Dissociable Catecholaminergic Modulation of Visual Attention
Differential Effects of Catechol-O-Methyltransferase and Dopamine Beta-Hydroxylase Genes on Visual Attention
Shalev, Nir; Vangkilde, Signe; Neville, Matt J.; Tunbridge, Elizabeth M.; Nobre, Anna C.; Chechlacz, Magdalena

Published in:
Neuroscience

DOI:
10.1016/j.neuroscience.2019.05.068

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

Document license:
CC BY

Citation for published version (APA):
Shalev, N., Vangkilde, S., Neville, M. J., Tunbridge, E. M., Nobre, A. C., & Chechlacz, M. (2019). Dissociable Catecholaminergic Modulation of Visual Attention: Differential Effects of Catechol-O-Methyltransferase and Dopamine Beta-Hydroxylase Genes on Visual Attention. Neuroscience, 412, 175-189. https://doi.org/10.1016/j.neuroscience.2019.05.068
Dissociable Catecholaminergic Modulation of Visual Attention: Differential Effects of Catechol-O-Methyltransferase and Dopamine Beta-Hydroxylase Genes on Visual Attention

Nir Shalev a, b, c, Signe Vangkilde d, Matt J. Neville e, f, Elizabeth M. Tunbridge g, h, Anna C. Nobre e, b, c, g and Magdalena Chechlacz i, j, k, *

a Department of Experimental Psychology, University of Oxford, Oxford, UK
b Oxford Centre for Human Brain Activity, University of Oxford, Oxford, UK
c Wellcome Centre for Integrative Neuroimaging, University of Oxford, Oxford, UK
d Department of Psychology, Center for Visual Cognition, University of Copenhagen, Copenhagen, Denmark
e Oxford NIHR Biomedical Research Centre, University of Oxford, Churchill Hospital, Oxford, UK
f Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford, UK
g Department of Psychiatry, University of Oxford, Oxford, UK
h Oxford Health NHS Foundation Trust, Oxford, UK
i Centre for Human Brain Health, University of Birmingham, Birmingham, UK
j School of Psychology, University of Birmingham, Birmingham, UK
k Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, USA

Abstract—Visual attention enables us to prioritise behaviourally relevant visual information while ignoring distraction. The neural networks supporting attention are modulated by two catecholamines, dopamine and noradrenaline. The current study investigated the effects of single nucleotide polymorphisms in two catecholaminergic genes – COMT (Val158Met) and DBH (444 G/A) – on individual differences in attention functions. Participants (n = 125) were recruited from the Oxford Biobank by genotype-based recall. They were tested on a continuous performance task (sustained attention), a Go/No-Go task (response inhibition), and a task assessing attentional selection in accordance with the Theory of Visual Attention (TVA). We found a significant effect of DBH genotype status on the capacity to maintain attention over time (sustained attention) as measured by the continuous performance task. Furthermore, we demonstrated a significant association between COMT genotype status and effective threshold of visual perception in attentional selection as estimated based on the TVA task performance. No other group differences in attention function were found with respect to the studied genotypes. Overall, our findings provide novel experimental evidence that: (i) dopaminergic and noradrenergic genotypes have dissociable effects on visual attention; (ii) either insufficient or excessive catecholaminergic activity may have equally detrimental effects on sustained attention. © 2019 The Authors. Published by Elsevier Ltd on behalf of IBRO. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Key words: attentional selection, sustained attention, COMT, DBH, individual differences, catecholamines.

INTRODUCTION

The term ‘visual attention’ refers to the set of cognitive processes that enables an individual to stay focussed on the task at hand by selecting behaviourally relevant visual information while ignoring distractors (Posner, 1980; Nobre and Kastner, 2014). Attention-related mechanisms are often distinguished on the basis of how attention is focussed or distributed over time (‘sustained attention’ and ‘alertness’; e.g., Parasuraman, 1998; Petersen and Posner, 2012; Posner and Petersen, 1990; Robertson et al., 1997; Sturm and Willmes, 2001) or over space or objects (i.e., ‘orienting attention’; Nobre and Mesulam, 2014; Petersen and Posner, 2012; Posner and Petersen, 1990). Most theories of attention share the basic assumption that it is best understood as a heterogeneous, multifaceted system, and different theoretical frameworks describe distinct parameters considered essential to specific types of attention (e.g., Duncan and Humphreys, 1989; Posner and Petersen, 2019).
The current study aimed to explore common and dissociable effects of catecholamines on visual attention by examining the impact of single nucleotide polymorphisms in two catecholaminergic genes – COMT (Val<sup>158</sup>Met) and DBH (444 G/A) – on inter-individual variability in performance on tasks measuring different aspects of attention function. In contrast to previous studies, we systematically explored the influence of catecholaminergic genotypes on distinct attention-related functions rather than restricting the enquiry to a single attentional function. We employed three theoretically motivated tasks, focussing on either the mechanisms of how attention is focussed and distributed over time or factors underlying efficiency of attentional selection. Specifically, we used two versions of the modified Continuous Performance Task (CPT), differing in the target–distractor ratio in order to measure either sustained attention or response inhibition (Shalev et al., 2016, 2018b; Young et al., 2018). Compared to other frequently used measures of sustained attention and response inhibition (e.g., Robertson et al., 1997; Ballard, 2001), the employed here CPT tasks use masking and conjunctive sets of stimuli. These modifications have been previously shown to increase sensitivity to temporal changes in performance patterns (Shalev et al., 2016, 2018b). To test attentional selection, we used a task implementing the computational theory of visual attention (TVA, Bundesen, 1990). The TVA model assesses attentional selection and capacity based on assumptions of limited processing resources and of the biased competition model of attention (Desimone and Duncan, 1995). According to TVA, visual attention is described as a parallel processing race in which visual objects compete simultaneously for representation in a short-term memory store with a limited capacity. The winners of the race are encoded in the short-term memory store and made available for conscious recognition and action. The probability of winning the race and the processing rate of a given object are influenced by attentional weights (i.e., the processing capacity allocated to each object) and perceptual biases (i.e., the tendency to categorise the object as belonging to a certain category). The mathematical implementation of the TVA model enables estimation of five theoretical parameters: visual short-term memory capacity, processing speed, perceptual threshold, spatial bias and top-down selectivity index (see methods section for full details; Bundesen, 1990; Kyllingsbaek, 2006; Kyllingsbaek et al., 2011). Importantly, it has been previously shown that attentional selectivity and capacity measures derived in accordance with the TVA model are unrelated to sustained attention measures (McAvinue et al., 2012; Shalev et al., 2018a). This ensures that the tasks employed here indeed provide measures of distinct, independent attention functions.

