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Neurocognitive Function in Dopamine-β-Hydroxylase Deficiency

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Dopamine-β-hydroxylase (DβH) deficiency is a rare genetic syndrome characterized by the complete absence of norepinephrine in the peripheral and the central nervous system. DβH-deficient patients suffer from several physical symptoms, which can be treated successfully with L-threo-3,4-dihydroxyphenylserine, a synthetic precursor of norepinephrine. Informal clinical observations suggest that DβH-deficient patients do not have obvious cognitive impairments, even when they are not medicated, which is remarkable given the important role of norepinephrine in normal neurocognitive function. This study provided the first systematic investigation of neurocognitive function in human DβH deficiency. We tested 5 DβH-deficient patients and 10 matched healthy control participants on a comprehensive cognitive task battery, and examined their pupil dynamics, brain structure, and the P3 component of the electroencephalogram. All participants were tested twice; the patients were tested once ON and once OFF medication. Magnetic resonance imaging scans of the brain revealed that the patients had a smaller total brain volume than the control group, which is in line with the recent hypothesis that norepinephrine has a neurotrophic effect. In addition, the patients showed an abnormally small or absent task-evoked pupil dilation. However, we found no substantial differences in cognitive performance or P3 amplitude between the patients and the control participants, with the exception of a temporal-attention deficit in the patients OFF medication. The largely spared neurocognitive function in DβH-deficient patients suggests that other neuromodulators have taken over the function of norepinephrine in the brains of these patients.

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INTRODUCTION

The locus coeruleus–norepinephrine (LC–NE) system is one of the major neuromodulatory systems in the brain. For a long time, investigators have associated this system with basic functions such as arousal and the sleep–wake cycle (Aston-Jones *et al*, 1984; Jouvet, 1969), and with various neuropsychiatric disorders such as depression and attention-deficit hyperactivity disorder (Ressler and Nemeroff, 2001; Siever and Davis, 1985). In addition, recent studies have shown that the LC–NE system is involved in more specific cognitive functions, such as memory, attention, perception, and decision making (Aston-Jones and Cohen, 2005; Robbins, 1997; Sara, 2009). These findings suggest that NE is essential for normal cognitive function in humans.

Dopamine-β-hydroxylase (DβH) deficiency is a rare genetic syndrome that is characterized by the congenital absence of the enzyme DβH, which is responsible for the conversion of dopamine (DA) to NE (Man in 't Veld *et al*, 1987a; Robertson *et al*, 1986). As a result, DβH deficiency is characterized by a complete lack of NE and epinephrine in both the central and the peripheral nervous system (Man in 't Veld *et al*, 1987a). There are currently approximately 15 patients with DβH deficiency known worldwide. These patients suffer from several physical symptoms, including severe orthostatic hypotension, fatigue, and impaired exercise tolerance (Robertson and Garland, 2010). The only

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effective treatment of DβH deficiency involves administration of the drug L-threo-3,4-dihydroxyphenylserine (DOPS, droxidopa), which is converted directly into NE via L-aromatic-amino-acid decarboxylase, thereby bypassing DβH (Biaggioni and Robertson, 1987; Goldstein, 2006; Man in 't Veld *et al*, 1987b). Studies in rats and mice have shown that DOPS crosses the blood–brain barrier, and activates the production of NE in the central nervous system as well as the peripheral nervous system (Ishikawa *et al*, 1987; Kato *et al*, 1987a, b; Semba and Takahashi, 1985; Thomas *et al*, 1998). Treatment with DOPS results in a dramatic relief of physical symptoms and a substantial improvement in the quality of life of DβH-deficient patients.

The biochemical features, autonomic physiology, and physical symptoms associated with human DβH deficiency have already been described in several studies (see, eg, Mathias *et al*, 1990; Robertson *et al*, 1991; Thompson *et al*, 1995; Timmers *et al*, 2004). In addition, a post-mortem microscopic examination of the brain of one DβH-deficient patient has revealed no histological abnormalities and no evidence for neuronal loss (Cheshire *et al*, 2006). However, to date there have been no systematic studies on the cognitive and brain function in DβH deficiency. Informal clinical observations suggest that even before starting treatment, DβH-deficient patients do not have obvious cognitive impairments, which is striking given the large amount of evidence that NE plays an important role in normal cognitive function (Sara, 2009). This suggests that more carefully controlled laboratory tests may reveal subtle neurocognitive deficits in DβH-deficient patients that have remained unnoticed in informal observations.

This study provides the first systematic evaluation of neurocognitive function in DβH deficiency. We tested five patients with DβH deficiency on a battery of cognitive tasks that have been proposed to depend on normal noradrenergic function, including an emotional working-memory task (Chamberlain *et al*, 2006; Oei *et al*, 2010) and a temporal-attention task (attentional-blink task; De Martino *et al*, 2008; Nieuwenhuis *et al*, 2005a; Warren *et al*, 2009), expecting that these tasks would reveal possible abnormalities in the DβH-deficient patients. In addition, we examined task-evoked changes in pupil diameter, and recorded the electroencephalogram (EEG) during a target-detection task to examine event-related potential (ERP) correlates of noradrenergic activity (Liu *et al*, 2009; Nieuwenhuis *et al*, 2005b; Pineda *et al*, 1989). To assess whether potential abnormalities in performance were restricted to NE-mediated tasks, we also tested the patients on a spatial-attention task that does not probe noradrenergic function (Greenwood *et al*, 2005; Nieuwenhuis *et al*, 2007). Finally, we acquired an MRI scan of the patients' brain to assess possible abnormalities in brain volume and structure. We tested the patients once ON and once OFF DOPS medication, and compared their results with those of a matched healthy control group.

