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Noradrenergic genotype predicts lapses in sustained attention

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Abstract

Sustained attention is modulated by the neurotransmitter noradrenaline. The balance of dopamine and noradrenaline in the cortex is controlled by the DBH gene. The principal variant in this gene is a C/T change at position -1021, and the T allele at this locus is hypothesised to result in a slower rate of dopamine to noradrenaline conversion than the C allele.

200 participants who were genotyped for the DBH C-1021T marker performed the Sustained Attention to Response Task (SART). DBH genotype was found to significantly predict performance; participants with more copies of the T allele made more errors of commission, indicative of lapses in sustained attention. A significant negative correlation was also observed for all participants between errors of commission and mean reaction time.

The decrease in noradrenaline occasioned by the T allele may impair sustained attention by reducing participants' ability to remain alert throughout the task and by increasing their susceptibility to distractors.

1. Introduction

Posner and Peterson's (1990) theory of attention posits a fronto-parietal alerting network responsible for arousal and vigilance which relies heavily on the actions of the

neurotransmitter noradrenaline. Closely linked with this network is sustained attention, the capacity to keep oneself alert or to maintain focus on a task in the absence of external drivers of attention (Robertson, Manly, Andrade, Baddeley & Yiend, 1997). Sustained attention is a requirement for maintaining focus on routine tasks, including those where the target requires inhibition of a response. A number of studies have demonstrated robustly that sustained attention tasks recruit a right-lateralised network in the brain encompassing areas of the frontal and parietal cortices (Fassbender, Murphy, Foxe, Wylie, Javitt, Robertson *et al.*, 2004; Pardo, Fox & Raichle, 1991; Wilkins, Shallice & McCarthy, 1987) which interact with sub-cortical regions (Paus & Zatorre, 1997; Sturm, Simone, Krause, Specht, Hesselmann, Radermacher *et al.*, 1999).

A number of neurotransmitters have been linked to aspects of sustained attention, including acetylcholine (Sarter, Givens & Bruno, 2001) and dopamine (Bellgrove, Hawi, Kirley, Gill & Robertson, 2005). Levels of dopamine in the brain have been linked to some measures of sustained attention (Collins, Roberts, Dias, Everitt & Robbins, 1998), and the dopamine agonist amphetamine improves sustained attention in healthy human controls (e.g. Mackworth, 1965; Silber, Croft, Papafotiou & Stough, 2006) and rats (Bizarro, Patel, Murtagh & Stolerman, 2004; Grilly, 2000), as well as ameliorating sustained attention deficits in people with ADHD (Oades, 1987; Sostek, Buchsbaum & Rapoport, 1980; Spencer, Biederman, Wilens, Faraone, Prince, Gerard *et al.*, 2001) and in animal models of the disorder (Chudasama, Nathwani & Robbins, 2005; Sagvolden & Xu, 2008). Amphetamine also has noradrenergic effects, however (Florin, Kuczenski & Segal, 1994), and it is noradrenaline which has been particularly linked to the right fronto-parietal 'alerting' system that is central to sustained attention (Posner & Peterson, 1990).

Noradrenaline is secreted in the locus coeruleus in the pontine formation, with a widespread cortical distribution with particular concentrations in the inferior parietal cortex, the temporo-parietal junction and the prefrontal cortex (Levitt, Rakic & Goldman-Rakic, 1984). There is also evidence for a greater right- than left-hemisphere distribution of noradrenaline in humans (Oke, Keller, Mefford & Adams, 1978). Locus-coeruleus-noradrenaline activity has also shown to be intimately linked with target detection (Nieuwenhuis, Aston-Jones & Cohen, 2005), and noradrenergic drugs such as clonidine influence the alerting component of sustained attention in humans (e.g. Coull, Middleton, Robbins & Sahakian, 1995), as well as in rats (Carli, Robbins, Evenden & Everitt, 1983; Coull *et al.*, 1995). Noradrenaline appears to improve attention both by narrowing the focus of attention, blocking out the effect of

distractors (Robbins, 1984; Smith, Wilson, Glue & Nutt, 1992) and via its interaction with underlying levels of arousal (Carli *et al.*, 1983; Coull, Jones, Egan, Frith & Maze, 2004; Smith & Nutt, 1996). These findings all point to a particularly strong relationship between the neurotransmitter noradrenaline and the right fronto-parietal sustained attention system.