The Val<sup>158</sup>Met COMT polymorphism (rs4680; guanine to adenine missense mutation at position 158, resulting in valine [Val] to methionine [Met] substitution; Chen et al., 2004; Lachman et al., 1996; Tunbridge et al., 2006; Tunbridge et al., 2007) affects activity of the COMT enzyme, involved in the degradation of the cortical dopamine (Matsudo et al., 2003a; Matsumoto et al., 2003b; Tunbridge et al., 2006; Yavich et al., 2007). The Met allele produces a
COMT isoform with reduced enzymatic activity, and subsequently Met/Met carriers are predicted to have the highest amounts of prefrontal dopamine, and Val/Val carriers the lowest (Lotta et al., 1995; Chen et al., 2004; Tunbridge et al., 2006; Tunbridge et al., 2007). The second studied here SNP, the 444 G/A DBH polymorphism (rs1108580; guanine to adenine substitution at position 444 within exon 2 of the DBH gene located on the chromosome 9) affects activity of DßH enzyme, which influences the balance between the two catecholamines by converting dopamine to noradrenaline (Kauffman and Friedman, 1965; Bourdelat-Parks et al., 2005; Zhang et al., 2010). The A allele has been associated with lower levels of the DßH enzyme and thus less noradrenaline compared to the G allele (Cubells et al., 1998; Cubells et al., 2000; Cubells and Zabetian, 2004).

Both COMT (Val158Met) and DBH (444 G/A) have been previously linked to variability in cognitive performance. The Val158Met COMT polymorphism has been predominantly studied with respect to its impact on executive function and working memory (e.g., Egan et al., 2001; Tunbridge et al., 2004; Bertolino et al., 2006; Barnett et al., 2007; Frank et al., 2007; Farrell et al., 2012; Tunbridge et al., 2012; Jaspar et al., 2015). Although, some studies have also examined its effects on attention-related functions, in particular cognitive benefits of higher dopamine levels on spatial orientation bias (Holmboe et al., 2010). While prior studies have only demonstrated a strong effect of 444 G/A DBH polymorphism on spatial working memory performance (Parasuraman et al., 2005; Greenwood et al., 2009), another DBH polymorphism (rs1611115, –1021 C/T SNP; cysteine to thymidine substitution at position 1021 within the promoter region of the DBH gene) has been reported to affect sustained attention (Greene et al., 2009).

Taken together, we hypothesised that we would find differential effects of COMT (Val158Met) and DBH (444 G/A) polymorphisms on visual attention. Specifically, we predicted that while the COMT Val158Met genotype status would affect attentional selection measures, namely visual short-term memory capacity, spatial bias and top-down selectivity index estimated in accordance with the TVA model, the DBH 444 G/A genotype status would be associated with differences in sustained-attention capacity.

**EXPERIMENTAL PROCEDURES**

**Participants**

One hundred and twenty-five participants (mean ± SD age = 44.8 ± 4.3) were recruited from the Oxford Biobank by genotype-based recall to warrant comparable allele frequency. The Oxford Biobank consists of a sample of more than 7124 genotyped male and female individuals (age 30–50) in Oxfordshire who have consented to be re-approached for a ‘recruit-by-genotype’ participation in various biomedical studies. Given known sexual dimorphisms in the function of one of the studied genes (COMT, Tunbridge and Harrison, 2011), only male participants who were either homozygous for COMT Val158Met or DBH 444 G/A were selected and contacted by post (n = 706). All individuals who responded positively (n = 174) were invited to attend cognitive testing as described below. Subsequently, a total of 125 participants completed one testing session conducted in a double-blind fashion (genotype status unknown to both experimenter and participant at the time of testing). Two separate sets of analyses were conducted (see Statistical Analyses section), and thus participants were split into groups based on either DBH (A/A group, n = 42; mean age 44.6; SD 4.6; G/G group, n = 47; mean age 44.9; SD 4.2; G/A group; n = 36; mean age 45; SD 4.4) or COMT (Val/Val group, n = 42; mean age 45.9; SD 4.2; Met/Met group, n = 43; mean 45.1 age; SD 4.3; Val/Met group, n = 40; mean age 43.4; SD 4.3) genotype status. All participants had either normal or corrected-to-normal vision. Both left- and right-handed participants were recruited for the study, and the hand dominance was assessed according to the Edinburgh handedness inventory (Oldfield, 1971; mean score 61.9, SD 51; 101 right handed, 13 left handed, 11 ambidextrous). None of the genotype groups differed significantly in their mean age and handedness. All study participants provided written informed consent, in compliance with the relevant protocols approved by the University of Oxford Central University Research Ethics Committee. All experimental procedures were conducted in accordance with the latest version of the Declaration of Helsinki.

**General procedure**

All participants were tested on three tasks, in the following order: 1) a Continuous Performance Task (CPT) to measure sustained attention (CPT-SA; approximately 15 min), 2) a CombiTVA task to assess selective attention (TVA-based assessment; approximately 45 min), and 3) a CPT Go/No-go version (CPT-GNG; approximately 15 min) to measure response inhibition. The whole testing session lasted 1.5 h. A personal computer with Intel i7 processor and a dedicated 2GB AMD video card was used for displaying stimuli and recording data. The two CPT tasks were generated and administered using Presentation software (Neurobehavioral Systems, Albany, CA), and the CombiTVA paradigm was generated and administered using E-prime 2 Professional software (Psychology Software Tools, Inc.). The stimuli were presented on a ViewSonic V3D245 LED monitor, with screen resolution of 1080×1920 and a screen refresh rate set at 100 Hz allowing display times varied in 10-ms gaps. At the start of each task all stimuli were pre-loaded to memory to minimise temporal noise.

**CPT-SA and CPT-GNG tasks**

We used two versions of the Continuous Performance Task (CPT; Shalev et al., 2018b), differing only in the target–distractor ratio as described below. Following the convention in testing inhibition and sustained attention, the CPT version with the high proportion of targets was used to measure response inhibition as a ‘Go/No-Go’ task i.e., CPT-GNG
task (e.g., Young et al., 2018) and the version with low target proportion was used to test sustained attention i.e., CPT-SA task (e.g., Shalev et al., 2016, 2018b).

Design and stimuli
A coloured mask (Mask), comprising of four superimposed figures in different colours (square, triangle, circle and hexagon) appeared at the centre of the screen. The total size of the mask occupied 3° × 3° visual angle. In order to avoid habituation effects, we generated minor movement of the Mask. The movement was generated by alternating every 10–20 ms between two mask-images, one of which had thicker outlines for the superimposed figures (the two alternating mask images are illustrated in Fig. 1B). The mask appeared at the centre of the screen and disappeared only when it was replaced by either a target or a distractor shape for 150 ms; the mask then reappeared immediately, generating pre- and post-masking of each target or distractor. The target shape was a red circle, and the distractor stimuli were either similar in colour to the target (red hexagon and red triangle), similar in shape (blue circle and yellow circle), or completely different (yellow hexagon and blue hexagon). All distractor types appeared in equal proportion. All distractors and target shapes fit in a square of 3° × 3° visual angle. The inter-stimulus interval was jittered between 1000 and 5000 ms (See Fig. 1A for a schematic outline of the experimental procedure). Participants were told that the constant shape which appeared at the centre of the screen (the Mask) would be replaced briefly by another shape every few seconds. The task was to press the response button as quickly as possible whenever participants recognised a red circle at the centre of the screen. Participants were further instructed to do nothing when they saw any other shape.

