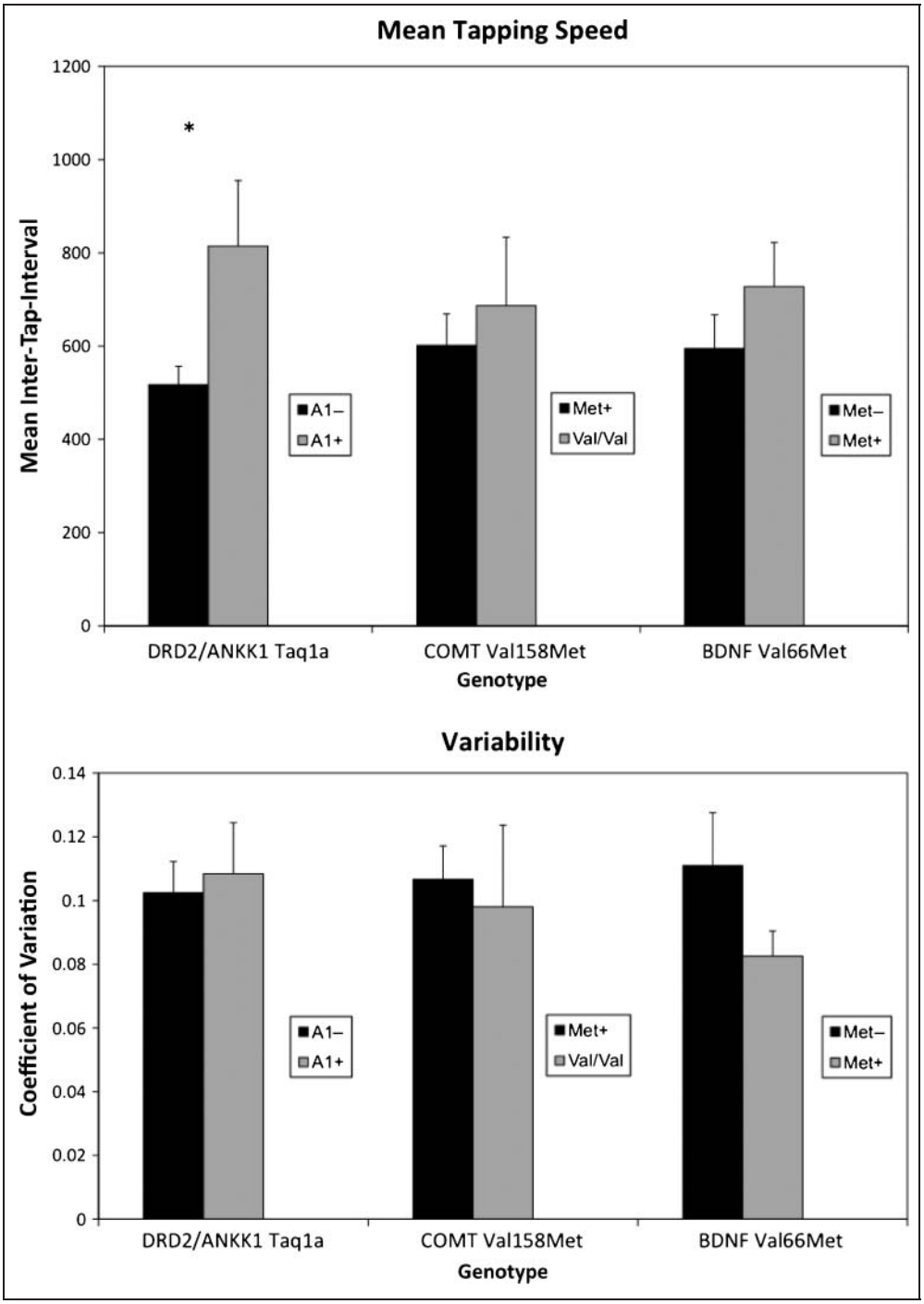

Figure 2. Mean tapping rate of subjects (+*SEM*) grouped by genotype demonstrates only a significant shift when subjects were grouped by the DRD2 genotype (Taq1a). A1+ indicates presence of the A1 allele; Met+ indicates presence of the Met allele for COMT and BDNF genotypes. Asterisks represent significance at $p < .05$.

associated with an increase in COMT enzyme activity; because of the relative scarcity of dopamine transporter proteins in pFC, the COMT Val158Met polymorphism is a potent index of prefrontal dopamine functioning (Meyer-Lindenberg et al., 2005; Egan et al., 2001). A disruption in supra-second duration timing may then be construed as a disruption of prefrontal dopamine tone.

Our finding is consistent with a number of previous studies that implicate pFC in supra-second interval timing (Lewis & Miall, 2006). Neuroimaging studies consistently demonstrate prefrontal activation during timing tasks, with greater activation likelihood for longer intervals (Wiener, Turkeltaub, & Coslett, 2010). Furthermore, TMS and patient–lesion studies both demonstrate timing impairments exclusively for supra-second durations following disruptions of pFC (Jones et al., 2004; Mangels et al., 1998).

