Chapter 2

Effects of carrying a pathogenic variant in the tyrosine hydroxylase gene on motivated action and valuation: A pilot study in family members with tyrosine hydroxylase deficiency

The very essence of instinct is that it's followed independently of reason.
- Charles Darwin

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Abstract

Catecholamines (particularly dopamine) have long been implicated in motivation, learning and behavioural activation. Benign variants in dopamine-regulating genes have widely been linked to these processes as well, yet the cognitive effects of carrying pathogenic variants in the gene coding for tyrosine hydroxylase, which transforms tyrosine into dopamine's direct precursor L-Dopa, have never been studied. Here, we assessed for the first time whether carriers of tyrosine hydroxylase deficiency (THD) show altered motivated action due to putative reductions in dopamine synthesis. To this end, we employed a motivational Go/NoGo learning task, which is sensitive to manipulations in dopamine function and compared 16 family members of THD patients with 20 education- and age-matched controls. In the first learning phase of this task, subjects learnt to make Go or NoGo responses to cues that predict reward vs. punishment. In the second transfer phase, the subjects were presented with pairs of cues and chose the one they preferred, in the absence of reinforcement. Cue valence strongly biased Go/NoGo responding in the learning phase, such that subjects made more Go responses to reward than punishment cues. The groups did not significantly differ in this motivational bias. However, the THD carriers exhibited a shift in preference from NoGo-to-Win to Go-to-Avoid cues relative to matched controls during the transfer phase. These results suggest that subjective valuation is altered in THD carriers, potentially due to catecholamine-dependent changes in reward expectations, whereas task performance was unaffected. This pilot study provides a first insight into the cognitive consequences of carrying pathogenic TH variants, focusing on alterations in the reward valuation system and motivational biases in action.

Introduction

The catecholamines (particularly dopamine) have long been known to play a role in motivational and cognitive functions (Brozoski et al., 1979; Schultz et al., 1997), such as motivation, learning, and behavioural activation and vigour (Berridge and Robinson, 1998; Cools et al., 2009; Frank et al., 2004; Robbins and Everitt, 2007; Salamone et al., 2005). Several hereditary neurometabolic disorders affecting synthesis, breakdown, and transport of the catecholamines have been described (Kurian et al., 2011), including tyrosine hydroxylase deficiency (THD). THD is an extremely rare autosomal recessive disorder in which tyrosine hydroxylase, i.e. the rate limiting step in catecholamine synthesis, is impaired (Bräutigam et al., 1999; Willemsen et al., 2010), see Figure 1. THD leads to neurological symptoms, ranging from mild motor distortions to severe, early onset encephalopathy and can be treated with L-Dopa supplementation (Willemsen et al., 2010). Although benign variants in dopamine-regulating genes, such as the dopamine transporter polymorphism (for which the functional consequences are less clear) have widely been linked to motivation, learning, and action (Frank and Fossella, 2011), the effect of carrying a pathogenic variant in the TH gene (for which the functional consequences are more severe)

on these processes has not been studied before. Here we assess for the first time the cognitive consequences of carrying pathogenic TH variants in relatives of THD patients.

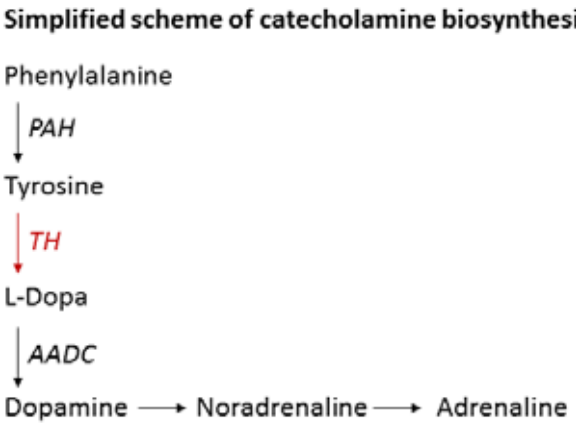


Figure 1. **Simplified scheme of the biosynthesis of the catecholamines dopamine, noradrenaline and adrenaline.**
Tyrosine hydroxylase deficiency (THD) affects the catecholamine synthesis by impairing enzymatic functioning of tyrosine hydroxylase (TH; marked in red) (Cansev and Wurtman, 2007), which catalyses the transformation of tyrosine into 3,4-dihydroxyphenylalanine (L-Dopa), the direct precursor of dopamine (Kurian et al., 2011). TH activity is the rate-limiting factor in catecholamine synthesis (Levitt et al., 1965), and consequently THD patients suffer from a critical reduction of catecholamine levels (Bräutigam et al., 1999; Willemsen et al., 2010). THD arises from an autosomal recessive pathogenic variant in both TH genes on chromosome 11p15.5 (OMIM #605407; Willemsen et al., 2010; Zafeiriou et al., 2009). Several pathogenic variants have been described (missense variants leading to partial loss of enzyme activity, deleterious variants leading to protein truncation, or pathogenic variants in the promoter region leading to reduced TH gene transcription) and patients can be homozygous or compound heterozygous (Willemsen et al., 2010). PAH = Phenylalanine; AADC = Aromatic amino acid decarboxylase.