Procedure
The task started with a short practice block (15 trials), and the experimenter monitored participants’ responses at this stage to ensure the instructions were clear. After finishing the practice session, the participants performed the whole session without any break until the task terminated after approximately 10 min. The task comprised 180 trials. In the CPT-SA task, the target appeared on 60 trials (33% target), and there were 120 distractor trials (67%) in which one of six possible distractors appeared on the screen with equal probability and in randomised order (red square / red triangle / blue circle / blue triangle / yellow circle / yellow triangle). The CPT-GNG design was the same except for the larger proportion of target stimuli (67%) relative to distractor stimuli (33%).

Estimation of the CPT parameters
For each participant, we extracted the following behavioural data: the number of correct responses to targets and their associated reaction times, the number of correct rejections of distractors, the number of false alarms (i.e., classifying a distractor as a target), and the number of missed targets. The time window for response was set to 1 s. To assess sustained attention, we calculated two outcome measures based on the CPT-SA task performance: the standard deviation of reaction times during the entire task (RT-SD) representing the stability of responses throughout the task; and the percentage change in perceptual sensitivity between two task-halves (d’-change), representing the capacity to maintain attention over time on task. The d’ was calculated based on the Signal Detection Theory (SDT) as the distance between the standardised values of correct response and false alarm rates (Green and Swets, 1966; Stanislaw and Todorov, 1999). To assess response inhibition based on the CPT-GNG task performance, we extracted the number of false-alarms and calculated the percentage of responses classifying a distractor as a target (false alarms). For the purpose of supplementary analysis, we also calculated perceptual sensitivity d’ based on the CPT-GNG task performance. For a detailed discussion on the continuous performance task design and the validity of derived sustained attention and response measures see Shalev et al. (2018b).

CombiTVA task
We employed the CombiTVA paradigm (Vangkilde et al., 2011; Fig. 2) to assess attentional selection parameters based on Bundesen’s TVA framework. Both whole- and partial-report tasks were intermixed on different trials (Bundesen, 1990).

Design and stimuli
At the beginning of each trial, a red fixation cross appeared in the centre of the screen for 1000 ms, followed by a blank screen presented for 100 ms and then by the stimulus display. The stimulus display could be of one of two conditions, presented in random order. In whole-report arrays either two
or six red letters appeared on the screen; in partial-report arrays two red target letters and four distractor blue letters appeared on the screen. The letters were presented within six fixed placeholders equally distributed on the perimeter of an invisible circle \((r = 7.5°\) of visual angle). The stimulus display consisted of letters chosen randomly without repeats from a set of 20 capital letters (ABDEFGHJKLMNORSTVXZ) with Arial font size corresponding to \(2.7° \times 2.3°\) of visual angle. The display appeared for one of six fixed durations of 10, 20, 50, 80, 140 or 200 ms (randomly presented and equally distributed) and was followed by a masking noise on each of the fixed placeholders lasting 500 ms. Following the mask, participants were presented with a blank response display and were prompted to recall as many red letters as they could, using the computer keyboard, and to press ‘SPACE’ key when done. The response display appeared for an unlimited time and the reported letters were visible on the screen until the initiation of the next trial following the press of ‘SPACE’ key.

**Procedure**

The task started with a short practice block (24 trials), during which the experimenter monitored participants’ responses to ensure that they understood the task instructions. Following the practice session, participants performed nine experimental blocks consisting of 36 trials each. The six possible exposure times of the stimulus displays, as well as the different three types of stimulus display appeared in a random order throughout the task. The target and distractor letters were chosen randomly on each trial. The participants were told that their reaction speed was not being monitored, and they should report all the red letters they were “fairly certain” of having seen and refrain from pure guessing. Such instructions are commonly used in TVA based tasks (e.g., Vangkilde et al., 2011; Vangkilde et al., 2012; Habe-kost et al., 2014). Following practise block and then each experimental block, the participants were informed of their accuracy rate. They were asked to try to maintain an accuracy range of 80%–90%; they were told that if their accuracy was higher, they should try to be less conservative when reporting letters, conversely, if their accuracy was lower, it meant they were guessing too many letters and they should try to be more accurate (more conservative). The whole procedure lasted approximately 45 min.

**Estimation of TVA parameters**

The TVA model (Bundesen, 1990) is a mathematical formalisation based on the “biased competition” account of visual attention. Visual categorizations of individual items (i.e., ascribing features to objects) are proposed to compete to be encoded into a limited capacity visual short-term memory (VSTM). The categorisation of a visual element is accomplished once it has been encoded to VSTM. This race model is normally described by two main equations: the rate equation and the weight equation. The rate equation describes the rate \(v(x, i)\) at which a particular visual categorisation ‘\(x\) belongs to \(i\)’ is encoded into VSTM. The rate is determined as a product of three terms: \(\eta(x, i)\) which
represents the strength of the sensory evidence in favour of
categorising \( x \) as belonging to category \( i \); \( \beta_i \) which re-

presents the perceptual decision bias associated with category
\( i \); and \( \frac{W_x}{\sum_{z \in S} W_z} \) which determines the relative attentional
weight of object \( x \) divided by the sum of the attentional
weights of all objects within the visual field (\( S \)). These three
terms comprise the rate equation:

\[
v(x, i) = \eta(x, i) \beta \left( \frac{W_x}{\sum_{z \in S} W_z} \right)
\]

The sum of all rate values (\( v \)) across the visual field
defines the overall processing speed (\( C \)), formally:

\[
C = \sum_{i \in S} v(x) = \sum_{i \in S} \sum_{x \in R} v(x, i)
\]

The second key equation, the weight equation, describes
how attentional weights (\( w \)-values) are allocated to the per-
ceived elements according to their pertinence value \( \eta_i \). The
pertinence value is defined by the momentary importance of
attending a perceived element \( x \) as belonging to a category
\( j \), where \( R \) is the set of all categories \( \eta(x, j) \). The weight equation:

\[
W_z = \sum_{y \in R} \eta(x, y) \pi_y
\]

Finally, we used a partial-report paradigm where partici-
pants were requested to attend and report targets while
ignoring irrelevant distractors (defined by a colour feature).
Under the assumption that every target on a given display
has approximately the same weight \( w_{\text{target}} \), and every dis-
tractor has the same weight \( w_{\text{distractor}} \) we determine the \( \alpha \)
value which defines the efficiency of top-down control as

\[
\alpha = \frac{W_{\text{distractor}}}{W_{\text{target}}}
\]