The enzyme dopamine β -hydroxylase is found in noradrenergic neurons, and is released into synapses at the same time as the catecholamines (Smith, de Potter, Moerman & de Scaepdryver, 1970) where it catalyses the conversion of dopamine to noradrenaline (Kaufman & Friedman, 1965). *D β H* therefore plays a critical role in controlling the balance of dopamine and noradrenaline available in the cortex. Variation in the *DBH* gene (9q34) has been shown to reliably affect the activity of the *D β H* enzyme, and consequently the proportion of dopamine converted to noradrenaline. A number of polymorphisms at and near the *DBH* gene have been associated with variation in *D β H* activity, most notably a C/T SNP at position -1021 in the promoter region of the gene which accounts for 35-52% of variation in plasma *D β H* activity (Zabetian, Anderson, Buxbaum, Elston, Ichinose, Nagatsu *et al.*, 2001). The T allele is considerably less frequent than the C allele, with a minor allele frequency of approximately .22 in European populations (Zabetian *et al.*, 2001). In all populations studied, individuals homozygous for the T allele, heterozygous, and homozygous for the C allele displayed very low, intermediate and high *D β H* plasma activity levels respectively. It has been suggested that the T allele of C-1021T diminishes gene transcription, resulting in lower levels of *D β H* than the C allele (Cubells & Zabetian, 2004). Although no direct research has been carried out into the effect of the *DBH* C-1021T marker on catecholamine levels in the human brain, a study on *DBH* knockout mice (Bourdelat-Parks, Anderson, Donaldson, Weiss, Bonsall, Emery *et al.*, 2005) has demonstrated that the gene directly affects the balance of catecholamines in the prefrontal cortex. The T allele at the C-1021T locus is hypothesised to result in greater availability of dopamine, and comparatively lower availability of noradrenaline in the cortex. Variation in cognitive performance between participants with different *DBH* genotypes would provide important collateral evidence that this SNP has a functional effect on the brain.

DBH has been identified as a possible risk gene for ADHD (Daly, Hawi, Fitzgerald & Gill, 1999; Hawi, Lowe, Kirley, Gruenhage, Nöthen, Greenwood *et al.*, 2003; Kirley, Hawi, Daly, McCarron, Mullins, Millar *et al.*, 2002; Roman, Schmitz, Polandzyk, Eizirik, Rohde & Hutz, 2002). Variants in this gene have been associated with sustained attention deficits (Bellgrove,

Hawi, Gill & Robertson, 2006) and global executive function deficits (Kieling, Genro, Hutz & Rohde, 2008) in *individuals with ADHD* and with spatial working memory in healthy controls (Parasuraman, Greenwood, Kumar & Fossella, 2005). To date, no association between the DBH gene, and in particular the functional C-1021T SNP, and measures of attention has been demonstrated in healthy controls.

The aim of this study was to determine the effect of the DBH gene on sustained attention in a healthy population. The Sustained Attention to Response Task (SART) requires participants to withhold a prepotent response to a rare target and places demands on the fronto-parietal sustained attention network, as demonstrated by PET and fMRI studies (Fassbender *et al.*, 2004; Manly, Owen, McAvinue, Datta, Lewis, Scott *et al.*, 2003). The SART involves elements of both sustained attention and response inhibition processes, as participants must remain vigilant throughout the task and continue to respond to all go trials, while withholding response to no-go trials. It was expected that the lower levels of prefrontal noradrenaline and increased dopamine occasioned by the presence of the T allele of the DBH C-1021T polymorphism would reduce attentional capacity relative to participants in possession of the C allele.

2. Methods

2.1 Participants

201 participants (118 female, 83 male) were recruited by means of an advertising campaign. All participants were right-handed, as determined by the Edinburgh Handedness Inventory, aged between 18 and 30 (mean age = 20.58 years, SD = 2.54) and had completed or were engaged in third level education at the time of testing. Exclusion criteria included a history of ADHD, epilepsy or any psychiatric or neurological disorder.

Every effort was made to ensure the ethnic homogeneity of the sample in order to avoid population stratification effects. Ethnicity was established by means of a questionnaire detailing the national origins of the participants' 4 grandparents. 180 participants (89.5%) were classified as genetically Irish based on this measure. The remaining 21 participants were classified variously as European (14), American (3), Australian (1), Indian (1) and Chinese (2).

