Journal of Vestibular Research 24 (2014) 403–413
DOI 10.3233/VES-140526
IOS Press

Assessment of cerebral dopamine $D_{2/3}$-receptors in patients with bilateral vestibular failure

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Received 1 January 2014
Accepted 28 May 2014

Abstract.
BACKGROUND: Absence of peripheral vestibular input in bilateral vestibular failure (BVF) has been suggested to induce plastic reorganization in various brain regions. Among several neurotransmitters, dopamine is known to play a key role in cortico-striatal-sensorimotor processing. However, the role of dopamine in vestibular plasticity is scantly documented.
OBJECTIVE: Assessment of $D_{2/3}$-receptors in patients with BVF.
METHODS: $D_{2/3}$-receptor-PET using [^{18}F]fallypride and MRI examinations were performed in 12 BVF-patients and 13 healthy controls.
RESULTS: BVF-patients showed reduced $D_{2/3}$-receptor availability (approximately 40%) in the temporo-parieto-occipital cortex bilaterally, including the multisensory vestibular cortex and visual motion-sensitive areas (MT/MST), as well as in the striatum and the right thalamus. Longer illness duration was associated with bilaterally lower $D_{2/3}$-receptor availability in the middle/superior temporal gyrus (GTm/s). $D_{2/3}$-receptor availability in the right GTm/s and bilateral insula decreased with severity of symptoms. BVF-patients with oscillopsia showed reduced $D_{2/3}$-receptor availability in the right MT/MST and midbrain tectum.
CONCLUSIONS: Reduced $D_{2/3}$-receptor availability in multisensory vestibular cortical network areas and basal ganglia may indicate a receptor down-regulation due to the lack of peripheral vestibular input. The more pronounced decline in $D_{2/3}$-receptor availability in the multisensory vestibular cortex in patients with prolonged illness suggests the occurrence of progressive changes in dopamine transmission.

Keywords: [^{18}F]FP, PET, dopamine $D_{2/3}$-receptors, bilateral vestibular failure

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ISSN 0957-4271/14/$27.50

1. Introduction

It still remains speculative which neurotransmitter systems mediate vestibular signalling and processing within the multisensory vestibular cortical network (for review [15]). First insights into the basis of neurotransmission in the peripheral and central vestibular systems have been furnished [15], however, the importance of neurotransmitter changes for pathophysiology and clinical symptomatology in vestibular disease like bilateral vestibular failure (BVF) remains to be clarified.

The initially severe symptoms following uni- and bilateral vestibular damage ameliorate with time as a function of vestibular compensation. Experiments in animals have shown that amplified non-labyrinthine sensory inputs following the onset of BVF may explain the early recovery of postural stability and orthostatic tolerance, without compensating the permanent loss of the vestibulo-ocular reflex (VOR) and impaired spatial cognition [29]. In humans with BVF, cerebral blood flow activation studies with $H_2^{15}O$ PET during caloric vestibular stimulation showed a significantly attenuated activation of the vestibular network [6]. In contrast, in a fMRI study of BVF-patients undergoing visual stimulation an enhanced activation of the visual cortex occurred bilaterally, which is suggestive of visual cortical substitution as a mechanism for compensation of the chronic BVF [13].

Several types of dopamine receptors are implicated in processes leading to cortico-striatal synaptic plasticity [23], but nothing is known about the specific role for dopamine in vestibular neurotransmission or cortical reorganisation in humans with vestibular failure. Pharmacological studies in animals and humans suggested involvement of the dopaminergic system in the recovery of clinical symptoms in vestibular syndromes [16,44]. Moreover, bilateral labyrinthectomy in rats resulted in age-dependent changes in striatal dopamine $D_{2/3}$-receptors [18], suggesting that subcortical dopaminergic mechanisms contribute to aspects of cortico-striatal plasticity and compensatory mechanisms.

Based upon these observations on a dopaminergic role in central vestibular compensation, and against the background of the relatively high density of dopamine receptors in areas important for vestibular processing (e.g. striatum, thalamus, hippocampus, temporoparietal and insular cortex [30], we hypothesized that $D_{2/3}$-receptor expression is altered in patients with BVF and therefore conducted an exploratory PET study of dopamine $D_{2/3}$-receptors in patients with established BVF using the high affinity $D_{2/3}$-ligand [^{18}F]fallypride.