As THD is an autosomal recessive disorder, heterozygous carriers of pathogenic variants in the TH gene ('THD carriers') are thought to be free of neurological symptoms (i.e., no overt cognitive, neurological and psychiatric impairments have been observed). However, given the clear parallels between THD and other monoamine neurotransmitter disorders, it is reasonable to assume that THD carriers express lower TH enzyme activity than non-carriers. For example, lower enzyme activity has been determined for first- and second-degree relatives of patients with aromatic L-amino acid decarboxylase (AADC) deficiency by Verbeek and colleagues (2007). Enzymatic activity analyses showed that the unaffected carriers had 35-40% lower AADC enzyme activity than healthy controls, usually in the absence of any clinical signs. AADC deficiency parallels TH deficiency because both are enzyme deficiency disorders affecting the catecholamine system, but each affects the biosynthesis of catecholamines at different stages (Figure 1) and AADC additionally affects the biosynthesis of serotonin (Willemsen et al., 2010). Accordingly, we hypothesised that carrying a pathogenic variant in the TH gene, which likely leads to decreased TH enzymatic activity and consequently decreased

dopamine biosynthesis, would be associated with subtle adaptations in motivated action and learning that surface only when probing behaviour using sophisticated catecholamine-sensitive experimental paradigms. Here we focus on a paradigm that has been previously established to be sensitive to manipulation of catecholamines, namely a motivational Go/NoGo learning paradigm (Guitart-Masip et al., 2014b; Swart et al., 2017).

Dopamine has been linked to behavioural activation in the context of reward (Taylor and Robbins, 1986, 1984), where enhanced dopamine facilitates instrumental activation in the context of reward conditioned cues (Wyvell and Berridge, 2000), and lowered dopamine levels reduce instrumental activation in the context of these cues (Dickinson et al., 2000; Hebart and Gläscher, 2015; Lex and Hauber, 2008). Conversely, punishment conditioned cues suppress instrumental responding (Davis and Wright, 1979; Huys et al., 2011), and striatal dopamine has been proposed to also contribute to such aversively motivated behaviour (Faure et al., 2008; Lloyd and Dayan, 2016). These motivational biases in action (i.e., behavioural activation and inhibition by reward and punishment cues respectively) is consistent with current accounts of striatal dopamine function (Collins and Frank, 2015b, 2014, Frank, 2006, 2005; Lloyd and Dayan, 2016), suggesting that dopamine bursts elicited by predicted rewards potentiate the basal ganglia direct 'Go' pathways, thereby promoting behavioural activation. Consequently, relatively enhanced dopamine responses would further facilitate behavioural activation. In contrast, dips in dopamine firing elicited by predicted punishments potentiate the basal ganglia 'NoGo' pathway, promoting behavioural inhibition. In this study, we hypothesized that THD carriers might show weaker motivational biases in action compared with controls, due to reduced dopamine function.

We set out to investigate the consequences of carrying a pathogenic TH genetic variant on motivational biases in action. To this end, we employed a motivational Go/NoGo learning task that requires subjects to learn to make Go or NoGo responses to cues in order to obtain reward or avoid punishment (cf. Guitart-Masip et al., 2011; Swart et al., 2017). The task quantifies the degree to which subjects are biased towards Go responding when pursuing reward, and NoGo responding when avoiding punishment. The task also allowed us to assess the valuation of these motivational Go and NoGo cues, by assessing explicit, subjective cue preferences after learning (Cavanagh et al., 2013). We contrasted THD carriers with an education- and age-matched control group in a between-subject design.

Methods

Subjects

For this study, all known Dutch families of a child with THD (n=8) were approached. We tested one group of THD carriers (n=16; sample size limited by the THD prevalence) and one education- and age-matched control group (n=20; see Table 1 for demographics). All subjects were native Dutch speakers. The THD carrier group consisted predominantly of the biological parents of TH

deficient children (8 mothers, 7 fathers), and of one other family member (aunt) who was a known THD carrier. Because THD is an autosomal recessive heritable disorder, both biological parents are obligated carriers of a pathogenic variant in one TH allele (Lüdecke et al., 1995), and genetic assessments confirmed the presence of a pathogenic variant in the TH gene. The THD carrier group was recruited via the treating child neurologists (MW and TW), and the control group via the Radboud University campus. Potential subjects received information prior to the testing day and signed informed consent prior to participation. THD carriers also signed a consent form that allowed us to request results of their genetic assessments at according hospitals to confirm their pathogenic TH variant. Subjects with abnormal vision (e.g., colour-blindness) were excluded from this study, resulting in the exclusion of one THD carrier (this subject did not complete the task). One other THD carrier could not complete the task due to prior medical reasons. Additional exclusion criteria for the control group were use of dopaminergic medication, (history of) neurological and psychiatric treatment, and alcohol or drug dependence. Subjects received a reimbursement for travel expenses and EUR8,- per hour for their time-investment.