When applied to the CombiTVA data, these equations
(see also, Bundesen, 1990) allow for the extraction of multi-
ple independent theoretical parameters representing differ-
ent aspects of attention (Vangkilde et al., 2011). The
extraction of the theoretical attentional parameters from
TVA-based data is based on a maximum-likelihood fitting
procedure introduced by Kyllingsbaek (2006) and elabo-
rated by Dyrholm et al. (2011). The output of the fitting algo-

rithm includes five theoretical parameters: (1) Parameter \( K \)
is an estimation of the visual short-term memory capacity,
measured in number of letters that can be stored; (2) Parameter \( t_0 \) is the perceptual threshold, defined as the minimum
exposure duration required to evoke conscious perception,
measured in milliseconds; (3) Parameter \( C \) is the visual pro-
cessing speed, or processing rate, measured in number of
letters processed per second; (4) The spatial bias param-
eter \( w_{\text{index}} \) which represents the ratio between the sum
of the attentional weights assigned to items on the left,
and the overall sum of all attentional weights. The
parameter ranges between 0 and 1, with a value of 0.5 indi-
cating symmetrical attentional weighting; a value closer to 0
indicates an attentional bias to the right, and a value higher
than 0.5 indicates an attentional bias to the left side of the
visual field; (5) The top-down selectivity index \( \alpha \) defined as
the ratio between the attentional weights allocated to a dis-
tractor and to a target. The resulting \( \alpha \) value ranges
between 0 and 1, with the lowest score indicating perfect
selectivity (no attentional weight given to irrelevant distrac-

tors). In total, the applied model had 9 degrees of freedom
(\( df \)): \( K \), 5 \( df \) (the \( K \) value reported is the expected \( K \) given
a particular distribution of the probability that on a given trial
\( K = 1, 2, 3, 4, 5, \) and 6); \( t_0 \), 1 \( df \); \( C \), 1 \( df \); \( w_{\text{index}} \), 1 \( df \;\) and \( \alpha \), 1
\( df \). For a detailed overview of the TVA-derived attentional
selection parameters and their correlates, see Habekost
(2015).

The equations are implemented in the MATLAB (Math-
Works Inc.) software, the LibTVA modelling toolbox
(Dyrholm, 2011) which is available from the website http://
www.machlea.com/mads/libtva.html.

The supplementary analyses examining how COMT gen-
otype status affects the perceptual threshold were carried
out using raw data instead of \( t_0 \) parameter calculated as
above. Specifically, based on the raw data we
estimated and entered into our analyses, the mean number
of errors made and the mean number of identified letters at
each exposure duration (10, 20, 50, 80, 140 and 200 ms).

**Model diagnostics**

We performed the goodness-of-fit calculations to provide
estimation of the variation in the observed individual mean
scores accounted for by the maximum-likelihood fits and
the difference between the observed and the predicted
data. The variation was calculated per participant as the
\( \text{R}^2 \) between the observed and predicted values. The
difference between the observed and the predicted mean
scores was calculated per participant as the squared numerical
difference between the observed and the predicted scores
for each condition divided by the number of conditions and then
taking the root of the result. The obtained maximum-
likelihood fits were excellent, accounting for an average of
88% of the variation in the observed individual mean
scores (i.e., the percentage of variance in the observed individ-
ual mean scores accounted for by the maximum-likelihood fits),
and correspondingly, the difference between observed and
predicted mean scores was on average of 0.26 across all
conditions. Please see also Fig. 3 for a direct comparison
between the observed (i.e., mean number of correctly
reported letters) and the predicted data at different exposure
durations. The mean Pearson’s correlation between the
observed data and the predicted data was \( r = 0.94 \) (\( p < .001 \)). Finally, we conducted ANOVA tests for inde-
pendent samples, with the variation in the observed indivi-
dual mean scores and the difference between the
observed and the predicted data as the dependant vari-
ables, and the genotype groups (COMT and DBH) as the
independent variables. The ANOVA tests indicated that
there were no differences between genotype groups in the
We employed a stepwise regression analysis with the two genotypes being used as genotype status on different aspects of attention, we used a type status (DBH 444 G/A versus COMT Val 158Met) on distinct measures of attention as assessed by the three tasks. The dependent variables were: 1) d’-change, representing capacity to maintain attention over time (sustained attention) based on CPT-SA task performance; 2) RT-SD, representing response stability as assessed based on CPT-Sorting task performance; 3) false-alarms rate, representing response inhibition as assessed based on CPT-GNG task performance; further dependent variables estimated based on the CombiTVA task performance included: 4) Visual-Short Term Memory (VSTM) capacity; 5) Perceptual threshold; 6) Visual processing speed; 7) Top-down selectivity index; and 8) Spatial bias.

Following the regression analysis, we conducted a series of additional analyses to further explore the observed effects. To do so, we carried out a series of t tests and ANOVA’s with either DBH or COMT Val allele dosage as the independent factors.

All statistical analyses were performed using either MATLAB (MathWorks Inc.) or SPSS (Ver 24; IBM Corp, 2016).

**RESULTS**

As illustrated in Table 1 a stepwise regression analysis showed a significant effect of DBH genotype on the capacity to maintain attention over time (d’-change, sustained attention) as measured by the CPT-SA task performance, and a significant effect of the COMT genotype on the perceptual threshold estimated based on the CombiTVA task performance. In the following sections we systematically report results of the additional analyses conducted to further explore these effects. Figs. 4 and 5 present descriptive data for the distinct measures of attention assessed by the three

---

**Table 1.** The output from the stepwise regression analysis employed to examine the effect of DBH 444 G/A and COMT Val158Met genotype status and their interactions (independent factors) on different aspects of attention (dependent variables). Significant results are reported in bold.

| Attention index | Factors | Coefficients | Standard Errors | p-values |
|-----------------|---------|--------------|-----------------|----------|
| d’-change (‘sustained attention’) | COMT | 0.0236 | 0.0448 | 0.59 |
| False-alarms rate (‘response inhibition’) | DBH | 0.1164 | 0.0454 | 0.01* |
| False-alarms rate (‘response inhibition’) | COMT X DBH | 0.0104 | 0.0196 | 0.59 |
| RT-SD (‘performance stability’) | DBH | 4.4739 | 3.2910 | 0.17 |
| Visual short-term memory capacity | COMT | 5.2376 | 3.3418 | 0.11 |
| Visual short-term memory capacity | COMT X DBH | 1.8233 | 1.0834 | 0.09 |
| Perceptual threshold | DBH | 0.0016 | 0.0039 | 0.68 |
| Processing speed | DBH | 0.0030 | 0.0040 | 0.93 |
| Spatial bias | DBH | 0.0019 | 0.0013 | 0.47 |
| Top-down selectivity index | COMT X DBH | 0.0377 | 0.0247 | 0.13 |

---

**Statistical analyses**

To assess the effect of DBH 444 G/A and COMT Val158Met genotype status on different aspects of attention, we used a regression analysis with the two genotypes being used as predictors, and task indices as the dependent variables. We employed a stepwise fitting procedure, in which the first step included the genotype status, and the second step included the interaction between the two genotypes. In accordance with our hypotheses as presented in the introduction, we expected to find a differential effect of the genotype status (DBH 444 G/A versus COMT Val158Met genotype) on distinct measures of attention as assessed by the three tasks. The dependent variables were: 1) d’-change, representing capacity to maintain attention over time (sustained attention) based on CPT-SA task performance; 2) RT-SD, representing response stability as assessed based on CPT-Sorting task performance; 3) false-alarms rate, representing response inhibition as assessed based on CPT-GNG task performance; further dependent variables estimated based on the CombiTVA task performance included: 4) Visual-Short Term Memory (VSTM) capacity; 5) Perceptual threshold; 6) Visual processing speed; 7) Top-down selectivity index; and 8) Spatial bias.