2. Methods

2.1. Subjects

12 BVF patients from the IFB$^{\mathrm{LMU}}$, German Center for Vertigo and Balance Disorders, and the Department of Neurology, as well as 13 age- and sex-matched healthy controls (HC) were included in the study. Aetiology of BVF was a bilateral manifestation of Menière's disease in two patients; all other cases were of idiopathic origin without evidence for additional inner ear or brain disease or injury. Exclusion criteria were the following: 1) medications known to act on vestibular or ocular motor functions, 2) dopaminergic medications, 3) diagnosis of typical or atypical Parkinson syndrome, or 4) past medical history of any major neuropsychiatric disorder. All subjects gave their informed, written consent to participate in the study, which was in compliance with the declaration of Helsinki and approved by the Ethics Committee of the Ludwig-Maximilians-University of Munich, Germany.

2.2. Clinical neurological and neuro-ophthalmological examinations

All subjects underwent a neuro-otologic examination, including neuro-orthoptic analysis. BVF was defined by a diminished calorically elicited nystagmus of $< 5°$/s slow phase velocity (SPV) [3] and/or a pathologic head impulse test bilaterally [21]. All patients were asked for presence of oscillopsia (disturbance of the visual scene during movement). Vestibular testing and MRI scans were performed on the same day as the PET imaging.

2.3. Self-rating scales

In order to assess subjective symptom burden, functioning and quality of life, we performed several self-rating scales: 1) The two subscales of the *Vertigo Symptom Scale (VSS)*, i.e. *Vertigo and Related Symptoms Score (VER*), which examines symptoms of balance system dysfunction and *Somatic Anxiety and Autonomic Arousal Score (AA)*, which assesses accompanying anxiety related symptoms [42]; 2) *Vertigo Hand-*

Table 1
Patient characteristics

Patient	Age	Sex	Duration (years)	Aetiology	Oscillopsia	VER*	AA*	VHQ*
1	71	m	3	Menière's disease	yes	0.41	0.62	36
2	62	f	3	Idiopathic	yes	1.94	0.00	14
3	71	m	3	Idiopathic	yes	0.7	1.15	34
4	89	m	8	Idiopathic	yes	0.7	0.38	22
5	70	f	3	Idiopathic	yes	0.53	1.23	68
6	66	f	4	Menière's disease	no	0.53	1.23	47
7	44	m	2	Idiopathic	yes	0.76	1.38	68
8	63	m	4	Idiopathic	no	0.02	1.23	5
9	58	m	11	Idiopathic	no	2.11	0.92	66
10	52	f	2	Idiopathic	no	2.82	0.38	37
11	70	m	2	Idiopathic	yes	0.41	0.38	10
12	28	f	1	Idiopathic	yes	0.94	1.23	24
Mean $\pm$ SD	62.0 ± 15.5		3.8 ± 2.9			0.99 ± 0.84	0.84 ± 0.47	35.9 ± 22.4

VER: Vertigo and Related Symptoms Score (subscore of Vertigo Symptom Scale); AA: Somatic Anxiety and Autonomic Arousal Score (subscore of Vertigo Symptom Scale); VHQ: Vertigo Handicap Questionnaire.

icap Questionnaire (VHQ) to document physical and psychosocial impairments of vertigo or dizziness [43]; 3) *Beck Depression Inventory (BDI*) to test for depression and impulsivity [4]; 4) *Edinburgh Laterality Quotient for Handedness* [36] to account for aspects of hemispherical dominance in the human multisensory vestibular cortex [14].

2.4. MR-imaging and analysis

In all subjects, anatomical MRI (3D T1-weighted sequences with a slice thickness of 1 mm) was performed for anatomical co-registration and exclusion of structural brain disease with 3.0 Tesla magnets (Signa HDx, 3T GE Healthcare, Milwaukee, USA). In addition, an explorative voxel-based morphometry (VBM) analysis was performed by means of SPM 8 (Wellcome Trust Centre for Neuroimaging, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). In brief, MRIs were segmented by using the New Segment option implemented in SPM 8 and the resulting gray matter images were afterwards spatially normalized in the standardized anatomic space using the DARTEL algorithm [1]. To preserve gray matter volume within each voxel, images were modulated by the Jacobean determinants derived from the spatial normalization by DARTEL and then smoothed by using an 8 mm FWHM Gaussian kernel. The resultant values represent a quantitative measure of gray matter tissue volume per unit volume of the spatially normalized images [2]. Clusters were considered as significant for $p < 0.01$ (uncorrected).