MATERIALS AND METHODS

Participants

We tested 5 DβH-deficient patients (two Dutch, two American, and one Canadian) and 10 healthy controls (all Dutch). The two American patients were brothers, and the other patients were unrelated (see Supplementary Table 1 for the demographic and clinical details of the patients). The genetic mutations in the *DβH* gene have been identified for all patients. Patient 1 is homozygous for the IVS1 + 2T > C mutation, a mutation of the 5′ splice site in the first intron that leads to abnormal splicing and hence a dysfunctional protein. Patient 2 is homozygous for a missense mutation in 764G > T (C255F; Deinum *et al*, 2004). Patients 3 and 4 are heterozygous for both the IVS1 + 2T > C mutation and the 991G > A (D331N) missense mutation. Patient 5 is homozygous for two missense mutations in 259G > A (V87M) and 991G > A (D331N). Patient 5 also has a rare mosaic deletion at chromosome 11p13 (46,XX,del(11)(p12p14)/46,XX), which is unrelated to her *DβH* deficiency (Erez *et al*, 2010).

Table 1 Demographic Details of the Control Group and the Patient Group (Means ± SD)

	Control group (*N* = 10)	Patient group (*N* = 5)
Age (years)	24.6 ± 11.0	24.4 ± 10.0
Sex (proportion female)	6/10	3/5
Interval between test sessions (days)	7.5 ± 3.2	7.6 ± 2.7
Scaled WAIS-III vocabulary score	8.6 ± 2.3	11.4 ± 3.4
Raven's SPM score	44.5 ± 6.9	45.6 ± 4.6
Estimated IQ (based on SPM score)	106.5 ± 11.1	107.2 ± 8.6

Abbreviations: SPM, standard progressive matrices, highest possible score = 66; WAIS, Wechsler adult intelligence scale, highest possible scaled vocabulary score = 19.

The patient and control group were matched for age, sex, and IQ (Table 1). We used the Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS III, Wechsler, 1997) and the Raven's Standard Progressive Matrices test (SPM; Raven *et al*, 1988) to estimate IQ. The Dutch patients and their controls were matched for educational level as well. Given the different educational systems in the United States and the Netherlands, it was not possible to match the American patients and their Dutch control participants in terms of educational level; hence, we matched for estimated IQ instead of educational level. Participants gave written informed consent before participation, and the study was approved by the medical ethics committee of the Leiden University Medical Center and the institutional review board of Vanderbilt University.

General Procedure

All participants were tested twice on the same cognitive-task battery, with an intervening period of 6 to 13 days. Participants were seated in a chair during performance of all tests. The patient and control groups had similar intervening periods (Table 1). Two patients were tested ON medication on the first test day and OFF medication on the second test day, and the other three patients were tested in the opposite order. Two of these patients had never been on DOPS medication before and started taking medication at least 2 days before the second test day. The other patients stopped taking their daily medication 4 to 13 days before

the OFF-medication test day and stayed off medication up to and including this day. Preceding and during the ON-medication test day, the patients took their DOPS medication as usual.

The task battery included five cognitive tasks, described below and, in more detail, in the Supplementary Methods. At the beginning and end of each test day, participants completed the Positive Affect and Negative Affect Schedule (PANAS; Watson *et al*, 1988; translated into Dutch by Peeters *et al*, 1996). To measure catecholamine levels, we collected blood and 24-h urine samples from the patients, before each test session (Table 1). Blood samples were taken after 15 min of supine rest. We also collected blood samples from most control participants. As we expected no differences in catecholamine levels between the two sessions for the control participants, their blood samples were collected only once. Finally, on one of the test days a structural T1-weighted MRI brain scan was acquired (see Supplementary Methods for details of acquisition and analysis).

Emotional Working-Memory Task

NE plays an important role in emotional memory (see, eg, Chamberlain *et al*, 2006). The well-known phenomenon that emotional events are memorized better than neutral events (see, eg, Cahill and McGaugh, 1998), for example, is associated with β-adrenergic-dependent modulations of amygdala–hippocampus interactions (Strange *et al*, 2003; Strange and Dolan, 2004). In addition, emotional distractor stimuli impair working-memory performance to a higher degree than neutral distractor stimuli (see, eg, Buchner *et al*, 2004; Dolcos and McCarthy, 2006; Oei *et al*, 2009, 2010), an effect that is reduced by administration of the β-adrenergic antagonist propranolol (Oei *et al*, 2010). We examined the effects of emotional and neutral distractor stimuli on performance in the working-memory task used by Oei *et al* (2009, 2010).

Each trial of this task started with the presentation of either one or four letters (the target set), which had to be held in memory for later recognition. The target set was followed by a 1500 ms delay period during which either a neutral picture or a negatively arousing picture was presented. After this, four letters (the probe set) were presented and participants had to indicate, as quickly and accurately as possible, whether or not the probe set contained a letter from the preceding target set.

Attentional-Blink Task

The attentional-blink paradigm is the most commonly used paradigm for investigating attentional selection in the temporal domain (for a review, see Martens and Wyble, 2010). The attentional blink refers to a deficit in processing the second of two target stimuli that are presented in close temporal succession. This deficit is most severe when the second target is presented within 200–400 ms after the first target (Raymond *et al*, 1992), and is thought to result from competition between the two target stimuli for limited attentional resources (Shapiro *et al*, 1997). When the two targets are presented within $\sim$200 ms, performance is often spared (see, eg, Hommel and Akyürek, 2005), a phenomenon termed 'lag-1 sparing'.

The temporal dynamics of the LC–NE system suggest that the LC–NE system mediates attentional selection in the temporal domain (Cohen *et al*, 2004; Dayan and Yu, 2006; Usher *et al*, 1999). LC neurons exhibit a phasic increase in activity shortly following task-relevant or otherwise motivationally significant stimuli (Aston-Jones *et al*, 2000). The resulting transient release of NE in cortical areas temporarily increases the responsivity of these areas to their input, which selectively facilitates the processing of the eliciting stimulus (Berridge and Waterhouse, 2003; Servan-Schreiber *et al*, 1990). Phasic increases in LC activity are followed by a brief refractory period during which LC–NE-mediated facilitation of information processing is temporarily unavailable (see, eg, Aghajanian *et al*, 1977). These temporal dynamics of the LC–NE system suggest that the attentional blink may be mediated by the LC–NE system (Nieuwenhuis *et al*, 2005a; Warren *et al*, 2009). Consistent with this idea, β-adrenergic blockade impaired detection of the second target in an attentional-blink task (De Martino *et al*, 2008).