Following the regression analysis, we conducted a series of additional analyses to further explore the observed effects. To do so, we carried out a series of t tests and ANOVA’s with either DBH or COMT Val allele dosage as the independent factors.

All statistical analyses were performed using either MATLAB (MathWorks Inc.) or SPSS (Ver 24; IBM Corp, 2016).

**RESULTS**

As illustrated in Table 1 a stepwise regression analysis showed a significant effect of DBH genotype on the capacity to maintain attention over time (d’-change, sustained attention) as measured by the CPT-SA task performance, and a significant effect of the COMT genotype on the perceptual threshold estimated based on the CombiTVA task performance. In the following sections we systematically report results of the additional analyses conducted to further explore these effects. Figs. 4 and 5 present descriptive data for the distinct measures of attention assessed by the three
tasks as a function of either the DBH 444 G/A or the COMT Val158Met genotype status, respectively.

**The effect of DBH 444 G/A genotype status on sustained attention (d’ change)**

The regression analysis revealed that the DBH genotype status affects how the performance on CPT-SA task changes over time (d’ change; Table 1). We next conducted a series of complementary analyses to identify the source of the observed effect.

First, we wanted to examine whether the difference in the d’-change index was driven by a significant difference in performance between the two task-halves among the three DBH 444 G/A genotype groups. Thus, we carried out a
repeated measures ANOVA, with the task half as a within-subjects factor and DBH 444 G/A genotype as a between-subjects factor and target sensitivity – $d'$ (calculated based on CPT-SA task performance) – as the dependent factor. In the above analysis we included COMT Val$^{158}$Met genotype status as a covariate to assure there were no interactions and to co-vary out the effect of other genotype. ANOVA showed a significant interaction of Genotype × Half ($F(2,117) = 7.837; p = .001$; Partial $\eta^2 = 0.118$). There were no other main effects and the COMT genotype did not interact with any of the variables (all $p$'s $\gg 0.1$). To validate specificity of the effect of DBH genotype on sustained attention, we conducted a supplementary ANOVA (as above) contrasting the three DBH genotype.

Fig. 5. The effect of COMT Val$^{158}$Met genotype status on the measures of attention functions: sustained attention (A) $d'$ change and (B) RT-SD as assessed by the CPT-SA task performance; (C) response inhibition as assessed by the CPT-GNG task performance; (D) processing speed; (E) VSTM capacity; (F) perceptual threshold; (G) top-down selectivity index and (H) spatial bias as estimated based on the CombiTVTA task performance. The Val/Val group showed a significantly lower perceptual threshold compared to other two groups (*$p < .05$). No other group differences in attentional function were found with respect to the COMT genotype. Each column chart represents mean task measures ±SE.
groups but with respect to the change in perceptual sensitivity d’ between two halves of the CPT-GNG task. The CPT-GNG and CPT-SA tasks have a very similar overall experimental design (same stimulus set and task length) but a different target–distractor ratio. The higher number of targets in CPT-GNG task lowers the requirement for sustained attention, compared to the CPT-SA task. In contrast to the CTG-SA task, no group differences were found with respect to the DBH genotype and d’ measure of change in target sensitivity between two halves of the CPT-GNG task (p = .565).

As illustrated in Fig. 4A, DBH heterozygotes showed a striking increase in performance over time. In contrast, both homozygote groups showed a slight decrease in their performance over time. Post-hoc tests for independent samples demonstrated a significant difference between the performance-change index (d’-change) in the G/A group when compared with the A/A group (t(76) = −2.926; p = .005; 95% CI [−0.05;−0.09]) and with the G/G group (t(81) = −2.866; p = .005; 95% CI [−0.42;−0.07]). The A/A and the G/G groups did not differ from one another (p = .5).

These results survived Bonferroni correction for multiple comparisons (a level, P = .017, corrected for 3 comparisons). Taken together our findings indicate a specific association between the DBH 444 G/A genotype status and sustained attention.

The effect of COMT Val158Met genotype status on perceptual threshold

The regression analysis revealed a significant effect of COMT genotype on perceptual threshold but not on any other measures of selective attention as derived in accordance with the TVA model (Table 1).

As illustrated in Fig. 5F, the perceptual threshold significantly decreased with increased Val allele dosage. Subsequent post-hoc comparison showed a lower perceptual threshold in the Val/Val group compared with both the Val/Met group (t(80) = 2.515; p = .014; 95% CI [0.02;0.20]) and the Met/Met group (t(83) = 2.609; p = .011; 95% CI [1.27;9.44]) groups. The Val/Met and the Met/Met groups did not differ (p = .79). These results survived Bonferroni correction for multiple comparisons (a level, P = .017, corrected for three comparisons). This trend was also confirmed using a specific test for a linear contrast, with the COMT Val allele dosage as the independent factor. The linear trend contrast was found significant (F(2,122) = 7.516; p = .007).

The perceptual threshold we examined here was defined in accordance with the TVA model (see Kyllingsbaek, 2006) and thus calculated as the minimum exposure duration (i.e., the minimum visual display duration in milliseconds) required to evoke conscious perception. To explore how COMT genotype was related to perceptual threshold, we carried out supplementary analyses focussing on the effect of the COMT genotype on direct measures of behavioural performance, namely on the mean number of errors made and the mean number of identified letters at each exposure duration (10, 20, 50, 80, 140 and 200 ms). Our aim was to examine whether the Val allele dosage indeed affects the overall sensitivity to perceptual signals versus whether it results in different performance strategies.

We first focussed on the effect of COMT genotype on the mean number of errors made at each exposure duration (Fig. 6). A 3 (between subjects factor: COMT genotype) × 6 (within subjects: exposure duration) ANOVA revealed a significant main effect of exposure duration (F(5,610) = 61.246; p < .001; Partial η² = 0.334). There was an interaction between exposure duration and COMT genotype (F(10,610) = 2.202; p = .016; Partial η² = 0.035) but no main effect of COMT genotype (p = .226). Post-hoc comparisons revealed that the interaction was driven by significant differences in the number of errors made between Val/Val genotype compared to Val/Met and Met/Met genotypes at the two shortest exposure durations (10 ms and 20 ms).

Specifically, there was a significant difference in the mean number of errors made between the Val/Val group and the Val/Met groups at 10 ms (t(80) = 2.515; p = .014; 95% CI [0.02;0.20]) and 20 ms (t(80) = 2.335; p = .022; 95% CI [0.01;0.22]) exposure durations, as well as between the Val/Val group and the Met/Met group at 20-ms exposure duration (t(83) = 2.151; p = .034; 95% CI [0.00;0.22]). In contrast, post-hoc comparisons revealed no significant group differences in the mean number of errors made at longer exposure durations i.e., 50, 80, 140 and 200 ms.