2.5. Radiochemistry and PET-imaging

[^{18}F]fallypride (FP) was synthesized as described previously [34]. PET data were acquired with an ECAT EXACT HR^{+} PET tomograph (Siemens/CTI, Knoxville, TN, USA). The patient's head was comfortably immobilized within the aperture using a foam cushion. Following a 15 minute transmission scan with a rotating [^{68}Ge] point source, a three hour continuous dynamic 3D emission recording was started immediately upon administration of approximately 200 MBq [^{18}F]fallypride (mean dose 202 $\pm$ 7 MBq) as a slow intravenous bolus. The dynamic emission data consisted of 39 time frames (3×20 s, 3×1 min, 3×2 min, 3×3 min, 21×5 min, 2×8 min and 4×10 min). All studies were reconstructed using a 3D filtered back-projection algorithm, including correction for scatter, random coincidences, attenuation, decay and dead-time. Since head motion is very likely to occur during the protracted PET image acquisition procedure, a frame-by-frame based movement correction was applied as described in detail elsewhere [11,35]. No differences in head movement were found between the BVF and HC group.

2.6. PET-image analysis

The entire motion-corrected data were linearly co-registered to the corresponding T1-weighted MR image using automated algorithms implemented in SPM8. Anatomical brain MR images were then spatially normalized into the Montreal Neurological Institute standard template (MNI, McGill University, Montreal QC, Canada) using an affine transformation (12 parameters for rigid transformations) [17], and these parameters were applied to the coregistered motion-corrected PET data. Then, the program pip (Aarhus University PET Centre) was used to calculate voxel-wise parametric maps of the [^{18}F]fallypride binding potential (BP_{ND})

Table 2
Areas with reduced $D_{2/3}$-receptor availability in BVF-patients compared to age-matched controls

Cerebral hemispheres	Cluster	P	T	x	y	z	BP_{ND}P	$BP_{ND}HC$
Decreased $D_{2/3}$-receptor availability								
L temporo-occipital lobe (MT/MST)	838	0.003	3.05	−52	−66	−10	0.44 ± 0.22 (−41%)	0.75 ± 0.28
R temporo-occipital lobe (MT/MST)	219	0.003	2.99	42	−78	8	0.27 ± 0.12 (−41%)	0.46 ± 0.12
L inf. parietal lobule	130	0.013	2.39	−58	−48	22	0.34 ± 0.19 (−37%)	0.54 ± 0.22
L middle temp. gyrus	42	0.011	2.45	−58	−30	−14	0.54 ± 0.16 (−25%)	0.73 ± 0.22
R sup. temp. gyrus	151	0.005	2.79	56	0	−2	0.41 ± 0.15 (−34%)	0.62 ± 0.22
R inf. parietal lobule	50	0.009	2.55	40	−56	30	0.14 ± 0.06 (−39%)	0.23 ± 0.11
R occipital lobe (lingual gyrus)	91	0.002	3.30	18	−70	−10	0.10 ± 0.08 (−63%)	0.27 ± 0.17
L insula (incl. PIVC)	505	0.007	2.67	−34	12	4	0.89 ± 0.31 (−34%)	1.34 ± 0.47
R anterior insula	293	0.003	2.97	26	24	0	1.12 ± 0.43 (−35%)	1.71 ± 0.51
R posterior insula (incl. PIVC)	501	0.005	2.81	44	−22	0	0.26 ± 0.13 (−41%)	0.44 ± 0.19
Anterior cingulum	193	0.008	2.58	0	22	−8	0.69 ± 0.24 (−36%)	1.07 ± 0.54
L cingulum	53	0.007	2.68	−10	4	40	0.22 ± 0.08 (−31%)	0.32 ± 0.10
L parahippocampal gyrus	113	0.005	2.78	−42	−20	−16	0.31 ± 0.15 (−35%)	0.48 ± 0.15
R thalamus	149	0.001	3.71	18	−12	10	4.04 ± 1.12 (−28%)	5.58 ± 0.93
L striatum	494	< 0.001	4.45	−20	14	0	17.95 ± 2.72 (−14%)	20.96 ± 2.08
R striatum	289	0.001	3.45	18	22	0	9.47 ± 2.94 (−35%)	13.49 ± 2.71

Significance level $p < 0.05$, uncorrected; extrastriatal changes are presented after exclusion of basal ganglia; R: right, L: left, Cluster: cluster size in voxels, P: p-value T: T-value, x, y, z: coordinates in MNI space, BP_{ND} P: mean $BP_{ND} \pm$ standard deviation in BVF-patients, BP_{ND} *HC:* mean $BP_{ND} \pm$ standard deviation in healthy controls.