On each trial of this task, participants viewed a rapid serial visual presentation (RSVP) stream consisting of two target stimuli (T1 and T2; digits) and multiple distractor stimuli (letters), presented for $\sim$100 ms each. The temporal distance between T1 and T2 was 1, 2, 3, or 7 items. Following each stream, participants were asked to report T1 and T2.

Visual-Search Task

This task examined attentional selection in the spatial domain. The spatially nonspecific pattern of LC projections to the cortex suggests that the LC–NE system does not mediate spatial attention (Cohen *et al*, 2004; Greenwood *et al*, 2005; Nieuwenhuis *et al*, 2007). This task was included to assess whether possible performance abnormalities of the DβH-deficient patients were restricted to NE-mediated tasks. On each trial of this task, participants searched for a target stimulus (a red vertical bar) among a variable number of distractor stimuli (green vertical bars and red horizontal bars) in a visual-search array, and indicated as quickly as possible whether the target stimulus was present or absent.

Oddball Tasks Combined with EEG Measurement

We examined the P3, a prominent component of the scalp-recorded event-related brain potential. The P3 component is a broad, positive, large-amplitude potential that peaks between 300 and 400 ms following presentation of stimuli in any sensory modality (Sutton *et al*, 1965), and is largest over central-parietal midline electrodes. The amplitude of the P3 is strongly affected by the subjective probability and motivational significance of the eliciting stimulus: P3 amplitude increases with decreasing probability and with increasing motivational significance of the eliciting stimulus. In contrast, with the exception of tone intensity (Roth *et al*, 1984), P3 amplitude is relatively insensitive to physical stimulus properties. Several lines of evidence suggest that the P3 reflects the phasic response of the LC–NE system to the outcome of stimulus evaluation and decision making, and the consequent effects of the noradrenergic

potentiation of information processing (reviewed in Nieuwenhuis *et al*, 2005b; see also Liu *et al*, 2009; Pineda *et al*, 1989).

The most common paradigm for studying the P3 is the oddball task, in which infrequent target stimuli are embedded in a series of frequently presented non-target stimuli (standards), and participants have to respond to each target stimulus but not to the standard stimuli. We measured participants' EEG while they performed visual and auditory versions of the oddball task, and assessed the P3 elicited by target stimuli.

Pitch-Discrimination Task Combined with Pupillometry

We examined participants' pupil diameter during performance of a pitch-discrimination task. Although the luminance level is the most important determinant of pupil diameter, there are also small but reliable changes in pupil diameter related to cognitive processing (Beatty and Wagoner, 1978; Kahneman, 1973). A large number of studies have shown that task processing is accompanied by a rapid increase in pupil diameter, and that the size of this pupil dilation reflects the information-processing load (see, eg, Hess and Polt, 1964).

Several studies have reported that DβH-deficient patients have small pupils, but a normal pupillary light reflex and accommodation response (Biaggioni *et al*, 1990; Man in 't Veld *et al*, 1987a; Robertson *et al*, 1986). In addition, one study reported a prolonged redilation time following the light reflex in a sibling pair with DβH deficiency (Smith and Smith, 1999). The light reflex and accommodation response both produce pupil constrictions, which are subserved by the iris sphincter muscles. These muscles are innervated by cholinergic input from the parasympathetic nervous system. In contrast, pupil dilation is controlled by the iris dilator muscles that are activated primarily via noradrenergic innervation of α-1 adrenoceptors (Hoffman and Taylor, 2001). This suggests that task-evoked pupil dilations in DβH-deficient patients might be abnormal.

On each trial of this task, a sequence of two tones was presented, and participants had to indicate whether the second tone was higher or lower in pitch than the first. We analyzed the baseline pupil diameter of the participants and their pupil dilation in response to the second tone.

RESULTS

The behavioral, EEG, and pupil data of the control participants were analyzed using repeated-measures ANOVAs, with session (session 1 *vs* session 2) and the independent task variables as within-subject factors. We tested whether the critical measures/effects in each patient OFF medication deviated from those in the control group using a modified *t*-test developed specifically to compare individual patients with a small control group (Crawford and Howell, 1998). In addition, we examined the effects of medication on the patients' scores, using the regression-based method developed by Crawford and Garthwaite (2006; see Supplementary Methods for details of these analyses).

We focus our description of the results on the critical measures/effects of each task. The full factorial analyses of the data, the PANAS (ie, subjective state) data, and results of the individual participants are reported in the Supplementary Results.

Table 2 Plasma and Urine Catecholamine Concentrations in the Control Group and the Patient Group OFF and ON Medication (Means ± SD)

	Healthy controls[a]	Patients OFF	Patients ON
Plasma NE	1.46 ± 0.45	0.10 ± 0.12	0.57 ± 0.13
Urine NE	—	5.50 ± 5.40	9682 ± 4839
Plasma DA	0.06 ± 0.02	1.28 ± 1.43	0.40 ± 0.40
Urine DA	—	1271 ± 903	793 ± 379

Abbreviations: OFF, off medication; ON, on DOPS medication.
[a]Plasma concentrations were determined for six control participants.
All concentrations are in nmol/l; see Supplementary Table 2 for the catecholamine concentrations of the individual patients and missing data.