Our findings also have implications for the roles of the D_1 and D_2 dopamine receptors in timing. The COMT Val158Met polymorphism does not appear to influence D_2 receptor availability in either pFC or striatum (Hirvonen et al., 2010). Rather, this polymorphism has been shown to have preferential action on D_1 receptors in the cortex, with

no effect on striatal D_1 availability (Slifstein et al., 2008). These findings suggest that supra-second timing impairments may be attributable to an alteration in the D_1/D_2 receptor ratio. A change in the D_1/D_2 activation ratio in pFC has been hypothesized to decrease the signal-to-noise ratio, thereby disrupting performance during cognitively intense tasks (Winterer & Weinberger, 2004). Additionally, neural computation studies suggest that D_1-receptors in the cortex mediate a high-energy state that is necessary for maintaining representations in the face of distractor stimuli (Durstewitz & Seamans, 2008); such a state may be particularly useful for storing the longer durations experienced in a supra-second timing task. Finally, several reports now indicate timing impairments in rats following D_1-specific drug administration (Cheung et al., 2007; Matell, Berridge, & Wayne-Aldridge, 2006; Frederick & Allen, 1996; but see Drew, Fairhurst, Malapani, Horvitz, & Balsam, 2003); to our knowledge, D_1-specific pharmacological agents have not been utilized to study timing performance in humans.

The differences between the behavioral effects of polymorphisms in dopamine genes have implications for neural models of interval timing. Several models have been developed in the past decade that incorporate hypotheses regarding the role of dopamine in temporal processing (Rivest, Kalaska, & Bengio, 2010; Shea-Brown et al., 2006; Matell & Meck, 2004). Furthermore, a more general role for dopamine in reward prediction has been suggested by research demonstrating an effect of midbrain dopaminergic activity on predictive associations (Bromberg-Martin & Hikosaka, 2009; Fiorillo, Newsome, & Schultz, 2008). However, these models do not differentiate between mesocortical or nigrostriatal dopamine pathways. Our results suggest that both are relevant but have different roles. Mesocortical dopamine appears to be necessary for supra-second processing, whereas nigrostriatal dopamine is necessary for sub-second processing (see also Rammsayer, 2008). These differences may reflect the suitability of neurons in each pathway for the differential processing demands in sub-second (i.e., fast, high-frequency changes) and supra-second (i.e., slow, delayed responses) processing. Further specification of timing models will be necessary to account for these distinctions between dopamine systems and duration.

In the present study, we found no effect for the BDNF Val66Met polymorphism. Although BDNF has not previously been specified to have a role in timing operations, the Met allele of the Val66Met polymorphism has been implicated in episodic memory tasks and hippocampal activity (Egan et al., 2003). The lack of an effect for Val66Met does not preclude the involvement of the hippocampus in time perception, as lesions in animals have demonstrated that the hippocampus is necessary for maintaining temporal information under certain circumstances (Meck, Church, & Olton, 1984; but see Dietrich, Allen, & Bunnell, 1997). We note that the absence of an effect of the Val66Met polymorphism serves as a useful control genotype in the present study.

Behavioral and Cognitive Effects of Genotype

Numerous cognitive models of timing have been developed over the past several decades; most postulate that a single procedure underlies timing. The demonstration that different polymorphisms are associated with distinct patterns of performance for sub- and supra-second stimuli, however, suggests that timing procedures may be fractionated with respect to the duration of the interval to be timed and/or the involvement of different brain regions. Our findings, then, provide strong support for Musterburg's claim that different mechanisms underlie the timing of short (sub-second) and long (supra-second) stimuli. Recent work by Lewis and Miall (2009) attempted to isolate whether behavioral responses across a wide range of intervals exhibited a "break-point" in responding that could separate timing mechanisms. Unfortunately, their data did not demonstrate a reliable break-point in behavioral responses. Although our data do not argue for a specific break-point, they suggest it is somewhere between 500 and 2000 msec, providing support for a multiple-timer hypothesis.

A hallmark of most models of timing is the so-called scalar property of time; that is, the variability of timing judgments increases linearly with duration, demonstrating a constant CV (Gibbon, Malapani, Dale, & Gallistel, 1997; but see Lewis & Miall, 2009, for a dissenting view). In the present study, DRD2/ANKK1-Taq1a (A1+) and COMT Val158Met (Val/Val) subjects demonstrated violations of the scalar property, whereas A1−, Met+, and BDNF Val66Met (Val/Val, Met+) variant subjects exhibited preserved scalar timing. However, behavioral models of timing generally incorporate multiple elements from which increases in variability may arise (Gallistel & Gibbon, 2000; Matell & Meck, 2000; Wearden, 1999). Furthermore, increases in variability may arise from nontemporal sources, such as attention or arousal (Droit-Volet & Meck, 2007; Rakitin, 2005). Both the DRD2/ANKK1-Taq1a and COMT Val158Met polymorphism have been studied in the context of attentional mechanisms. However, we note that, whereas several studies suggest a possible link between attentional disorders and DRD2/ANKK1-Taq1a (Fossella et al., 2006; Rodriguez-Jimenez et al., 2006) or COMT Val158Met (Giakoumaki, Roussos, & Bitsios, 2008; Blasi et al., 2005), several other studies fail to find such a connection (Bombin et al., 2008; Cheuk & Wong, 2006; Faraone et al., 2005). In light of these considerations, the cause(s) of the observed disruptions in variability, with regards to behavioral models of timing, cannot be stated with certainty. It should be noted, however, that the selective effects of the polymorphisms for different intervals suggests that the nonspecific effects of attention cannot entirely explain our data. For example, Rammsayer and Ulrich (2005) demonstrated that attentional manipulations during timing tasks in humans equally disrupted both sub-second and supra-second timing tasks; as such, a general attentional deficit would equally disrupt timing at both