Table 3
Areas of reduced $D_{2/3}$-receptor availability in BVF-patients correlated with A) longer disease duration, B) higher Vertigo Handicap Questionnaire (VHQ) Score, and C) presence of oscillopsia

Cerebral hemispheres	Cluster	P	T	x	y	z
A) Disease duration						
R middle/sup. temp. gyrus	261	0.000	6.34	48	−48	8
R middle temp. gyrus	120	0.010	3.14	58	−10	−12
L sup. temp. gyrus	73	0.003	4.28	−60	−38	16
R lingual gyrus	86	0.008	3.28	20	−55	−10
B) Vertigo handicap questionnaire (VHQ) score						
R lingual gyrus	320	0.001	4.74	14	–46	−8
R middle temp. gyrus	137	0.001	4.49	44	−64	20
Anterior cingulum	155	0.003	3.50	−4	26	−12
L anterior insula	115	0.008	2.97	−30	20	−8
R sup. temporal gyrus	75	0.008	2.95	56	−18	4
R insula	190	0.014	2.63	34	12	2
L striatum	1403	0.002	3.92	−12	10	14
R striatum	561	0.012	2.72	28	18	6
R thalamus	99	0.008	2.94	22	−28	6
C) Oscillopsia						
Midbrain tectum	62	0.000	10.64	0	−42	−20
R middle/inf. temp. gyrus	145	0.000	5.46	58	−44	−4

Multivariate analysis, significance level $p < 0.05$, uncorrected; Multivariate regression analysis corrected for age and VHQ-score; R: right, L: left, Cluster: cluster size in voxels, P: p-value T: T-value, x, y, z: coordinates in MNI space.

using the Logan linear graphical method [28], with the cerebellum serving as the reference tissue.

BP_{ND}-maps of BVF-patients were compared with those of the normal control group in a voxel-wise manner using SPM8 for between-group analysis. Significance level was defined as $p < 0.05$ and 0.01 if applicable (uncorrected) and cluster size > 40 voxels. In a separate SPM analysis intended to optimize the detection of subtle group differences in receptor availability in extra-striatal brain areas, the entire striatum was masked with an AAL-Atlas based striatal template [40]. Additional SPM multivariate regression analyses were performed to test the effect of illness duration as well as symptom load represented by VHQ score. In order to exclude age as a confounding factor, patient's age was included as a covariate. Furthermore, we tested if $D_{2/3}$-receptor availability in BVF patients was related to the presence of oscillopsia as a

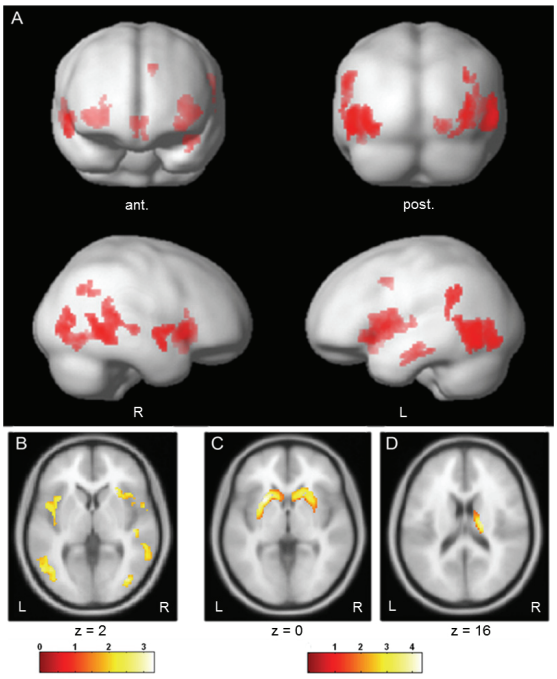

Fig. 1. Comparison of patients vs. age-matched healthy controls ($p < 0.05$; uncorrected): Cortical $D_{2/3}$-receptor availability was decreased bilaterally in the motion sensitive areas (MT/MST), the temporo-parieto-occipital cortex, the anterior insula, as well as in the cingulum (A and B; for illustration purposes subcortical clusters were excluded). Subcortical $D_{2/3}$-receptor availability was decreased bilaterally in the striatum (C) and in the right thalamus (D) (for illustration purposes cortical clusters were excluded in C and D).

symptom by means of two-sample t-test implemented in SPM. For the visualization of the T-score statistics, significant voxels were projected onto the 3-D rendered brain or a standard high-resolution MRI template provided by SPM8, thereby allowing anatomical identification. The nomenclature of anatomical structures follows Talairach and Tournoux [39]. The clusters obtained with the individual SPM analyses were extracted using the program Marsbar implemented in SPM [8]. Mean BP_{ND} values within these clusters were calculated for both the HC and BVF patient groups.