Experimental procedure

The study contained one test session, including self-paced breaks. The test session took place at the Donders Institute or at the subjects' home. The test session consisted of a cognitive task battery (~95 min) and a neuropsychological assessment (~60 min). The THD carrier group additionally completed a neurological and psychiatric screening (~60 min). The cognitive task battery included a probabilistic reversal learning task (den Ouden et al., 2013), a delayed match-to-sample task (Fallon and Cools, 2014), a motivational Go/NoGo learning task (see below), and the Listening Span Test (Daneman and Carpenter, 1980). In this chapter, I focus on the motivational Go/NoGo learning task, but note that we intend to publish an overarching paper combining all independent assessments. The neuropsychological assessment consisted of i) neuropsychological tasks, namely the Dutch reading test (NLV; Schmand et al., 1991), Story Recall Test (Wechsler, 1997), Box Completion (Salthouse, 1994), Number Cancellation (Mesulam, 1985), Stroop task (Stroop, 1935), Verbal Fluency (Benton and Hamsher, 1983), and ii) of self-report questionnaires, namely the Barratt Impulsiveness Scale (BIS-II; Patton et al., 1995), Obsessive Compulsive Inventory revised (OCI-R; Foa et al., 2002), NEO personality inventory (NEO-FFI; Costa and McCrae, 1992), Need for Cognition Scale (NfC; Cacioppo et al., 1984), Perceived Stress Scale (PSS; Cohen et al., 1983), Beck Depression Inventory (BDI; Beck et al., 1996), and the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983). The neurological and psychiatric screening consisted of a general health assessment, standardized neurological exam (Clarke et al., 2016), Unified Parkinson's Disease Rating Scale (UPDRS-III; Fahn and Elton, 1987), Fahn-Marsden Dystonia Movement Scale (FMDM; Burke et al., 1985), and the Mini International Neuropsychiatric Interview questionnaire (MINI; Sheehan et al., 1998). The study was approved by the local ethics committee (CMO / METC Arnhem Nijmegen: CMO2014/288), and in line with the Declaration of Helsinki.

	THD carriers (n=14)	Control group (n=20)	Group difference
Matching criteria			
Gender (women / men)	9 / 5	11 / 9	$p = .588$
Age (Mean (SD), range)	49.9 (8.8), 36 - 65	50.8 (9.5), 30 - 63	$p = .788$
Education (n)			$p = .946$
Lower education	8	11	
Higher education	5	8	
University	1	1	
NLV (Mean (SD))	79.6 (15.3)	80.1 (9.2)	$p = .914$
Control measures			
BDI (Mean (SD))	4.6 (4.1)	4.4 (6.0)	$p = .921$
HADS (Mean (SD))	7.1 (4.3)	7.3 (4.8)	$p = .910$
PSS (Mean (SD))	11.0 (5.2)	12.0 (5.2)	$p = .588$
Measures of interest			
BIS-II (Mean (SD))	55.4 (6.0)	62.9 (8.4)	$p = .007$*

Table 1. **Demographics for the THD carrier group (n=14) and the matched control group (n=20).** The control group was successfully matched to the THD carrier group in terms of gender, age, education, and verbal intelligence (NLV). We checked whether the THD carriers showed increased perceived stress (PSS; Perceived Stress Scale) and depressive or anxiety symptoms (BDI; Beck Depression Inventory. HADS; Hospital Anxiety and Depression Scale) as a potentially direct consequence of caring for a child with severe medical problems. The groups did not significantly differ on any of these control measures. Finally, we assessed whether the groups significantly differed in terms of trait impulsivity (BIS; Barratt Impulsiveness Scale), which has been linked to dopamine function with PET (Buckholtz et al., 2010; Kim et al., 2014; Lee et al., 2009; Reeves et al., 2012) and has commonly been used as a proxy variable for baseline dopamine function within our group (Frobose et al., 2017; Swart et al., 2017). The THD carriers had significantly lower trait impulsivity scores than the matched controls.

Motivational Go/NoGo learning task

We employed a motivational Go/NoGo learning task (similar to Guitart-Masip et al., 2011; Swart et al., 2017), in which cue valence (Win vs. Avoid cue) was orthogonal to the instrumental response (Go vs. NoGo). In this task, subjects needed to learn to make Go or NoGo responses in order to obtain rewards (Win cues) or avoid punishments (Avoid cues). Each cue had one correct response, which subjects needed to learn by trial-and-error based on feedback. See Figure 2 for an overview of the task.

Each trial started with a cue presentation (1.2s) during which subjects could either press the spacebar (Go response) or wait until the cue disappears (NoGo response). Each cue had a coloured edge indicating the cue valence. A green edge was indicative of a Win cue, which could only be followed by reward or a neutral outcome. Conversely, a red edge was indicative of an Avoid cue, which could only be followed by a punishment or a neutral outcome. The cue was followed by a fixation cross (0.5s), and response-dependent feedback (1s). More specifically, correct responses to Win cues were followed by reward 75% of the time, and by neutral outcomes otherwise. Similarly,

correct responses to Avoid cues were followed by neutral outcomes 75% of the time, and by punishment otherwise. For incorrect responses, these probabilities were reversed. In total there were four cue types for which cue valence was orthogonalised to the required action (Figure 2). Reward consisted of a green '+100' text and a flourish sound. Neutral outcomes consisted of a grey '000' text and neutral beep. Punishment outcomes consisted of a red '-100' text and a low buzz. Trials ended with a randomized inter-trial interval (1.25-2s) during which a fixation cross was presented.

The task was preceded by instructions, including two practice rounds. Subjects were instructed i) that each cue had one optimal response, ii) that each cue could be followed by either reward or punishment, and iii) about the probabilistic nature of the feedback. Subjects received a self-paced break halfway during the task. Each cue was presented 30 times in pseudorandomized order. The task was performed twice with independent, counterbalanced stimulus sets.