This research was approved by the School of Psychology Research Ethics Committee, Trinity College Dublin. All participants provided informed consent prior to taking part in the study.

2.2 Sustained Attention to Response Task (SART)

The SART (Robertson *et al.*, 1997) tests sustained attention by requiring participants to respond continuously to a stream of single digits 1-9, and to withhold response to a low frequency digit, 3 (11%). Though it has a response inhibition component, it has been validated as a sensitive measure of sustained attention in EEG, fMRI and behavioural studies (Fassbender *et al.*, 2004; Johnson, Kelly, Bellgrove, Barry, Cox, Gill *et al.*, 2007; O'Connell, Dockree, Bellgrove, Turin, Ward, Foxe *et al.*, 2008). Single white digits between 1 and 9 were presented on a black screen in a variety of font sizes for a period of 250ms, followed a 900ms mask consisting of a white X in a circle that appeared to 'flash'. Participants were required to respond with a button press to every number except 3, and were instructed to time their responses to coincide with the flash. The digits were presented in pseudo-random fashion, preventing the participant from anticipating the appearance of the target digit. Participants performed two blocks of the SART; each block lasted approximately four minutes, and contained 225 trials. The number 3 was presented in 25 of these trials. The total

number of errors of commission (button press when the number 3 was onscreen), errors of omission (failure to press the button when any other number was onscreen) and mean reaction time were calculated across the two blocks.

Genotyping

Saliva samples were collected from all participants using ORAgene™ DNA Self-Collection Kits produced by DNAgenotek. DNA was extracted from saliva in accordance with the manufacturer's instructions. The DBH C-1021T SNP (rs1611115) was genotyped using an Applied Biosystems TaqMan assay for allelic discrimination on an Applied Biosciences 7900HT Real Time PCR machine.

Results

Genotype counts for the DBH C-1021T marker were as follows: C/C=113; C/T=75, T/T=13. Allele frequencies were in Hardy-Weinberg equilibrium ($\chi^2 = .014$, $p = .995$) and similar to those previously reported.

Despite the instruction that participants' responses should be time-locked with the flashing X, mean reaction times varied between 239 and 696 ms. Total number of errors of commission, errors of omission and mean reaction time across DBH genotype are listed in Table 1. Initial inspection of the data indicated that the distributions for all three variables were positively skewed. Subsequent analyses were therefore performed on data which had been subjected to a square root transformation, after which they were observed to be normally distributed. Three large outliers were removed from the data as it was felt that the exceptionally high number of errors committed by these individuals reflected a failure to perform the task correctly rather than a deficit in attention.

A strong negative correlation ($r = -.74$, $p < .001$) was observed between errors of commission and mean reaction time, indicating that participants who reacted more quickly failed to withhold their response to the presentation of the number 3 more frequently. A weaker, but nonetheless significant, positive correlation was observed between mean reaction time and errors of omission ($r = .206$, $p < .001$). No significant correlation was observed between errors of commission and omission.

One-way analyses of variance indicated no significant differences in performance of any measure between participants classified as Irish and those from other ethnic backgrounds.

Simple linear regressions were performed to determine the effect of DBH C-1021T genotype on the three variables of interest. Following Bonferroni correction, C-1021T genotype was found to significantly predict errors of commission ($F = 6.905$, $p < .05$; $r^2 = .034$). Fig. 1 displays a linear increase in errors of commission with increasing T allele dosage. It can be seen from this figure that participants homozygous for the T allele made considerably more errors of commission than participants with 1 or 2 copies of the C allele. The descriptive statistics listed in Table 1 indicate that T homozygotes also tended to make more errors of omission and use a faster reaction time than participants possessing any copies of the C allele, *however these differences were not significant at the .05 level ($F = .347$, $p > .05$, $r^2 = .002$; $F = .652$, $p > .05$, $r^2 = .003$ respectively).*

Discussion

This is the first study to demonstrate an association between a functional DBH gene polymorphism and sustained attention in healthy participants. DBH genotype was found here to predict sustained attention lapses; participants with more copies of the DBH T allele committed more errors of commission in the SART than those with fewer copies. These participants also tended to make more errors of omission and to react more quickly, but these differences were not statistically significant.