Catecholamine Concentrations

Table 2 shows the average plasma and urine NE and DA concentrations in the patient group ON and OFF medication, and the plasma concentrations in the control group (see Supplementary Table 2 for the data from the individual patients). When OFF medication, two of the patients (patients 3 and 4) had plasma NE concentrations that were significantly lower than that in the control group (p's (one-tailed) <0.03; modified t-test of Crawford and Howell, 1998) and the other patients had undetectable plasma NE concentrations. The apparent extremely low residual plasma NE concentration in patients 3 and 4 were likely due to technical artifacts, as plasma concentrations of the NE metabolite dihydroxyphenylglycol (DHPG) were extremely low in these patients when they were OFF medication. DHPG concentrations in patients 3 and 4 OFF medication were <0.03 nmol/l, which is $<1\%$ of normal. As expected, the plasma and urine NE concentrations of all patients were higher when ON compared with OFF medication, and this effect was especially pronounced for the urine concentrations. For the ON-medication session, the plasma NE concentrations of patients 1 and 5 did not differ significantly from the control group (one-tailed $p=0.09$ and 0.08, respectively), but the plasma NE concentrations of patients 3 and 4 were still lower than that in the control group (one-tailed $p=0.048$ and 0.049, respectively).

When OFF medication, all patients had higher plasma DA concentrations than the control group (all p's <0.001). Although the plasma DA concentrations of most patients were lower when ON compared with OFF medication, the ON medication concentration was still larger than that in the control group for all but one patient. The medication effects on the urine DA concentrations were less consistent; patients 1 and 2 had higher urine DA concentrations when ON medication, whereas patients 3–5 showed the opposite effect.

Emotional Working-Memory Performance

The critical measure in this task was the interfering effect of emotional relative to neutral distractors on reaction time

(RT). As expected, the control participants responded more slowly on trials with emotional compared to neutral distractors ($F(1,7) = 14.7$, $p = 0.006$). In addition, consistent with previous studies (Oei *et al*, 2009, 2010), distractor type interacted with target presence ($F(1,7) = 16.3$, $p = 0.005$), indicating that the emotional-interference effect on RT was significant on target-present trials ($F(1,7) = 43.9$, $p < 0.001$; effect range = 80–299 ms) but not on target-absent trials ($F(1,7) = 0.75$, $p = 0.42$).

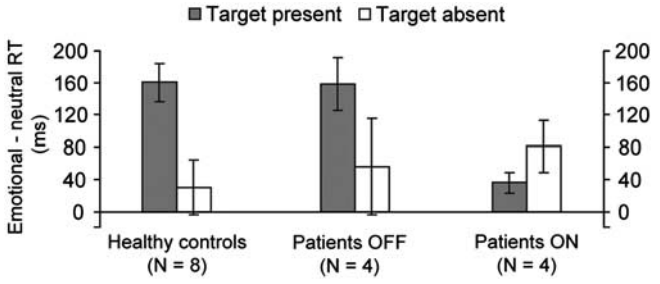

Figure 1 Average emotional-interference effect (ie, RT on trials with emotional relative to neutral distractors) for the control group and the patient group OFF and ON medication, as a function of target presence (error bars are SEM). Because session did not interact with distractor type or target presence in the control group, the results from the control group are averaged across the two sessions.

Figure 1 shows the average increase in correct RT on trials with emotional relative to neutral distractors as a function of target presence, in the control group and in the patient group OFF and ON medication. When OFF medication, all patients showed an emotion-related slowing of responses on target-present trials that did not differ from the effect in the control group (effect range = 72–226 ms; all t's (7) < 0.8; p's > 0.24; Table 3; see Supplementary Figure 2 for the individual effects). In addition, all patients showed a smaller emotional interference effect when they were ON compared to OFF medication, but this medication effect did not differ significantly from the control group's practice effect in any of the patients (all p's > 0.08; Table 3). The normal emotional-interference effect in the patients OFF medication, and the finding that this interference effect was less pronounced when the patients were ON medication are both remarkable given the evidence that emotional-interference effects are normally mediated by NE.

Table 3 For Each Critical Effect/Measure, the *P*-Value Reflecting the Significance of the Difference Between Each Patient's OFF Medication Score and the Average Score of the Control Group (Crawford and Howell, 1998), and the *P*-Value Indicating the Significance of the Deviation of Each Patient's Medication Effect from the Control Group's Practice Effect (Crawford and Garthwaite, 2006)

	Patient				
	1	**2**	**3**	**4**	**5**
Patient OFF medication vs control group					
Emotional-interference effect on RT in target-present trials	—	0.44	0.25	0.29	0.41
Attentional-blink size	0.051	—	0.19	0.10	0.38
Visual search efficiency in target-present trials	0.36	0.15	0.14	0.15	0.41
Visual search efficiency in target-absent trials	0.41	0.23	0.36	0.24	0.50
P3 amplitude auditory oddball task	0.10	0.34	0.16	0.09	**0.04**
P3 amplitude visual oddball task	0.27	0.32	0.13	**0.048**	**0.01**
Baseline pupil diameter	—	**0.03**	0.45	0.22	**0.002**[a]
Pupil dilation response	—	**0.03**	**0.003**	0.21	**0.001**
Brain volume (dm^3)	0.29	**0.006**	**0.03**	**0.01**	**0.02**
% Gray matter	0.46	0.16	0.16	0.10	0.053
% White matter	0.33	0.39	0.33	0.46	0.12
% Cerebrospinal fluid	0.39	0.30	0.45	0.30	0.35
Patient's medication effect vs control group's practice effect					
Emotional-interference effect on RT in target-present trials	—	0.19	0.09	0.18	0.19
Attentional-blink size	**0.045**	—	**0.003**	**0.049**	0.24
Visual search efficiency in target-present trials	0.45	0.28	0.28	0.28	0.39
Visual search efficiency in target-absent trials	0.22	0.11	0.18	0.50	0.16
P3 amplitude auditory oddball task	0.19	0.44	0.41	0.38	0.19
P3 amplitude visual oddball task	0.21	0.27	0.29	0.36	0.35
Baseline pupil diameter	—	0.25	0.20	**0.003**	0.21
Pupil dilation response	—	0.34	**0.03**	**0.04**	0.08

[a]This patient had significantly larger pupils than the control group, which was due to a genetic defect unrelated to DBH deficiency: a mosaic deletion at chromosome 11p13 (Erez *et al*, 2010).
The *p*-values < 0.05, which indicate that the estimated percentage of the normal population that would show a more extreme effect is $< 5\%$, are bold-faced.
(—) Indicates that no data were collected.