3. Results

3.1. Patient characteristics

Detailed patient characteristics are presented in Table 1. All patients had pathological head-impulse tests bilaterally and except for one pathological values ($<$ 5°/s) for SPV of caloric nystagmus (mean: 2.8 $\pm$ 1.3°/s). Eight patients reported oscillopsia on head movement. One patient had bilaterally reduced vibration sensation of the legs (mild polyneuropathy) and one had a descreet saccadic gaze pursuit and a bilateral gaze evoked nystagmus without any other signs of cerebellar disorder. All patients had stable stance on Romberg's-Test with eyes open. On sensorial perturbation, i.e., eyes closed or tandem stance, body sway markedly increased, but all patients performed these tasks without help.

In BVF-patients, mean VSS was 0.9 $\pm$ 0.63 (mean range 0–4) with mean VER-subscore of 0.99 $\pm$ 0.84 and mean AA-subscore of 0.84 $\pm$ 0.47 (mean range 0–4 each), mean VHQ-score was 35.92 $\pm$ 22.43 (range 0–100), indicating a mild to medium burden of symptoms and disability. BDI-scores were different between patients and HC (mean values 6.3 vs. 2.5; mean range 0–63), however, for both groups markedly below the threshold ($<$ 11) for diagnosis of a mild and manifest depression.

3.2. $D_{2/3}$-receptor binding in patients vs. healthy controls

BVF-patients presented with widespread bilateral reductions in $D_{2/3}$-receptor availability in cerebral cortical and subcortical areas (Table 2). Considering first the cortical regions, the most significant reduction of $D_{2/3}$-receptor availability was found bilaterally in the temporo-parieto-occipital cortex, comprising clusters assigned to multisensory vestibular areas, e.g., the inferior parietal lobule (IPL), the insula, especially the parieto-insular vestibular cortex (PIVC) as well as the cingulum, and motion-sensitive areas (MT/MST). Clusters of reduced BP_{ND} were also detected in the bilateral striatum and in the right thalamus; mean voxel-wise reductions within the clusters were in the range of 25–60% (Table 2 and Fig. 1). Mean BP_{ND} maps show the reduced $D_{2/3}$-receptor availability bilaterally in the temporo-parieto-occipital cortex as well as in the striatum in BVF-patients in comparison with the age-matched control group (Fig. 2). Additional VOI-based analysis revealed no significant differences in mean BP_{ND} values of BVF-patients and HC in other cortical areas such as frontal cortex, central region and brainstem.

3.3. $D_{2/3}$-receptor binding in correlation with duration of illness

Multivariate regression analysis corrected for age and VHQ-score revealed that longer disease dura-

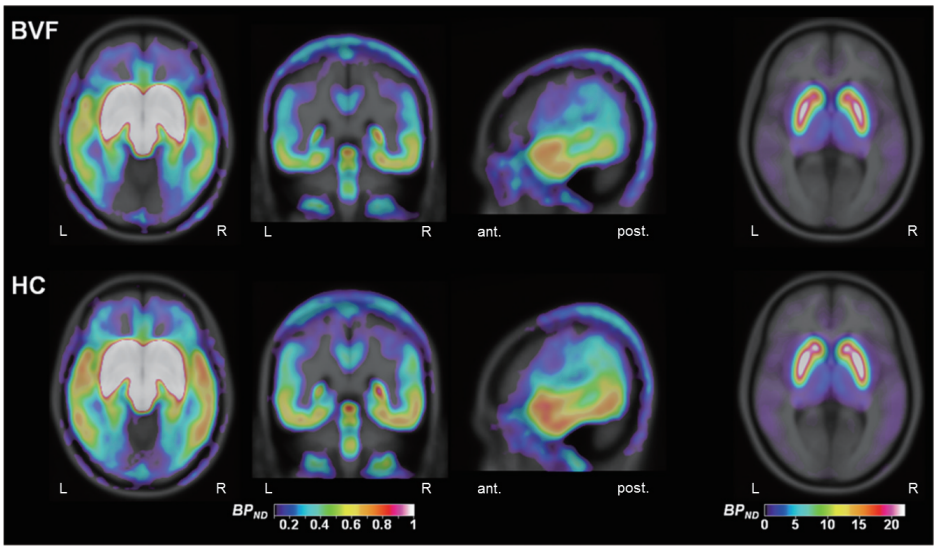

Fig. 2. Mean BP_{ND} maps showing the reduced $D_{2/3}$-receptor availability bilaterally in the temporo-parieto-occipital cortex as well as in the striatum in BVF-patients (upper row) in comparison with the age-matched control group (lower row).