The T allele leads to a slower rate of dopamine-noradrenaline conversion than the C allele (Zabetian *et al.*, 2001), and is therefore presumed to result in higher levels of extrasynaptic dopamine and relatively lower levels of noradrenaline. The reduced availability of noradrenaline occasioned by the T allele may have had its effect on sustained attention in a number of ways. Noradrenaline is thought to improve alerting during sustained attention tasks (Coull *et al.*, 1995), and so decreased levels of noradrenaline may reduce participants' capacity to remain alert throughout the task. This, in combination with the findings that noradrenaline plays a role in target detection (Nieuwenhuis *et al.*, 2005) and reduces susceptibility to distractors (Robbins, 1984), may at least in part explain the failure of participants with greater T allele dosage to withhold their response to the target digit.

Errors of commission may be taken as evidence of failures in both sustained attention and response inhibition (O'Connell *et al.*, 2008). Previous research has indicated that lowered noradrenaline levels may lead to decreased ability to inhibit inappropriate responses (Chamberlain, Muller, Blackwell, Clark, Robbins & Sahakian, 2006; Eagle, Bari & Robbins, 2008). Possession of the T allele, and in particular two copies of that allele, may therefore predispose participants towards more frequent errors. A strong negative correlation was observed between errors of commission and mean reaction time, indicating that participants who make more slips of attention also tend to respond more quickly. This suggests that the poorer attentional capacity of these participants may lead to increased automaticity of responding and a corresponding speeding of responses, as faster response times have been shown to precede commission errors (Dockree, Kelly, Robertson, Reilly & Foxe, 2005; Robertson *et al.*, 1997). An alternative explanation may be that the T allele is linked with a faster, more impulsive style of responding than the C allele, however the notable, though statistically insignificant, increase in errors of omission in participants with two copies of the

T allele seems to support the notion of a drifting of attention in these participants, and a general failure to stay on task.

In summary, a functional SNP within a noradrenergic gene (DBH) has been shown here to be associated with performance on a well-validated test of sustained attention in healthy participants. We suggest that genetic variation in the DBH gene may influence sustained attention via its effects on the physiological efficiency of fronto-parietal networks.

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Figures and tables

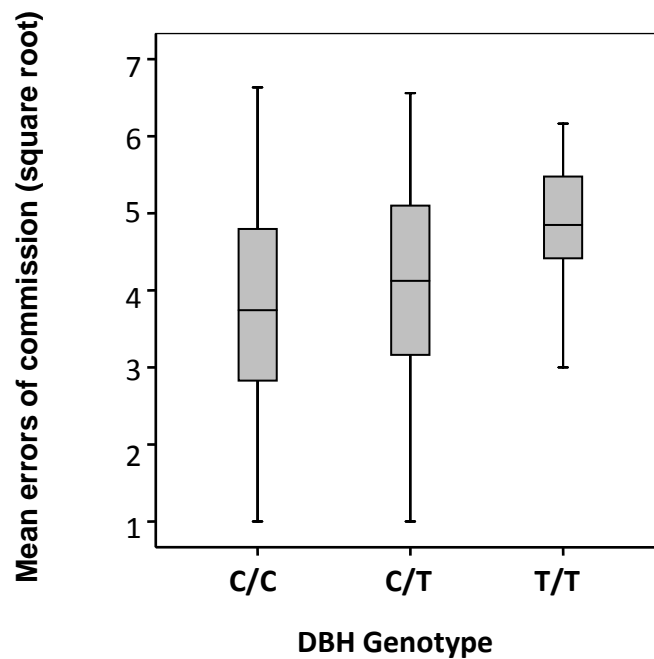


Fig. 1. SART errors of commission following square root transformation as a function of DBH genotype

Table 1

Means and standard deviations of errors of commission, errors of omission and reaction time for each DBH genotype group¹

<i>DBH C-1021T genotype</i>	<i>Commission errors Mean (SD)</i>	<i>Omission errors Mean (SD)</i>	<i>Reaction time (ms) Mean (SD)</i>	<i>N</i>
C/C	15.92 (9.5)	3.05 (6.7)	386.50 (84.42)	113
C/T	17.69 (10.75)	3.40 (5.45)	388.81 (94.09)	73
T/T	22.46 (9.36)	4.54 (7.5)	359.64 (62.11)	12

¹All mean values in this table are based on raw (untransformed) data