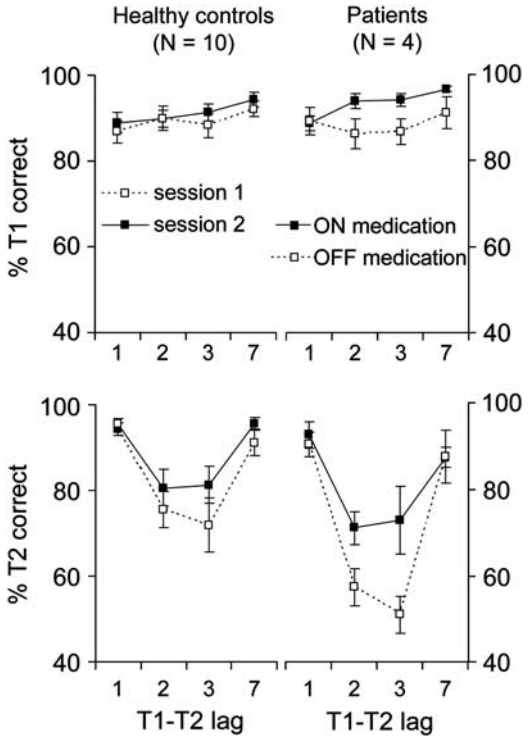

Figure 2 Average T1 and T2 identification accuracy in the attentional-blink task for the control group and the patient group, as a function of lag and session (error bars are SEM). Trials on which T1 and T2 were accurately identified but in the wrong order were treated as correct. As is usual, T2 accuracy is reported contingent on accurate identification of T1.

The full factorial analysis of the effects of target presence, working-memory load, distractor type, and session on correct RT and accuracy in the control group is reported in the Supplementary Results and in Supplementary Figure 1.

Attentional-Blink Performance

Figure 2 shows the average T1 accuracy (upper panels) and T2 accuracy (lower panels; contingent on correct T1 identification) in the control group and the patient group, as a function of lag (1, 2, 3, or 7) and session. The T2 accuracy curves show a pattern that is characteristic of attentional blink data: lag-1 sparing, followed by a drop in performance for lags 2 and 3 (ie, the attentional blink), and a recovery of performance at lag 7. This pattern was expressed in a significant effect of lag in the control group ($F(3, 27) = 12.1$, $p = 0.001$).

The critical measure in this task is the size of the attentional blink, which we defined as the decrease in T2 identification accuracy at lags 2 and 3, relative to lag 7 (Maclean and Arnell, 2010). When OFF medication, the patient group showed a larger attentional blink than the control group (average = 33.5 *vs* 16.7%), but the difference from the control group only approached significance in patient 1 (Table 3; see Supplementary Figure 3 for the individual T2 accuracy curves). In addition, the patients showed a smaller attentional blink when they were ON compared with OFF medication: for three of the four patients tested on this task, the effect of medication on attentional-blink size was significantly larger than the practice effect in the control group (p's < 0.05; Table 3). The fourth patient also showed a marked increase in T2 accuracy when ON compared with OFF medication, but this did not result in a significant effect on attentional-blink size because the enhancing effect of medication was present at lags 2, 3, and 7. Together, these findings suggest that T2 identification accuracy during the attentional blink was impaired in the patients OFF medication, and that this impairment was restored by the DOPS medication.

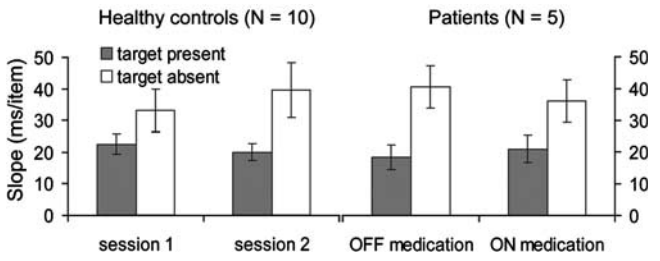

Figure 3 Average visual-search slopes for the control group and the patient group, as a function of target presence and session (error bars are SEM).

Visual-Search Performance

The critical measure in this task was the effect of set size (ie, the total number of items in the search display) on RT. As expected, RT in the control group showed an increasing trend with set size ($F(2, 18) = 29.7$, $p < 0.001$), and set-size effects were larger for target-absent than target-present trials ($F(2, 18) = 7.8$, $p = 0.004$). The variation in set size allowed us to derive the function relating RT to set size. The slope of this function measures the cost for adding additional items to the display and is often interpreted as 'search efficiency', with steeper slopes indicating slower, less efficient search.

Figure 3 shows the average slopes for the control group and the patient group, as a function of target presence and session. The average slopes in the patient group were very similar to those in the control group, both ON and OFF medication. In the OFF-medication session, none of the patients' slopes deviated significantly from the control group (all t's (9) < 1.2; p's > 0.13; Table 3; see Supplementary Figure 5 for the individual slopes). In addition, the effects of medication did not differ significantly from the control group's practice effect in any of the patients (all p's > 0.11; Table 3). These results indicate that the patients had normal visual search efficiency, both ON and OFF medication.

The full factorial analysis of the effects of target presence, set size, and session in the control group is reported in the Supplementary Results and in Supplementary Figure 4.