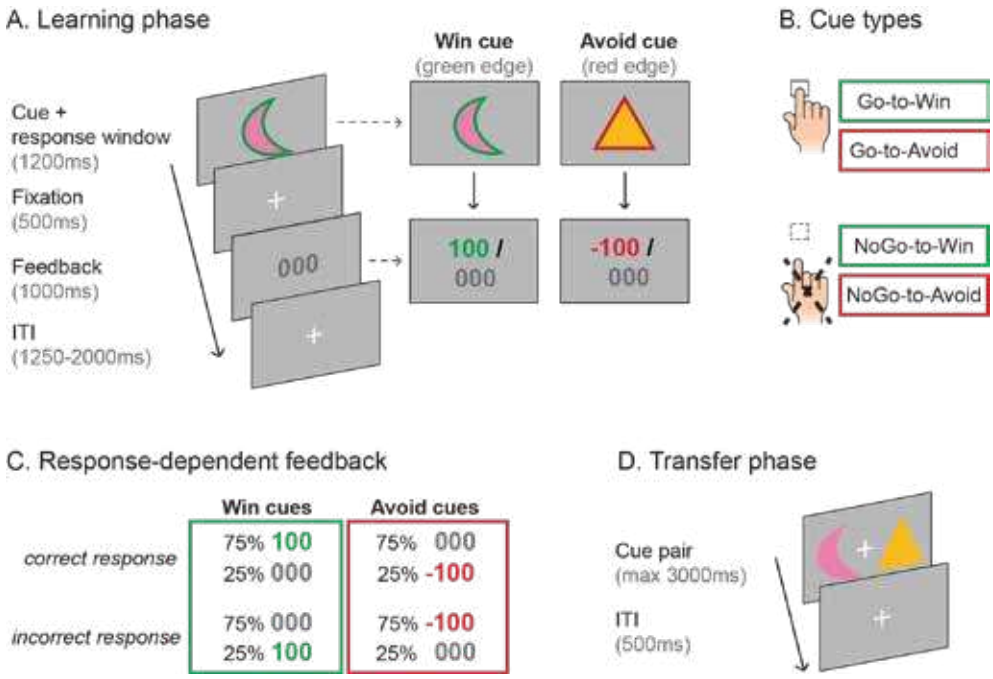


Figure 2. **Motivational Go/NoGo learning task.**
(**a**) Trials start with a cue, indicating the response window, followed by feedback. Win cues can be followed by reward, whereas Avoid cues can be followed by punishment. Image adapted from (Swart et al., 2017). (**b**) There are four cue-types for which cue valence (Win vs. Avoid) are orthogonalised to the required action (Go vs. NoGo). (**c**) Each cue has one correct response, which subjects need to learn by trial-and-error based on the feedback. Correct responses are followed by reward (Win cues) and neutral outcomes (Avoid cues) 75% of the time, or by neutral outcomes (Win cues) and punishment (Avoid cues) otherwise. These probabilities are reversed for incorrect responses. (**d**) The learning task is followed by a transfer phase. Cues are presented in pairs and subjects are instructed to select the most rewarding cue. The coloured cue edges are omitted during this phase.

After finishing the learning task, subjects completed a transfer phase (Cavanagh et al., 2013) in which we assessed the relative, subjective cue values. During this phase, cues from the last stimulus set were presented in pairs, and subjects were asked to select the most rewarding cue. This transfer phase allowed us to verify that subjects experienced the Win cues as more rewarding than the Avoid cues, but more importantly, whether subjects preferred the cues requiring active Go response over the cues requiring passive NoGo responses, as has been shown previously (Cavanagh et al., 2013; Swart et al., 2018). The transfer phase contained 48 trials. During this phase, the coloured cue edges signalling valence were omitted, in order to probe the learned relative preferences and minimize interference by the explicit cue valences.

Statistical analysis

In this study we investigated the consequences of carrying a pathogenic TH genetic variant on motivational biases in action. To this end, we first tested whether subjects adjusted Go/NoGo responding to the cue valence, which we refer to as the motivational bias, and then assessed whether the THD carriers showed a reduced motivational bias compared with the control group. We additionally assessed whether subjects adjusted Go/NoGo responding to the required action, in line with task learning, and whether the groups differed in terms of task learning. Accordingly, the statistical model for Go responses included the between-subject factor Group (THD carrier vs. control), and the within-subject factors Valence (Win vs. Avoid cue) and Required Action (Go vs. NoGo). We analysed reaction times (RTs) as a complementary measure of behavioural vigour. Here, we restricted the RT analysis to correct responses, i.e. to the Go cues, to reduce the model's effects structure and thereby increase statistical power. Thus, the RT model included the within subject factors Valence and the between subject factor Group. Given that we set out to test the hypothesis that the motivational biasing of action might be reduced in the THD carriers due to assumed dopamine depletion, we employed one-sided tests for the Valence x Group interactions. These one-sided tests are clearly indicated in the Results section.

We analysed trial-by-trial choices (RTs) with logistic (linear) mixed-effect models using lme4 in R (Bates et al., 2014; R Developement Core Team, 2015). The mixed-effect analysis has a clear advantage over ANOVA particularly for the RTs, as mixed-effect models take the number and consistency of RTs per subject into account, thereby accounting for within and between subject variability. RTs were log-transformed to improve normality and RTs<100ms were discarded from the analysis. The mixed models included all main effects and interactions, and a full random effects structure (Barr, 2013; Barr et al., 2013). We estimated effect sizes based on the corresponding repeated measures ANOVA performed within SPSS, given that there is no clear consensus on the estimation of effect size for mixed-models. We report partial eta squared (η_p^2) as a measure of effect size for all group

effects, where we interpret η_p^2>.14 as large effects, η_p^2>.06 as medium effects, and η_p^2>.01 as small effects, in line with (Cohen, 1992, 1988). Finally, we repeated all analyses including the control covariates age, gender and education to confirm that our conclusions remain the same.