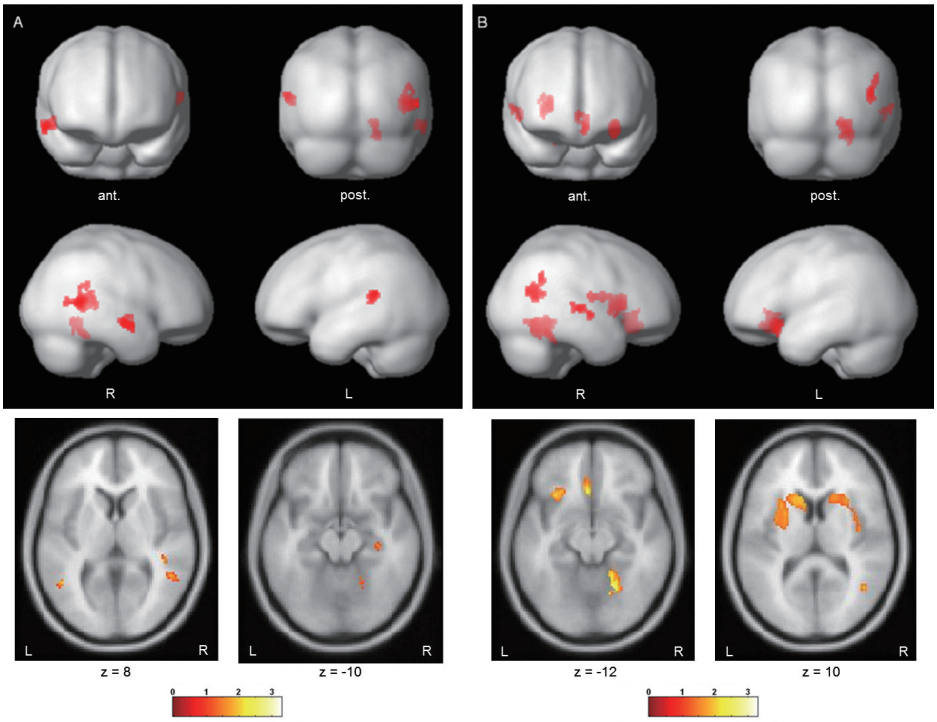

Fig. 3. A: Multivariate regression analysis revealed reduced $D_{2/3}$-receptor availability in BVF-patients with longer disease duration bilaterally in the middle/superior temporal gyrus and temporo-parieto-occipital junction included in multisensory vestibular cortex areas and in the right lingual gyrus ($p < 0.05$ uncorrected; age-corrected). B: Multivariate regression analysis showed reduced $D_{2/3}$-receptor availability in BVF-patients with higher VHQ score in the right middle/superior temporal gyrus, the IPL, the insula bilaterally, the right lingual gyrus and the anterior cingulum, representing multisensory vestibular cortex areas, as well as bilaterally in the striatum and the right thalamus ($p < 0.05$ uncorrected; age-corrected).

tion was associated with a relatively greater reduction in $D_{2/3}$-receptor availability bilaterally in the middle/superior temporal gyrus and temporo-parieto-occipital junction included in multisensory vestibular cortex areas and in the right lingual gyrus (Table 3A and Fig. 3A).

3.4. $D_{2/3}$-receptor binding in correlation with clinical symptoms, functioning and disability

The $D_{2/3}$-receptor availability was correlated inversely with indicators of functioning and disability (assessed by VHQ), as well as presence of clinical symptoms (e.g. oscillopsia) by means of a multivariate regression and supgroup-wise comparative analysis corrected for age and disease duration: higher VHQ-scores were related to lower $D_{2/3}$-receptor binding in the right middle/superior temporal gyrus, the IPL, the insula bilaterally, the right lingual gyrus and the anterior cingulum, representing multisensory vestibular cortex areas, as well as bilaterally in the striatum and the right thalamus (Table 3B, Fig. 3B). Multiple regression analysis was also performed for VSS-subscores (VER and AA). Only higher VSS-AA-scores were related to lower $D_{2/3}$-receptor in bilateral middle/superior temporal gyrus and anterior insula as well as in the anterior cingulum (data not shown). BVF-patients presenting with oscillopsia as a subjective symptom showed a trend towards reduced $D_{2/3}$-receptor availability in the motion-sensitive areas of the right middle temporal gyrus (MT/MST) and in the midbrain tectum near to the superior colliculi (Table 3C, Fig. 4).

3.5. VBM-analysis

In order to exclude that some of our results were related to atrophy effects an additional VBM analysis of the gray-matter volume was performed. When compared to HC BVF-patients revealed only smaller clusters with significant lower VBM values ($p < 0.01$ uncorrected) in the left cerebellar crus I, bilaterally in the central region, in the frontal cortex, in the right occipital cortex, in the left supramarginal gyrus and in the left middle temporal gyrus. Of note, the direct comparison of the location as well as the extent of the respective SPM clusters in our PET and VBM analysis was not congruent. In addition, another VBM analysis in BVF-patients presenting with and without oscillopsia revealed no difference between groups.