As illustrated in Fig. 6 and further demonstrated by the first series of comparisons (as above), the Val/Val carriers compared to the two other groups (Val/Met and Met/Met) were the least accurate (made highest number of errors) when comparing the responses made at the two shortest exposure durations i.e., 10 and 20 ms. To further explore the effect of performance strategy on the estimated perceptual threshold, we examined whether at the shortest exposure durations, the Val/Val group not only made more errors but also overall reported more letters irrespective of whether the reports are correct or not (Fig. 7). Thus, we applied a series of post-hoc tests comparing the mean number of reported letters at the different exposure durations between the genotype groups. There was a significantly larger number of reported letters in the Val/Val group.
Prior research indicates robust modulation of the PFC by catecholamines (e.g., Chandler et al., 2014; Clark and Noudoost, 2014), as well as some of the cognitive processes underlying visual attention (e.g., Bellgrove et al., 2007; Greene et al., 2009; Greene et al., 2010; Newman et al., 2012; Newman et al., 2014; Zozulinsky et al., 2014; Schneider et al., 2015). Even though in principle we replicate some of the previous findings linking functional polymorphisms in COMT and DBH to visual attention, in contrast to former reports our study directly demonstrates differential effects of these two polymorphisms on distinct cognitive processes underlying visual attention, rather than simply examines their effects on a singular attentional mechanism. Consequently, our findings provide novel experimental evidence that dopaminergic and noradrenergic genotypes exert dissociative cognitive effects on visual attention functions.

Furthermore, our study strongly supports the previously suggested notion of a non-linear “inverted U-shaped” association between levels of catecholamines and cognitive functioning (Arnsten and Goldman-Rakic, 1998; Arnsten and Li, 2005; Robbins and Arnsten, 2009; Cools and D’Esposito, 2011) by providing a novel genetic evidence that either insufficient or excessive catecholaminergic activity may have detrimental effects on sustained attention.

We present here experimental findings suggesting an association between COMT genotype and one of the selective attention measures, assessed based on the Bundesen’s TVA framework (Bundesen, 1990; Kyllingsbaek, 2006). When considering selective attention, the TVA model evaluates factors such as the capacity of the short-term memory supporting visual attention, the minimum exposure time required for visual stimuli to be perceived (perceptual threshold), the speed at which stimuli are processed once perceived, the attentional weights allocated to perceived elements (spatial bias), and the efficiency of top-down control (distractibility). Prior studies found associations between the Val158Met COMT polymorphism and cognitive performance indicative of working memory capacity, orientation bias, top-down control and distractibility (e.g., Bertolino et al., 2006; Tan et al., 2007; Holmboe et al., 2010; Zozulinsky et al., 2014; Jaspar et al., 2015; Schneider et al., 2015). Thus, we were somewhat surprised to find the effect of COMT genotype on perceptual threshold, rather than other TVA-derived attentional parameters, in particular visual short term memory, top-down selectivity or attentional weights. It should be also noted that in contrast to the prior studies indicating a cognitive benefit of Met allele (Holmboe et al., 2010; Jaspar et al., 2015; Schneider et al., 2015), our findings point to cognitive benefit of the Val allele, at least in the context of visual attention. Similar inconsistency has been previously reported in meta-analysis examining the cognitive effects of COMT (Val158Met) polymorphism, which have recounted various discrepancies and sometimes even opposing effects of the Met versus Val alleles on the performance of diverse cognitive tasks (Mier et al., 2010). However, our findings are also consistent with an alternative explanation. Namely, our secondary analyses indicate that the effect on Val allele dosage on the perceptual threshold (i.e., threshold below which no effective processing of visual

**DISCUSSION**

Here we show dissociable effects of catecholamines on visual attention, by means of examining the impact of two single-nucleotide polymorphisms in COMT (Val158Met) and DBH (444 G/A) on inter-individual variability in performance on behavioural tasks measuring sustained attention, response inhibition and selective attention assessed based on the TVA framework (Bundesen, 1990). Specifically, we demonstrate that effective threshold of visual perception in attentional selection is associated with COMT but not DBH genotype, and conversely sustained attention phenotype is associated with DBH but not COMT genotype.
stimuli takes place) might be a result of a trade-off between the number of reported letters and the number of errors made rather than directly on overall sensitivity to perceptual signals. At the short visual display durations, the increase in Val allele was associated with both an overall higher number of reported letters and errors made, potentially suggesting that Val allele is associated with pursuing a "high risk strategy" in performing the visual report task. In agreement with this observation, Farrell et al. (2012) reported an association between the Met allele and high-risk aversion ("low risk strategy"), as demonstrated by performance on a task involving a choice between gambling high versus low monetary amounts.

To assess links between inter-individual differences in sustained attention and catecholaminergic genotypes, we employed previously developed masked version of the continuous performance task (Shalev et al., 2018b). In contrast to a recent study by Park and Waldman (2014), who found an effect of the COMT (Val158Met) polymorphism on behavioural measures of sustained attention assessed with the continuous performance task, we did not observe any effects of COMT on any of the sustained attention indices. However, there were several possible explanations for this discrepancy. Firstly, Park and Waldman (2014) studied the influence of COMT (Val158Met) genotype status not in healthy participants (our study) but in a clinically selected sample consisting of children with a diagnosis of either ADHD, conduct disorder, or oppositional defiant disorder, and their healthy (not fulfilling the criteria for diagnosis) siblings and twins. This raises the possibility that COMT might be more relevant in clinical population, with sustained attention phenotype being one of the core functional trait of a disease. Secondly, while Park's and Waldman's study examined the association between the COMT (Val158Met) polymorphism and sustained attention in children of both genders (mean ± SD age, 12.2. ± 3.2), our study recruited only adult males (mean ± SD age, 44.8. ± 4.43) due to the previously reported sexual dimorphisms in the COMT function (Tunbridge and Harrison, 2011). Thus, the observed discrepancy, perhaps also result from developmental variance, consistent with changes in COMT expression levels and activity across human lifespan (Tunbridge et al., 2007). Finally, as both the task and the task-derived measures differ somewhat between the two studies, the derived findings may not be directly comparable (please see Shalev et al., 2018b for further discussion on the issue of continuous performance task design and the validity of derived sustained attention measures).

The data presented here suggest an effect of DBH (444 G/A) genotype on sustained attention. We observed here that G allele dosage was associated with the d’-change, indicative of change in target sensitivity over time i.e., indexing sustained attention. However, we have not observed any effects of DBH genotype on either performance fluctuation, as measured by the standard deviation of reaction times, or response inhibition. A similar association between DBH genotype and sustained attention has been reported by Greene and colleagues (Greene et al., 2009), although it should be noted that they showed the link between another common functional DBH polymorphism (−1021 C/T) and the number of commission errors during performance of a sustained attention to response task (SART). Greene et al. (2009) attributed the genotype differences in attentional performance to changes in noradrenaline (better cognitive performance resulting from increased levels of noradrenaline) based on known effects of noradrenaline on alertness and arousal (for review see Aston-Jones and Cohen, 2005; Thiele and Bellgrove, 2018). This noradrenaline-centric interpretation is consistent with the findings presented here, although an effect of dopamine (or the interaction between catecholamines) on the observed behavioural effects cannot be ruled out. As a caveat, the behavioural phenotype observed in DBH knock-out mice (who have a complete inactivation of DBH gene) has been attributed to both a complete lack of noradrenaline, and hypersensitive dopamine signalling (Mitchell et al., 2008). It should be also noted that studies examining the effects of DBH SNPs on decision-making performance and reward related behaviours have interpreted their findings in terms of dopaminergic rather than noradrenergic effects (e.g., Parasuraman et al., 2012).