Finally, we assessed whether the THD carrier group differed from the control group in their relative cue preferences during the transfer phase. To this end, we analysed how often each cue was chosen during the transfer phase relative to chance. We analysed the frequency data with repeated measures ANOVA in SPSS using the between-subject factor Group, and the within-subject factors Valence and Required Action.

Results

General task performance and subjective valuation

Before addressing differences between the THD carrier group and the control group, we established that expected task effects were present across groups. First, we assessed behaviour as a function of the required actions, related to task learning, and second, we assessed behaviour as a function of cue valence, related to motivational biases. Subjects made more Go responses to Go than NoGo cues (X^2_1=33.9, p<.001; Figure 3), indicating that subjects adjusted their responses to the instrumental requirements. Independent of the action requirements, subjects made more Go responses (X^2_1=44.7, p<.001; Valence x Required Action: X^2_1<1, p=.926) and faster Go responses (X^2_1=48.8, p<.001) to Win than Avoid cues, which we refer to as a motivational bias. Altogether, the current sample shows the commonly observed task effects related to task learning and motivational biases (Guitart-Masip et al., 2014a; Swart et al., 2018, 2017).

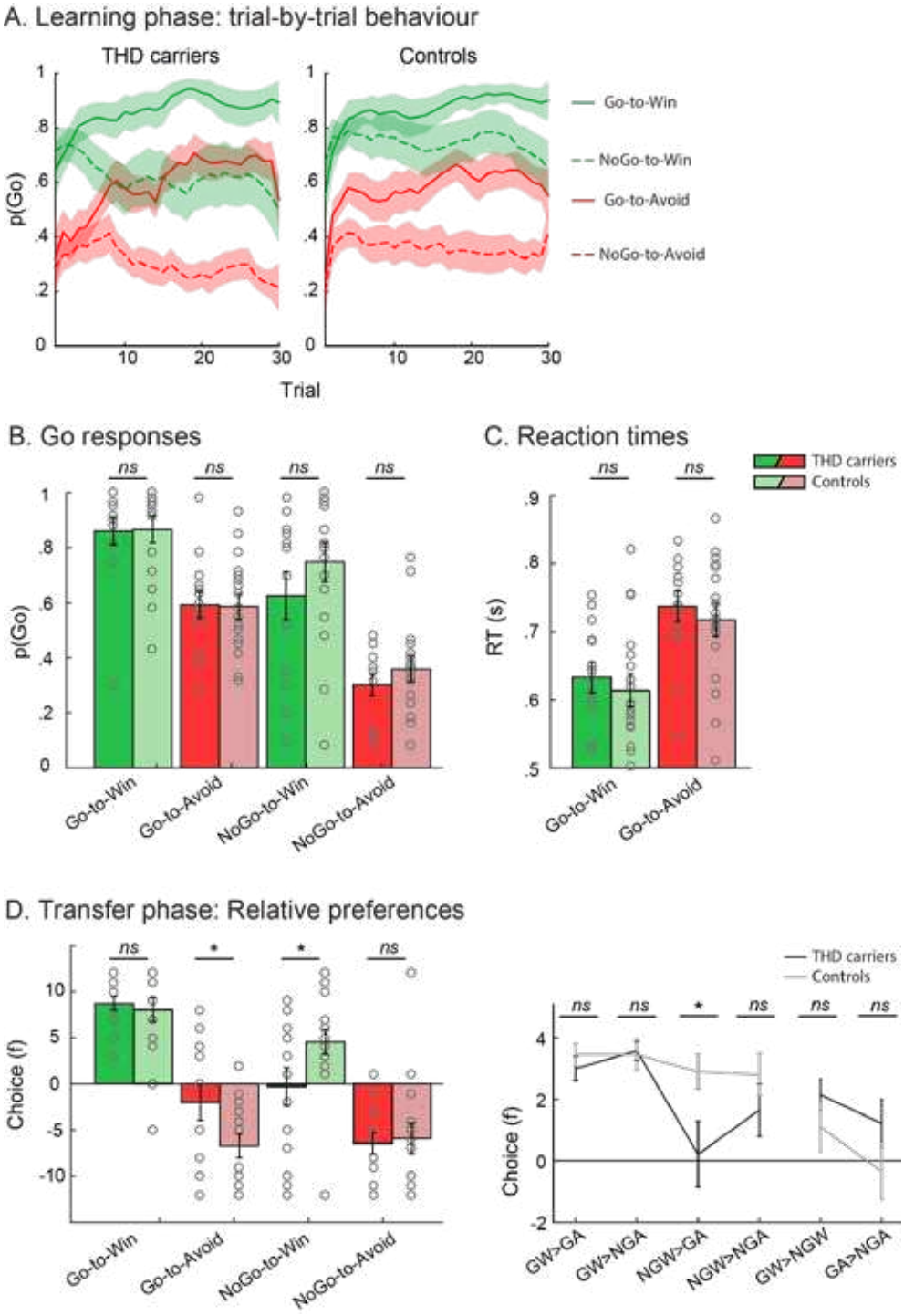
Before turning to the group differences, we assessed the choices during the transfer phase across groups. During the transfer phase, cue pairs were presented and subjects needed to select the most rewarding cue. Accordingly, subjects selected the Win cues more frequently than the Avoid cues ($F_{1,32}$=93.4, p<.001), indicating that subjects indeed considered Win cues more rewarding than the Avoid cues. Furthermore, subjects selected Go cues more often than NoGo cues ($F_{1,32}$=10.1, p=.003), which was particularly driven by the Win cues (simple effect of Required Action: $F_{1,32}$=19.6, p<.001), rather than the Avoid cues (simple effect of Required Action: $F_{1,32}$=1.3, p=.263; Required Action x Valence: $F_{1,32}$=7.5, p=.010). This pattern of results is also consistent with previous reports (Cavanagh et al., 2013; Swart et al., 2018), showing enhanced relative values for cues associated with Go responses relative to cues associated with NoGo responses.