The P3 Component of the EEG

P3 amplitudes were maximal at electrode Pz in both the control group and the patient group; hence, we focused our analyses on this electrode position. Figure 4 shows the grand-average waveforms for standard and target stimuli in the visual and auditory oddball task, for the control group and the patient group ON and OFF medication. As expected, P3s were much larger for target stimuli than for standard

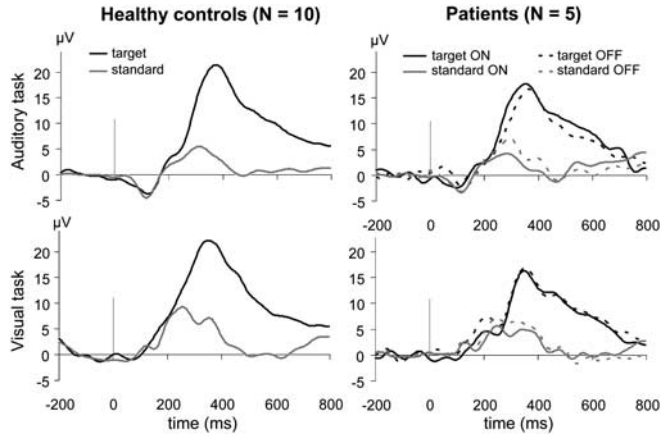

Figure 4 Grand-average waveforms for electrode Pz for the control group and the patient group, time locked to the onset of the target and standard stimuli, in the auditory and visual oddball tasks. Because P3 amplitude in the control group did not differ across sessions ($F(1,9) = 0.1$, $p = 0.72$), the data for the control participants are averaged across the two sessions.

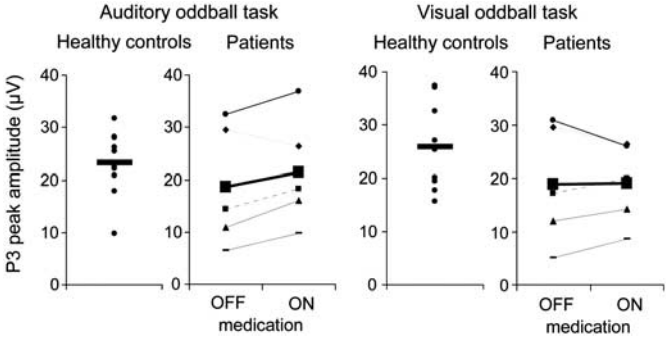

Figure 5 P3 amplitudes for the control participants and the patients in the auditory and visual oddball tasks. The bold lines indicate the grand-average amplitudes, and the thinner lines and points indicate the amplitudes of each individual participant. Because there was no effect of session in the control group, the data for the control participants are averaged across the two sessions.

stimuli. Figure 5 shows the P3 amplitudes of the individual participants.

When OFF medication, patient 5 showed a significantly smaller P3 amplitude than the control group in both the auditory and the visual oddball task, and patient 4 showed a significantly smaller P3 amplitude than the control group in the visual oddball task only (Table 3). For the other patients, P3 amplitude did not differ significantly from the control group. The effect of medication on P3 amplitude did not differ significantly from the control group's test–retest effect in any of the patients (all p's > 0.19; Table 3). These findings suggest that some but not all patients showed a P3 that was smaller than the P3 in the normal population, independently of whether they were ON or OFF medication.

The analyses of target-detection performance (RT and accuracy) are reported in the Supplementary Results and in Supplementary Figure 6.

Pupil Diameter during the Pitch-Discrimination Task

The average baseline pupil diameter in the control group was 3.86 mm (SD = 0.56), and did not differ across the two sessions ($t(7) = 0.31$, $p = 0.77$). When OFF medication, patient 2 had significantly smaller pupils than the control group. Patient 5 had significantly larger pupils than the control group, which was due to a mosaic deletion at chromosome 11p13, unrelated to her DβH deficiency (Erez *et al*, 2010). The baseline pupil diameter of the other patients did not differ significantly from the control group (Table 3; see Supplementary Table 1 for each patient's baseline pupil diameter). Remarkably, patient 4 had significantly smaller pupils when he was ON compared with OFF medication. For the other patients, there was no significant effect of medication on baseline pupil diameter (Table 3).

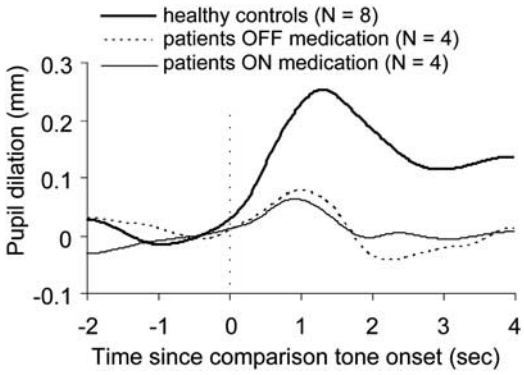

Figure 6 Time course of the grand-average pupil dilations in response to the comparison tone, for the control group and the patient group ON and OFF medication.

We next assessed the magnitude of the task-evoked pupil dilations. As expected, all control participants showed a substantial pupil dilation following the comparison tone (average pupil dilation = 0.16 mm; SD = 0.04). Pupil dilation in the control group was not significantly affected by session ($F(1,7) = 2.3$, $p = 0.17$) or tone-discrimination difficulty ($F(3,21) = 2.4$, $p = 0.09$). Figure 6 shows the time course of the grand-average pupil dilation following the comparison tone, for the control group and the patient group ON and OFF medication. When OFF medication, all but one patient showed significantly smaller task-evoked pupil dilations than the control group (see Supplementary Table 1 for each patient's average pupil dilation). Remarkably, patient 4 showed a significantly smaller pupil dilation when ON compared with OFF medication. The pupil dilation of patient 3 was also significantly affected by medication, but this result must be interpreted with caution because this patient's pupil dilations were negative in both sessions. For the other patients, there was no significant effect of medication on the task-evoked pupil dilation (Table 3).