Both rodent and primate studies provide compelling evidence for the model of an "inverted U-shaped" action of both dopamine and noradrenaline in the prefrontal cortex linked to cognitive abilities such as working memory and executive functions (e.g., Zahrt et al., 1997; Granon et al., 2000; Arnsten, 2007; Vijayraghavan et al., 2007). Similarly, using functional magnetic resonance imaging and pharmacological manipulations in human participants, Gibbs and D’Esposito demonstrated an inverted U-shaped dose effect of dopamine on working memory performance and brain activity (Gibbs and D’Esposito, 2005). Interestingly, in their review of pharmacological studies examining modulatory effects of catecholamines on cognitive performance, Robbins and Arnsten suggested that catecholamines might exert both linear and non-linear effects depending on the brain area under control and the nature of the performed cognitive task (Robbins and Arnsten, 2009). In the current study, we observed a significant cognitive benefit (relatively improved performance) in DBH 444 G/A heterozygotes compared to both A/A and G/G homozygotes, consistent with the hypothesis that both too little and too much catecholamine signalling (presumably here noradrenaline; see comments above) might impair sustained attention. In contrast, our COMT Val158Met findings reflect a linear allel-dose related model with regard to visual attention function, consistent with earlier studies of executive function (Egan et al., 2001; Holmboe et al., 2010; Jaspar et al., 2015; Schneider et al., 2015). Our findings therefore support the existence of a linear relationship between COMT genotype status and selective attention, with increasing Val allele dosage leading to a lower perceptual threshold potentially driven by a high-risk report strategy. Overall our findings are in agreement with Robbins and Arnsten’s proposal that the linear versus non-linear effects of catecholamines, dopamine and noradrenaline, vary depending on the brain area and cognitive function modulated by these neurotransmitters, highlighting the importance of high-precision...
behavioural testing which enable the dissociation of possible genetic effects on distinct attentional processes (Robbins and Amsten, 2009).

In conclusion, our findings provide novel genetic evidence for (i) dissociative dopaminergic and noradrenergic effects on visual attention; (ii) “inverted U-shaped” catecholaminergic action on human visual attention, specifically that either insufficient or excessive catecholaminergic activity may have equally detrimental effects on sustained attention. Thus, our study supports the notion of dissociative dopaminergic and noradrenergic modulation of the PFC, which exerts control over cognitive processes underlying visual attention, and indicates a need for precise pharmacological targeting of specific cognitive mechanisms in attention disorders.

ACKNOWLEDGEMENTS

This work was supported by European Union FP7 Marie Curie ITN Grant N. 606901 (INDIREA) and by the National Institute for Health Research (NIHR) Oxford Health Biomedical Research Centre. The Oxford Biobank is part of the NIHR National Biorepository which supported the recalling of the research volunteers. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. The Wellcome Centre for Integrative Neuroimaging is supported by core funding from the Wellcome Trust (203139/Z/16/Z). NS was funded by Marie Curie Early Stage Researcher Fellowship, and by Wellcome Trust Senior Investigator Award to Anna C Nobre (104571/Z/14/Z). MC held the British Academy Postdoctoral Fellowship (pf130059) and BRIDGE (Birmingham-Illinois Partnership for Discovery, Engagement and Education) Fellowship.

We thank the volunteers from the Oxford Biobank, NIHR Oxford Biomedical Research Centre, for their participation.

REFERENCES

Arnsten AF. (2007) Catecholamine and second messenger influences on prefrontal cortical networks of “representational knowledge”: a rational bridge between genetics and the symptoms of mental illness. Cereb Cortex 17(Suppl 1):i6-i15.

Arnsten AF, Goldman-Rakic PS. (1998) Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. Arch Gen Psychiatry 55:362-368.

Aston-Jones G, Cohen JD. (2005) An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci 28:403-450.

Ballard JC. (2001) Assessing attention: comparison of response-inhibition and traditional continuous performance tests. J Clin Exp Neuropsychol 23:331-350.

Barnett JH, Jones PB, Robbins TW, Muller U. (2007) Effects of the catechol-O-methyltransferase Val158Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. Mol Psychiatry 12:502-509.

Bellgrove MA, Mattingley JB. (2008) Molecular genetics of attention. Ann N Y Acad Sci 1129:200-212.

Bellgrove MA, Domschke K, Hawi Z, Kirley A, Mullins C, Robertson IH, Gill M. (2005) The methionine allele of the COMT polymorphism impairs prefrontal cognition in children and adolescents with ADHD. Exp Brain Res 163:352-360.

Bellgrove MA, Hawi Z, Kirley A, Gill M, Robertson IH. (2005) Dissecting the attention deficit hyperactivity disorder (ADHD) phenotype: sustained attention, response variability and spatial attentional asymmetries in relation to dopamine transporter (DAT1) genotype. Neuropsychologia 43:1847-1857.

Bellgrove MA, Chambers CD, Johnson KA, Daibhis A, Daly M, Hawi Z, Lambert D, Gill M, Robertson IH. (2007) Dopaminergic genotype biases spatial attention in healthy children. Mol Psychiatry 12:786-792.

Bellgrove MA, Johnson KA, Barry E, Mulligan A, Hawi Z, Gill M, Robertson I, Chambers CD. (2009) Dopaminergic haplotype as a predictor of spatial inattention in children with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 66:1135-1142.

Bertolino A, Blasi G, Latorre V, Rubino V, Rampino A, Sinibaldi L, Caforio G, Petruzella V, Pizzuti A, Scarabino T, Nardini M, Weinberger DR, Dallapiccola B. (2006) Additive effects of genetic variation in dopamine regulating genes on working memory cortical activity in human brain. J Neurosci 26:3918-3922.

Bourdelat-Parks BN, Anderson GM, Donaldson ZR, Weiss JM, Bonsall RW, Emery MS, Liles LC, Weissenker D. (2005) Effects of dopamine beta-hydroxylase genotype and disulfiram inhibition on catecholamine homeostasis in mice. Psychopharmacology (Berl) 183:72-80.

Briand LA, Gritton H, Howe WM, Young DA, Sarter M. (2007) Modulators in concert for cognition: modulator interactions in the prefrontal cortex. Prog Neurobiol 83:89-91.

Bundesen C. (1990) A theory of visual attention. Psychol Rev 97:523-547.

Chandler DJ, Waterhouse BD, Gao WJ. (2014) New perspectives on catecholaminergic regulation of executive circuits: evidence for independent modulation of prefrontal functions by midbrain dopaminergic and noradrenergic neurons. Front Neural Circuits 8:53.

Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, Kola-chana BS, Hyde TM, Herman MM, Apud J, Egan MF, Kleinman JE, Weinberger DR. (2004) Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet 75:807-821.

Clark CR, Geffen GM, Geffen LB. (1989) Catecholamines and the covert orientation of attention in humans. Neuropsychologia 27:131-139.