Figure 3 (right page). **Behavioural performance.**
(**a**) Trial-by-trial responses for the THD carriers (left) and controls (right) using a sliding average of 5 trials. The shaded areas indicate the standard error of the mean. Subjects increased Go responses for Go cues and NoGo responses for NoGo cues over trials (p<.001), indicative of task learning. From the first trial onwards, subjects made more Go responses to Win than Avoid cues (p<.001), which we refer to as the motivational bias. (**b-c**) Average proportion Go responses and reaction times. Circles indicate individual subjects and error bars indicate the standard error of the mean. The THD carrier group and the control group did not show any significant differences in proportion Go responses and reaction times (p>.05). ns indicates p>.05. (**d**) Cue preferences as measured in the transfer phase relative to chance level. Left: Total choice frequency per cue. Right: Choice frequency per cue pair. The groups particularly differed in their relative preferences when comparing the NoGo-to-Win and the Go-to-Avoid cues (p=.013; all other pairs: p>.05), where the THD carrier group selected the NoGo-to-Win cue significantly less often than the control group. Remarkably, this reduced preference for the NoGo-to-Win cues was not explained by a lower reward history, as the THD carriers performed numerically better for the NoGo-to-Win cues (panel b). * indicates p<.05. (N)GW=(No)Go-to-Win; (N)GA=(No)Go-to-Avoid.

Altered subjective cue valuation, but not task performance, in THD carriers vs. matched controls

Having established the presence of common task effects across groups in both the learning and transfer phase, we continued with contrasting the THD carrier group with the control group. First, we addressed whether the groups differed in terms of their motivational bias, that is, the differential responding to Win and Avoid cues. The groups did not differ significantly in the proportion of Go responses for Win vs. Avoid cues (X^2_1<1, p=.224, *one-sided test*, η_p^2=.006) or in terms of RTs (X^2_1<1, p=.394, *one-sided test*, η_p^2<.001), see Figure 3. We only observed a small effect size for a reduced valence effect in the THD carrier group on the NoGo trials, which did not reach statistical significance in the current sample (Required Action x Valence x Group: X^2_1<1, p=.872, η_p^2=.013). Taking together, we did not observe a significant reduction in the valence-based biases in the THD carriers compared with the matched controls. The groups also did not significantly differ in the extent to which they adjusted their Go/NoGo responses to the required action (X^2_1<1, p=.358, η_p^2=.047), nor in the overall proportion of Go responses or RTs (Go: X^2_1=2.3, p=.127, η_p^2=.051; RT: X^2_1<1, p=.515, η_p^2=.019). We confirmed that these results remained unchanged when including age, education, and gender as control covariates in the models. Altogether, we did not observe significant differences in the task performance between the THD carrier group and the control group in the learning phase.

Second, we addressed group differences in the subjective cue preferences as measured in the transfer phase. The THD carrier group showed a marginally weaker preference for the Win vs. Avoid cues (Group x Valence: $F_{1,32}$=3.7, p=.064, η_p^2=.103), and showed a significantly stronger preference for the Go vs. NoGo cues compared with the matched controls (Group x Required Action: $F_{1,32}$=4.5, p=.042, η_p^2=.123; Group x Valence x Required Action: $F_{1,32}$<.1, p=.934, η_p^2<.001). These group differences specifically reflected a shift in the valuation of


A. Learning phase: trial-by-trial behaviour
THD carriers
Controls
p(Go)
Trial
Go-to-Win
NoGo-to-Win
Go-to-Avoid
NoGo-to-Avoid
B. Go responses
C. Reaction times
THD carriers
Controls
RT (s)
D. Transfer phase: Relative preferences
Choice (f)
GW>GA
GW>NGA
NGW>GA
NGW>NGA
GW>NGW
GA>NGA
ns

the incongruent cues (i.e. Go-to-Avoid and NoGo-to-Win cues), see Figure 3. The groups indeed differed significantly in their choices on the NoGo-to-Win vs. Go-to-Avoid cue pairing (t_{32}=2.6, p=.013), and not on the other cue pairings (all: p>.05). To elaborate, the THD carriers selected the NoGo-to-Win significantly less often than the control group when choosing between the NoGo-to-Win vs. Go-to-Avoid cue, suggesting that the THD carriers' preferences were less affected by valence and more by the associated action. Importantly, this shift in cue preferences was not explained by a differential outcome history for the groups (NoGo-to-Win – Go-to-Avoid: t_{32}=1.5, p=.155; NoGo-to-Win: t_{32}=1.4, p=.158; Go-to-Avoid: t_{32}<.1, p=.925). If anything, the THD carriers received (numerically) more rewards for the NoGo-to-Win cues relative to controls, yet significantly preferred this cue less. This group difference was also not purely explained by the group difference in trait impulsivity; trait impulsivity did not significantly relate to the choices on the NoGo-to-Win vs. Go-to-Avoid cue pairing (R=.26, p=.140), and the group difference in cue preference remained significant when correcting for impulsivity (t_{31}=2.1, p=.043). The transfer results also remained unchanged when correcting for age, education, and gender in the model. Together these results raise the hypothesis that THD carriership affects relative cue preferences in the context of motivationally incongruent cues, while leaving motivational biasing of action unaltered.