The analyses of tone-discrimination performance (RT and accuracy) are reported in the Supplementary Results and in Supplementary Figure 7.

Brain Structure

Table 4 shows the average total brain volumes and the percentages of gray matter, white matter, and cerebrospinal fluid (CSF) in the patient group and the control group, separately for the male and female participants. Four of the five patients had a smaller total brain volume than the

Table 4 Whole-Brain Volume and Percentage of Gray matter, White Matter, and CSF for the Control Group and the Patient Group, Separately for the Male and Female Participants (Means ± SD)

	Control group		Patient group	
	Men ($N=4$)	**Women ($N=5$)**	**Men ($N=2$)**	**Women ($N=3$)**
Brain volume (dm^3)	1.72 ± 0.05	1.46 ± 0.05	1.51 ± 0.06	1.30 ± 0.11
% Gray matter	47.2 ± 0.7	44.1 ± 1.8	47.0 ± 1.5	44.7 ± 3.2
% White matter	38.7 ± 1.2	39.3 ± 2.0	38.5 ± 0.5	38.9 ± 2.2
% CSF	14.1 ± 1.7	16.5 ± 2.4	14.5 ± 1.0	16.4 ± 1.4

Abbreviations: CSF, cerebrospinal fluid.
We did not collect MRI data from one female control participant.

control group. However, the proportions of gray matter, white matter, and CSF did not differ from the control group in any of the patients (Table 3; see Supplementary Table 1 for the data of the individual patients).

The voxel-based morphometry analysis (Supplementary Material) revealed no significant topographic differences in gray matter density between the patient group and the control group. The TCFE-corrected *p*-values for both the controls > patients contrast and the patients > controls contrast were >0.34 in all voxels, suggesting that there were no trends for a group difference in gray matter density in any brain region. Together, these results suggest that most of the patients had an overall smaller brain than the control group, but that this difference was not confined to a specific tissue type or brain region.

DISCUSSION

This study was the first systematic investigation of neurocognitive function in DβH deficiency. We tested five DβH-deficient patients and a matched healthy control group on a comprehensive cognitive task battery. In addition, we examined whether the patients differed from the control group with regard to the P3 component of the EEG, pupil dynamics, and brain structure.

The performance of the patients on most cognitive tasks did not differ substantially from the healthy control group, irrespective of whether they were ON or OFF DOPS medication. More specifically, the patients showed normal visual-search efficiency, tone-discrimination performance, and target-detection performance, and a normal emotional-interference effect. In addition, we found an intact P3 component in most patients. As DOPS medication effectively ameliorates the orthostatic hypotension of DβH-deficient patients, medication-related changes in blood pressure and consequent effects on fatigue and affective state are important factors to take into account when comparing the performance of patients ON *vs* OFF medication. However, it is unlikely that these factors were responsible for the lack of medication effects on cognitive performance, for the following reasons. First, potential effects of fatigue or other physical symptoms on task performance would predict impaired performance when patients were OFF relative to ON medication, which was not found in most tasks. Second, the patients reported no substantial differences in affective state between the two sessions (Supplementary Table 3). Third, the critical measures in our cognitive tasks were difference scores (ie, differences between task conditions); hence general medication-related effects on performance would cancel out in these difference scores.

The only cognitive function that was affected in the patients OFF medication was attentional selection in the temporal domain, as reflected by an increased attentional blink (ie, impairment in processing the second of two target stimuli that are presented in close temporal succession). The attentional blink has not only been associated with NE (De Martino *et al*, 2008; Nieuwenhuis *et al*, 2005a; Warren *et al*, 2009), but also with DA (Colzato *et al*, 2008); Colzato *et al* (2008) have provided indirect evidence that higher DA levels are associated with a smaller attentional blink. Because DβH-deficient patients do not convert DA to NE, they are not only characterized by a lack of NE but also by increased DA levels (Man in 't Veld *et al*, 1987a), and DOPS medication both increases NE levels and reduces the excessive DA levels (Man in 't Veld *et al*, 1987b; Thomas *et al*, 1998). Thus, based on the DA levels of the patients, it would be predicted that the patients OFF medication would show a smaller attentional blink than the healthy control group, and that the patients would show a smaller attentional blink OFF medication than ON medication. Since the opposite effects were found, this strongly suggests that the increased attentional blink in the patients OFF medication was due to the absence of NE rather than the excess of DA.

The largely spared neurocognitive function in the DβH-deficient patients is remarkable given the large body of evidence suggesting that the LC–NE system plays an important role in many aspects of neurocognitive function (for recent reviews, see Robbins and Arnsten, 2009; Sara, 2009). For example, individual differences in noradrenergic genotype in the normal population are predictive of performance on cognitive tasks measuring attention (Greene *et al*, 2009) and working memory (Parasuraman *et al*, 2005), and have been related to vulnerability to several psychiatric disorders (see, eg, Cubells and Zabetian, 2004; Roman *et al*, 2002). In addition, DβH-knockout mice that lack NE because of a targeted disruption of the *DβH* gene show several behavioral deficits, including impairments in active-avoidance learning (Thomas and Palmiter, 1997a), memory retrieval (Murchison *et al*, 2004), and maternal and social behavior (Marino *et al*, 2005; Thomas and Palmiter, 1997b). Finally, pharmacological, neurophysiological, and

lesion studies in animals suggest that the LC–NE system plays a crucial role in regulating the optimization of behavioral performance (see, eg, Aston-Jones and Cohen, 2005; Bouret and Sara, 2005). However, it must be noted that our task battery did not address all aspects of cognitive function. For example, we did not assess higher-level cognitive functions such as executive control and exploratory behavior. Therefore, our results leave open the possibility that the patients have subtle cognitive deficits that were not revealed by our task battery. In addition, although our data clearly indicate that there were no substantial abnormalities in the performance of the patients on our test battery, it cannot be excluded that there were some subtle differences that failed to reach significance because of a lack of power of our experimental design.