Clark KL, Noudoost B. (2014) The role of prefrontal catecholamines in attention and working memory. Front Neural Circuits 8:33.

Cools R, D’Esposito M. (2011) Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry 69: e113-e125.

Coull JT. (1998) Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology. Prog Neurobiol 55:343-361.

Coull JT. (2001) Modulation of attention by noradrenergic alpha2-agonists varies according to arousal level. Drug News Perspect 14:5-11.

Cubells JF, Zabetian CP. (2004) Human genetics of plasma dopamine beta-hydroxylase activity: applications to research in psychiatry and neurology. Psychopharmacology (Berl) 174:463-476.

Cubells JF, van Kammen DP, Kelley ME, Anderson GM, O’Connor DT, Price LH, Malison R, Rao PA, Kobayashi K, Nagatsu T, Gelemtier J. (1998) Dopamine beta-hydroxylase: two polymorphisms in linkage disequilibrium at the structural gene DBH associate with biochemical phenotypic variation. Hum Genet 102:533-540.

Cubells JF, Kranzler HR, McCance-Katz E, Anderson GM, Malison RT, Price LH, Gelemtier J. (2000) A haplotype at the DBH locus, associated with low plasma dopamine beta-hydroxylase activity, also associates with cocaine-induced paranoia. Mol Psychiatry 5:58-63.

Daly G, Hawi Z, Fitzgerald M, Gill M. (1999) Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children. Mol Psychiatry 4:192-196.
Petersen SE, Posner MI. (2012) The attention system of the human brain: 20 years after. Annu Rev Neurosci 35:73-89.
Posner MI. (1980) Orienting of attention. Q J Exp Psychol 32:3-25.
Posner MI. (2008) Measuring alertness. Ann N Y Acad Sci 1129:193-199.
Posner MI, Petersen SE. (1990) The attention system of the human brain. Annu Rev Neurosci 13:25-42.
Ranganath A, Jacob SN. (2016) Doping the mind: dopaminergic modulation of prefrontal cortical cognition. Neuroscientist 22:593-603.
Robbins TW, Arnsten AF. (2009) The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. Annu Rev Neurosci 32:267-287.
Robertson IH, Manly T, Andrade J, Baddeley BT, Yiend J. (1997) 'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. Neuropsychologia 35:747-758.
Roman T, Schmitz M, Polanczyk GV, Eizirik M, Rohde LA, Hutz MH. (2002) Further evidence for the association between attention-deficit/hyperactivity disorder and the dopamine-beta-hydroxylase gene. Am J Med Genet 114:154-158.
Sara SJ. (2009) The locus coeruleus and noradrenergic modulation of cognition. Nat Rev Neurosci 10:211-223.
Schneider KK, Schote AB, Meyer J, Frings C. (2015) Genes of the dopaminergic system selectively modulate top-down but not bottom-up attention. Cogn Affect Behav Neurosci 15:104-116.
Shalev N, Humphreys G, Demeyere N. (2016) Assessing the temporal aspects of attention and its correlates in aging and chronic stroke patients. Neuropsychologia 92:59-68.
Shalev N, De Wandel L, Dockree P, Demeyere N, Chechlacz M. (2018) Beyond time and space: the effect of a lateralized sustained attention task and brain stimulation on spatial and selective attention. Cortex 107:131-147.
Shalev N, Humphreys G, Demeyere N. (2018) Manipulating perceptual parameters in a continuous performance task. Behav Res Methods 50:380-391.
Stanislaw H, Todorov N. (1999) Calculation of signal detection theory measures. Behav Res Methods Instrum Comput 31:137-149.
Sturm W, Willmes K. (2001) On the functional neuroanatomy of intrinsic and phasic alertness. NeuroImage 14:576-S84.
Tan HY, Chen Q, Goldberg TE, Mattay VS, Meyer-Lindenberg A, Weinberger DR, Callicott JH. (2007) Catechol-O-methyltransferase Val158Met modulation of prefrontal-parietal-striatal brain systems during arithmetic and temporal transformations in working memory. J Neurosci 27:13393-13401.
Thiele A, Bellgrove MA. (2018) Neuromodulation of attention. Neuron 97:769-785.
Tunbridge EM, Harrison PJ. (2011) Importance of the COMT gene for sex differences in brain function and predisposition to psychiatric disorders. Curr Top Behav Neurosci 8:119-140.
Tunbridge EM, Bannerman DM, Sharp T, Harrison PJ. (2004) Catechol-o-methyltransferase inhibition improves set-shifting performance and elevates stimulated dopamine release in the rat prefrontal cortex. J Neurosci 24:5331-5335.
Tunbridge EM, Harrison PJ, Weinberger DR. (2006) Catechol-o-methyltransferase, cognition, and psychosis: Val158Met and beyond. Biol Psychiatry 60:141-151.
Tunbridge EM, Weickert CS, Kleinman JE, Herman MM, Chen J, Kohchana BS, Harrison PJ, Weinberger DR. (2007) Catechol-o-methyltransferase enzyme activity and protein expression in human prefrontal cortex across the postnatal lifespan. Cereb Cortex 17:1206-1212.
Tunbridge EM, Huber A, Farrell SM, Stumpenhorst K, Harrison PJ, Walton ME. (2012) The role of catechol-O-methyltransferase in reward processing and addiction. CNS Neurol Drug Targets 11:306-323.
Vangkilde S, Bundesen C, Coull JT. (2011) Prompt but inefficient: nicotine differentially modulates discrete components of attention. Psychopharmacology (Berl) 218:667-680.
Vangkilde S, Coull JT, Bundesen C. (2012) Great expectations: temporal expectation modulates perceptual processing speed. J Exp Psychol Hum Percept Perform 38:1183-1191.
Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF. (2007) Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat Neurosci 10:376-384.
Ward NM, Brown VJ. (1996) Covert orienting of attention in the rat and the role of striatal dopamine. J Neurosci 16:3082-3088.
Wise RA. (2004) Dopamine, learning and motivation. Nat Rev Neurosci 5:483-494.
Yavich L, Forsberg MM, Karayiorgou M, Gogos JA, Mannisto PT. (2007) Site-specific role of catechol-O-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum. J Neurosci 27:10196-10209.
Young ME, Sutherland SC, McCoy AW. (2018) Optimal go/no-go ratios to maximize false alarms. Behav Res Methods 50:1020-1029.
Zahrt J, Taylor JR, Mathew RG, Arnsten AF. (1997) Supranormal stimulation of D1 dopamine receptors in the rodent prefrontal cortex impairs spatial working memory performance. J Neurosci 17:8528-8535.
Zhang X, Su J, Rojas A, Jiang C. (2010) Pontine norepinephrine defects in Mecp2-null mice involve deficient expression of dopamine beta-hydroxylase but not a loss of catecholaminergic neurons. Biochem Biophys Res Commun 394:285-290.
Zozulinsky P, Greenbaum L, Brande-Eilat N, Braun Y, Shalev I, Tomer R. (2014) Dopamine system genes are associated with orienting bias among healthy individuals. Neuropsychologia 62:48-54.

(Received 16 January 2019, Accepted 31 May 2019) (Available online 10 June 2019)