Discussion

Here we assessed the effects of carrying a pathogenic variant in the tyrosine hydroxylase (TH) gene on the motivational biasing of action by comparing family members of tyrosine hydroxylase deficient (THD) patients with education- and age-matched controls. In both the carriers and matched controls, cue valence strongly biased Go/NoGo responding, such that subjects made more Go responses when playing for reward (Win cues) than when trying to avoid punishment (Avoid cues). This motivational bias in Go/NoGo responding was not significantly reduced in the THD carriers relative to the controls. In contrast, the THD carriers differed from the matched controls in relative cue preferences. The carriers showed a reduced impact of valence on their subjective cue valuation, specifically in the context of incongruency between the action requirements and the valence. In other words, they liked NoGo-to-Win less, and Go-to-Avoid cues more, relative to controls.

This study is part of the first project addressing the neurocognitive consequences for heterozygous carriers of a pathogenic variant in the TH gene. In this chapter, we set out to specifically assess the consequences on the well-established motivational biases in action. We hypothesized that family members of THD patients have a mild reduction in dopamine synthesis that would result in reduced motivational biases in action, in line with current accounts of striatal dopamine function (Collins and Frank, 2015b, 2014; Frank, 2005; Frank

et al., 2004; Lloyd and Dayan, 2016) and prior results from our group showing that increases in catecholamine transmission with methylphenidate enhanced such motivational action biasing (Swart et al., 2017). We replicated commonly observed motivational biases in both active actions and response times (Guitart-Masip et al., 2014a; Swart et al., 2018, 2017), reflected in the increased proportion and speed of Go responses to Win relative to Avoid cues. This motivational biasing of Go responses and response times was not significantly reduced in the THD carrier group. These results might indicate that the motivational biasing of action is not sensitive to reductions in TH enzymatic activity. However, we did observe a small effect size for a reduced motivational bias on the NoGo cues, meaning that we cannot exclude the possibility that the lack of significance was due to a lack of statistical power. Indeed, patients with Parkinson's disease off dopaminergic medication (i.e., when striatal dopamine is severely depleted) have been shown to express enhanced NoGo-to-Win performance (Moustafa et al., 2008) and reduced willingness to exert effort for reward (Chong et al., 2015), which both normalize ON dopaminergic medication. Thus, our current sample sizes might have been too small to detect significant group differences.

On the other hand, the absence of a significant reduction in motivational biasing of action in the carriers might be due to a degree of evolutionarily preprogrammed redundancy in (and thus compensatory capacity of) monoamine synthesis enzymatic activity (Wassenberg et al., 2012). Put simply, although heterozygous state must result in lower tyrosine hydroxylase enzymatic activity in carriers, this might have no clinical significance on catecholamine levels. We argue that this is less likely given that benign variants in the monoamine pathways without known functional effects on protein level have long been thought to be associated with subtle motivational and/or cognitive deficits, and to contribute to several neuropsychiatric disorders (Haavik et al., 2008).

The absence of significant group differences in the motivational biases might raise the question whether dopamine function is indeed altered in THD carriers. More direct measures of dopamine function, for example dopamine synthesis capacity or turnover, are required to conclusively answer this question, yet various aspects of the data support the assumptions that dopamine function is altered. First, the THD carriers displayed significantly lower trait impulsivity scores than the matched controls, and trait impulsivity has been linked to dopamine function with PET (Buckholtz et al., 2010; Kim et al., 2014; Lee et al., 2009; Reeves et al., 2012). Thus, the significant group difference in trait impulsivity is consistent with the assumptions that THD carriers express altered dopamine function. Second, the THD carriers show modulated relative cue preferences, which we will cautiously link to dopamine function below. Finally, carriers of a pathogenic variant in the related AADC gene also express significantly lower AADC enzyme activity (Verbeek et al., 2007). Considering the parallels between AADC and TH deficiency (also described in the introduction of this chapter), we expect a similar decrease in TH enzyme activity

(and consequently dopamine synthesis) in THD carriers. Taken together, we stand by our initial assumption that dopamine function is altered in THD carriers, yet we acknowledge that future studies measuring TH enzyme activity or dopamine function more directly are needed to verify this assumption.

At the end of the learning task, subjects were asked to select the most rewarding cue out of presented cue pairs. During this transfer phase, the carrier group showed altered relative cue preferences compared with the matched control group, as evidenced by a shift in preference from the NoGo-to-Win cues towards the Go-to-Avoid cues. The altered cue preferences in the absence of altered motivated action is particularly remarkable when considering that motivation and valuation typically go hand in hand (Niv et al., 2007). Yet, it has been shown that these processes can be dissociated (Miller et al., 2014), suggesting that these processes might rely on differential mechanisms. Although the transfer phase was not the primary measure of the current study, we will discuss potential explanations for the observed group differences in the following section.