Although the relatively normal performance of the patients on our cognitive task battery is striking, it is consistent with informal clinical observations that DβH-deficient patients do not have obvious cognitive impairments or psychiatric disorders. Indeed, the absence of mental problems in most DβH-deficient patients who have been encountered so far has intrigued investigators in the areas of depression and schizophrenia (Cubells and Zabetian, 2004). It is especially remarkable that the patients OFF medication did not show impaired performance on cognitive tasks that are normally mediated by the LC–NE system (eg, the emotional working-memory task), and showed a relatively intact P3 component, which is thought to reflect the noradrenergic potentiation of information processing (Liu *et al*, 2009; Nieuwenhuis *et al*, 2005b; Pineda *et al*, 1989). These findings suggest that alternative neural mechanisms and/or neuromodulatory systems compensate for the absence of NE in DβH-deficient patients. Previous findings that DβH-deficient patients have a relatively normal sleep pattern (Tulen *et al*, 1990, 1991), although the sleep–wake cycle is normally mediated by the LC–NE system (Hobson *et al*, 1986; Jouvet, 1969), are consistent with this idea.

Since DβH is responsible for the conversion of DA to NE, it is thought that DA rather than NE is stored and released by noradrenergic neurons in DβH-deficient patients. Indeed, plasma DA levels in DBH-deficient patients respond to various physiological and pharmacological manipulations that normally affect plasma NE levels (Man in 't Veld *et al*, 1987a; Robertson *et al*, 1986), although it remains to be determined whether this also applies to DA levels in the central nervous system. Thus, a possible explanation for the spared neurocognitive function in DβH deficiency is that DA has, to some extent, taken over the function of NE in the brains of DβH-deficient patients. Obviously, a functional replacement of NE by DA would require the presence of postsynaptic receptors with DA affinity in noradrenergic synapses. Studies in mice suggest that some α2-adrenergic receptor subtypes have a comparable affinity for DA and NE (Zhang *et al*, 1999), whereas α1- and β-adrenergic receptors have a much lower affinity for DA than for NE (Zhang *et al*, 2004). However, as the congenital absence of NE may have altered the affinity of adrenergic receptors, it is unknown whether the same receptor characteristics apply to DβH-deficient patients. Another possible explanation for a functional replacement of NE by DA is that DβH-deficient patients have an increased density of postsynaptic DA receptors on noradrenergic synapses. A recent positron emission tomography (PET) study in mice suggests that DβH-knockout mice have a normal density of D2 dopamine receptors in the high-affinity state (Skinbjerg *et al*, 2010), which does not support this hypothesis. However, as results from DβH-knockout mice might not be generalizable to human DβH-deficient patients, the assessment of DA receptor densities in human DβH-deficient patients, for example using PET scanning, remains an important objective for future studies.

It is interesting to note that the first study that used gene targeting to produce DβH-deficient mice found that the majority of DβH-deficient embryos died in mid-gestation and only 5% reached adulthood (Thomas *et al*, 1995). To prevent embryonic lethality, subsequent studies using DβH-knockout mice have supplied the embryos with adrenergic agonists (isoproterenol and phenylephrine) and DOPS via the maternal drinking water, such that NE is present in the DβH-knockout mice until birth. The results of Thomas *et al* (1995) suggest that the human DβH-deficient patients may represent the minority of DβH-deficiency cases who have survived this condition. If this is true, an interesting speculation is that these patients were able to survive because they happened to have optimal dopaminergic or noradrenergic genotypes to compensate for the absence of NE. Future studies might assess this possibility by examining whether the frequency of occurrence of specific alleles of dopaminergic and noradrenergic genes (eg, the COMT, DAT, and the dopamine and noradrenergic receptor genes) in DβH-deficient patients deviates from those in the normal population.

In contrast to the generally normal neurocognitive function in the DβH-deficient patients, we did find clear abnormalities in their task-evoked pupil dilation response. The task-evoked pupil dilation was very small or absent in most of the patients, which might be due to a decreased noradrenergic innervation of the iris dilator muscle. However, it is also possible that the abnormal pupil dynamics in some of the patients resulted from ocular abnormalities unrelated to their DBH deficiency; this might explain why the pupil-dilation response was not restored by DOPS medication. Importantly, the small or absent task-evoked pupil dilations of the patients did not reflect a decreased processing of the task-related stimuli, as their performance on the tone-discrimination task, during which their pupils were measured, was not impaired.

The patient group also differed from the control group with regard to total brain volume: all but one patient had a significantly smaller brain volume than the control group, but the relative proportions of gray matter, white matter, and CSF, and the distribution of gray matter volume across the brain did not deviate from those in the control group. The smaller brain volume in most of the DBH-deficient patients is in line with recent findings suggesting that NE has a neurotrophic effect on cortical neurons (see, eg, Counts and Mufson, 2010; Kalinin *et al*, 2007; Madrigal *et al*, 2007, 2009). Apparently, the decreased brain volume of the patients did not result in cognitive impairments; this suggests that although the patients have a smaller number of neurons, their neurons are intact and make proper connections.

To conclude, our findings suggest that neurocognitive function in human DβH-deficient patients is largely spared,

even when they are OFF medication, but that their total brain volume is smaller than that of the normal population. The normal neurocognitive function in DβH-deficient patients is striking given the important role of NE in normal cognition, but corroborates informal clinical observations that most patients do not have obvious cognitive impairments. Our findings suggest that DβH-deficient patients have developed alternative mechanisms to compensate for the absence of NE in the brain, possibly through a functional replacement of NE by DA; the nature of these compensatory mechanisms remains to be explored by future studies.

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DISCLOSURE

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)