duration ranges. However, given the differences in phenotype between both polymorphisms, an attentional explanation may still be possible; indeed, as the COMT Val158Met polymorphism is putatively associated with prefrontal dopamine, one might expect a greater influence on attentional processing for this polymorphism (Arnsten, 2009).

An additional finding in the present study is that subjects with the DRD2/ANKK1-Taq1a (A1+) polymorphism tapped at a slower self-generated pace. This finding is similar to earlier work demonstrating that D_2 receptor density is positively correlated with maximum tapping speed (Volkow et al., 1998). In contrast to the maximal tapping rate that may, at least in part, reflect the efficiency of the motor system, the SMT task has been hypothesized to serve as a behavioral measure of internal tempo (Boltz, 1994); furthermore, SMT rate correlates with preferred listening tempo (McAuley et al., 2006). Two additional relevant findings are that both SMT rate and striatal D_2 density decrease with normal aging (McAuley et al., 2006; Wong et al., 1984), suggesting that decreased striatal D_2 density in subjects with the DRD2/ANKK1-Taq1a (A1+) polymorphism lowers the rate of internal tempo. If striatal D_2 levels influence neural thresholds for action (Ivry & Spencer, 2004), one might speculate that lower D_2 levels serve to raise the necessary threshold of activation, thus delaying timed motor responses and decreasing natural tapping rate. Such a change may not be expected from alterations in mesocortical dopamine levels by the COMT Val158Met polymorphism, as mesocortical dopamine has been shown to have little influence on motor responses (Cools, 2008; Brozoski, Brown, Rosvold, & Goldman, 1979). This finding suggests a further dissociation between motor and perceptual timing tasks and dopamine systems in humans, wherein nigrostriatal dopamine influences both motor and perceptual elements, whereas mesocortical dopamine selectively processes perceptual timing functions.

The observed differences as a function of genotype are fairly consistent with previous pharmacological work. The majority of Rammsayer's earlier work demonstrated increases in variability during temporal discrimination following acute administration of dopamine antagonists (cf. Rammsayer, 2008). However, the performance of DRD2/ANKK1-Taq1a (A1+) subjects on temporal discrimination is at odds with earlier work by Rammsayer (1993, 1997a, 1999). Rammsayer attributed disruption of both sub and supra-second timing to the effects of haloperidol on D_2 receptors in both mesocortical and nigrostriatal pathways; our subjects with DRD2 polymorphisms only demonstrated an effect for sub-second processing. However, as the DRD2/ANKK1-Taq1a polymorphism is only known to affect D_2 density in the striatum (Hirvonen et al., 2009), one possible account is that unimpaired supra-second performance was because of preserved mesocortical D_2 function in these subjects.

Studies of subjects with focal lesions of BG have reported inconsistent effects on timing. However, most studies included subjects with unilateral lesions, raising the possibility that timing functions could be mediated by the intact BG (Trivino, Correa, Arnedo, & Lupianez, 2010; Aparicio, Diedrichsen, & Ivry, 2005). We recently reported two patients with large bilateral lesions of BG who performed abnormally on a paced finger-tapping task but performed well on a duration judgment task with a 600-msec standard similar to that reported here (Coslett, Wiener, & Chatterjee, 2010). We argued that these patients with chronic lesions had adapted to the loss of a procedure specialized for processing sub-second intervals by employing timing procedures that were optimized for longer intervals. We believe that the data from these subjects are not inconsistent with the findings reported here. On both accounts, timing routines that are dependent on BG are assumed to be involved in sub-second timing.

Conclusion

The results of the present study demonstrated a double dissociation between dopamine genes and timing abilities in humans. Polymorphisms resulting in reduced striatal D_2 density led to an increase in variability for a sub-second interval during temporal discrimination and a decrease in preferred tapping rate. In contrast, a polymorphism resulting in increased activity of the COMT enzyme and putatively reduced prefrontal dopamine levels was associated with increased variability for a supra-second interval during temporal discrimination, with no changes in tapping variability. Timing abilities in humans vary widely. Although attention and arousal may partially account for this variability, our results reveal that individual differences in timing are in part determined by genotype.

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