First of all, the altered relative preferences in the carriers might reflect changes in the outcome predictions, presumably due to reduced dopamine function. Dopamine has classically been linked to reward prediction (Schultz et al., 1998, 1997), and has been linked to the prediction of hedonic pleasure as well (Sharot et al., 2009), even though the role of dopamine in instant hedonic pleasure or 'liking' has been disputed (Berridge, 2009; Berridge et al., 2009). Sharot and colleagues showed that administration of a dopamine-enhancing drug (L-Dopa) increased subjective estimations of future hedonic pleasure to positive future life events. Similarly, administration of L-Dopa enhanced the optimism bias (for a review see Sharot, 2011), as L-Dopa reduced negative expectations about the future (Sharot et al., 2012). Consistent with these findings, the assumed dopamine reduction in the THD carriers might have led to attenuated expectations of reward outcomes and associated hedonic pleasure. Such a dopamine-dependent attenuation in reward expectations would explain why the carriers indicated the Win cues less often as rewarding compared with the matched controls.

Notably, the attenuated preference of Win cues in the carrier group was specific to the context where cue valences were motivationally incongruent with the action requirements (i.e. NoGo-to-Win vs. Go-to-Avoid cues). In other words, the group difference in value-based preferences only surfaced when these preferences were inconsistent with action-based preferences. To elaborate, subjects expressed an overall relative preference of the Go cues over the NoGo cues, in line with previous studies (Cavanagh et al., 2013; Swart et al., 2018). In general, approach and avoid behaviour are known to respectively increase positive and negative valuation of novel stimuli (e.g. Huijding et al., 2011; Laham et al., 2014; Woud et al., 2013, 2008), and approach-avoid training is even used to retrain approach tendencies of harmful consumption behaviour, such as alcohol use and unhealthy eating (Kakoschke

et al., 2017). Similarly, freely chosen options tend to enhance relative preferences, whereas discarded options tend to decrease relative preferences ('choice bias'; e.g., Cockburn et al., 2014; Sharot et al., 2010, 2009). Here, the active Go and inactive NoGo responses might have influenced the affective valuation of the cues in a similar manner. This action-based affective valuation was clearly present in the carrier group, and was enhanced relative to the control group. Thus, the relative contribution of action-based and valence-based cue valuation were shifted in the carrier group, with an increased relative contribution of the associated action (or, 'the actor') and a decreased relative contribution of the cue valence (or, 'the critic'). A shift in the relative contribution of the associated action and valence values would explain why the THD carriers expressed a shift in relative preferences only when the action- and valence-based preferences were incongruent. Although i) reduced reward expectations are consistent with current views of reduced dopamine function, and ii) unaffected action-based contribution would be consistent with the unaffected task performance in the learning phase, future research is needed to disentangle the absolute changes in the contribution of these complementary mechanisms.

Alternative to reflecting affected reward expectations, the attenuated relative preferences for Win and Avoid cues in the carrier group could reflect a disruption in value-based *learning*, which also has been widely linked to dopamine function (Collins and Frank, 2014; Frank et al., 2004; Montague et al., 2004; Schultz et al., 1997; Wise, 2004). If either the valuation or learning of reward and punishment outcomes is disrupted, that would explain why the THD carrier group indicated the Win cues as relatively less rewarding. Although one might have expected a disruption in value-based learning or decision-making based on current views of dopamine function, such a disruption seems unlikely given that the carrier group did not perform significantly differently from the control group during the learning phase. We cannot rule out compensation strategies (e.g., enhanced contribution of working memory or additional prefrontal functions), or enhanced engagement in the THD carriers (particularly given the personal relevance of the study), and that the carrier group thereby could compensate for a disruption in value-based learning, yet such a combined account is less parsimonious.

We have linked the group differences in relative preferences to changes in dopamine function above, yet it should be noted that the TH enzyme does not only affect dopamine synthesis, but affects catecholamine synthesis in general (Levitt et al., 1965), as dopamine is the precursor for noradrenaline (Kurian et al., 2011; Figure 1). Thus, even though these results are consistent with altered dopamine function, we cannot exclude the possibility that the other catecholamines contributed to the observed group differences.

Finally, given that the groups particularly differed in their relative preferences for the motivationally incongruent cues (i.e., NoGo-to-Win and Go-to-Avoid), one might wonder whether the carriers showed enhanced discounting for exerting control (cf. Cavanagh et

al., 2014). On the incongruent trials, instrumental requirements conflict with prepotent, Pavlovian response tendencies elicited by the cue valence, and this Pavlovian conflict is thought the require increased levels of control over behaviour (Cavanagh and Frank, 2014; Swart et al., 2018) and to be inherently aversive (Cavanagh et al., 2014). Although the carriers indeed preferred the NoGo-to-Win cues less than the controls, they preferred the Go-to-Avoid cues *more* than the matched controls, which argues against enhanced discounting of conflict in the THD carrier group.

Conclusion

We set out to assess for the first time the cognitive consequences of carrying a pathogenic variant in the TH gene. We specifically assessed the impact of being of carrier of THD on the well-established motivational biases in action on the one hand and subjective valuation on the other. In both the THD carriers and matched controls, anticipated rewards and punishment elicited Go and NoGo responses respectively. While the groups did not significantly differ in this motivational biasing of Go responding, the groups strikingly differed in their relative valuation of the cues. The THD carrier group valued the NoGo-to-Win cues less than the matched control group, while preferring the Go-to-Avoid cues more. Our results suggest that motivational biases in action are unaffected in THD carriers, whereas subjective cue valuation is altered relative to matched controls, potentially due to catecholamine-dependent changes in reward expectations. This pilot study provides a first insight into the subtle cognitive changes in a highly unique and hitherto unstudied genetic population involving the catecholamine system.

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