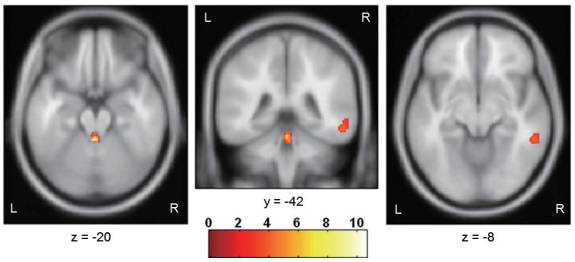

Fig. 4. Comparison of patients with and without oscillopsia ($p < 0.01$; uncorrected): a trend towards reduced $D_{2/3}$-receptor availability was found in the right middle temporal gyrus and in the midbrain tectum/superior colliculi.

4. Discussion

In healthy subjects, a network of separate and distinct cortical vestibular areas was described in the temporo-parieto-occipital cortex bilaterally [45], which includes the PIVC in the posterior insula, the visual temporal sylvian area (VTS) and retroinsular cortex, the superior temporal gyrus, the IPL, the anterior cingulum and the hippocampus. Together, these regions form a multisensory cortical circuit, with the PIVC serving as its core region with reciprocal connectivity to the other cortical regions as well as to the thalamus and the vestibular nuclei [15]. Compensatory changes such as up- and down-regulation of neuronal activity in different cortical areas, especially in the visual and vestibular cortex, have been described in association with loss of vestibular failure input, which might also be indicative for a plastic cortical reorganization of the multisensory vestibular cortical network [5,13,15]. These adaptations are thought to minimize the intersensoric mismatch and to facilitate the process of central compensation. The underlying changes in neurotransmission as well as the neurotransmitters involved in accommodation to vestibular failure systems, however, are scarcely established. Several lines of evidence implicated changes of dopamine in these processes, not just in the vestibular cortex, but also in the basal ganglia. Thus, a rodent study [16] gave initial evidence that the dopaminergic system might play an important role for the central processing of vestibular information as well as in adaptive processes associated with recovery from vestibular asymmetries: treatment with a dopamine D_2-receptor agonist improved vestibular compensation after unilateral labyrinthectomy in aged rats, facilitated the decline of spontaneous nystagmus and improved motor performance as well as coordination [16]. Similar effects were also seen in hemi-labyrintectomized guinea

pigs after treatment with the D_2-like receptor agonist bromocriptine, which was found to accelerate the compensation of postural and ocular symptoms, whereas conversely treatment with a D_2-like antagonist delayed the regaining of symmetrical posture and stable ocular motility [32]. In contrast, treatment with a dopamine $D_{2/3}$-antagonist facilitated recovery of humans with unilateral vestibular dysfunction [44]. In summary, these animal studies in unilateral vestibular failure indicate that the dopaminergic system plays an important role in vestibular processing. However, its functional importance in humans with bilateral vestibular dysfunction is not clear yet.

4.1. Dopaminergic neurotransmission in the multisensory vestibular cortical network in BVF

In line with these previous findings, our results speak for a prominent role of cerebral dopamine transmission in the compensatory adaptation of the multisensory vestibular cortical network. While some $D_{2/3}$-receptors in cerebral cortex are associated with astrocytes, the preponderance are found in spines and dendrites and in both excitatory and inhibitory axon terminals [31] of interneurons and small pyramidal cells [41], where they may be poised to mediate aspects of synaptic plasticity. Compared to HC, BVF-patients presented with bilaterally reduced cortical $D_{2/3}$-receptor availability in the IPL, the middle temporal gyrus, the anterior and posterior insula and cingulum, the latter areas all belonging to the multisensory vestibular cortical network [7,14,15]. The magnitudes of these cortical reductions were approximately 40% relative to mean values in the age-matched control group, thus exceeding the reductions in binding of an alternate dopamine $D_{2/3}$-receptor ligand reported in hippocampus of Alzheimer's disease patients [25] or in temporal and frontal cortex of Parkinson's disease patients [24]. Duration of disease in BVF was associated with a progressive decrease of $D_{2/3}$-receptor availability in the multisensory vestibular cortical areas of the temporo-parieto-occipital junction, which might be suggestive of long-term dynamics in synaptic plasticity in patients with vestibular deficits [27]. Present findings are probably not attributed to atrophy, since our additional VBM analysis, although reflecting a trend only, did not reveal an overlap with areas of reduced $D_{2/3}$-receptor availability. Yet, we could replicate some of the findings of reduced gray-matter volume after unilateral vestibular deafferentation, such as in the cerebellar crus I and in the central region [22]. These regions showed no alterations of $D_{2/3}$-receptor availability in our PET analysis.

Importantly, the relation of $D_{2/3}$-dopamine availability in the multisensory vestibular cerebral network with self-rated severity of disease, disability and functioning in our BVF-patients reveals a functional significance of these dopaminergic changes for pathophysiology and clinical symptomatology. The cortical areas with decreased $D_{2/3}$-receptor availability are responsible for the cortical processing of information pertinent to maintaining balance. The core region PIVC, located at the parieto-insular junction of the non-dominant hemisphere, is thought to be a multimodal sensory cortex that integrates vestibular, proprioceptive as well as visual information [10,14,15]. The vestibular network is represented in both hemispheres, with a functional predominance of the right hemisphere in right-handers [6,14]. This seems consistent with the present over-all finding of apparently greater decreases in cortical $D_{2/3}$-receptor availability in the right hemisphere (see Fig. 3A) of our patients most of whom were right-handed.

4.2. Dopaminergic neurotransmission in the motion-sensitive visual cortical network in BVF

Additional structures within the visual processing network closely working with these vestibular cortical areas to maintain balance are the motion-sensitive areas MT/MST. Recent data from rhesus monkeys suggest that dorsal MST (MSTd) is an early stage of sensory convergence involved in transforming visual information (optic flow) into a head-centered reference frame that facilitates integration with vestibular signals [19]. In our study, area MT/MST also showed reduced cortical $D_{2/3}$-availability in parallel to the reduction within the vestibular cortex. As the vestibular input is reduced in BVF-patients, the need for integration of visual signals with vestibular signals accordingly declines [36], resulting, we suppose, in the observed decrease of $D_{2/3}$-receptor availability in MT/MST. A suppression of cortical visual motion processing was also reported in patients with unilateral vestibular failure with fMRI during visual motion stimulation [12]. The diminished activation of visual motion processing areas was explained by an adaptive mechanism that suppresses distressing oscillopsia in patients with unilateral vestibular failure and thereby stabilizes the perceived visual surroundings. Interestingly, in our study presence of oscillopsia as a complaint was accompanied by a reduced $D_{2/3}$-receptor

availability in the motion-sensitive area MT/MST and the midbrain tectum near the superior colliculi. As a potential interpretation these changes of dopamine transmission may hamper multisensory or ocular motor compensation processes of VOR-deficiency. Especially synaptic plasticity in the superior colliculus, which is an important center in saccade generation pathways, may propagate a visually-guided anticipatory substitution of the deficient VOR during head movement by covert saccades [20].

4.3. Dopaminergic neurotransmission in the subcortical network in BVF

Reduced availability of dopamine $D_{2/3}$-receptors was found in the right thalamus and bilateral striatum. These subcortical findings seem relevant to the neuronal pathway from the vestibular nucleus complex via thalamus to striatum [7]. Indeed, some previous animal studies indicated the loss of vestibular sensory input in BVF manifests in altered dopamine $D_{2/3}$-receptor expression in striatum [18,33], as well as in thalamus, which mediates the integration of multisensory information from cortical and subcortical structures [38]. The magnitude and direction of the $D_{2/3}$-receptor alterations reported in the several rats studies have been variable, and stand in partial contrast to our findings of clearly decreased striatal $D_{2/3}$-receptor binding, evident in the caudate nucleus to visual inspection (Fig. 2). In our elaborate neurological examination, none of the patients presented with signs of hypokinesia or rigidity, which might be explained by the relatively slight reduction of striatal $D_{2/3}$-receptor availability when compared to the reductions seen in patients with atypical Parkinson's syndrome [26]. However, a reduced walking speed was reported in BVF-patients [37], which might be partially explained by striatal dopamine loss [9]. Thus, our finding of reduced striatal $D_{2/3}$-receptor availability would further corroborate the potential role of striatal dopaminergic mechanisms underlying gait and balance dysfunction. Alternately, these findings may be indicative of an adaptive mechanism also in subcortical structures, whereby down-regulation of striatal $D_{2/3}$-receptor binding may contribute to compensation of sensorimotor integration in the absence of vestibular input, or in association with functional substitution by visual pathways. Notably, the striatal $D_{2/3}$-receptor reduction, while bilateral, was more pronounced on the right side, and the reduction in [^{18}F]-fallypride BP_{ND} in thalamus of the patient group, which was restricted to the right side, was even more pronounced (-43%) with longer disease duration, consistent with the predominance of vestibular cortical changes in the non-dominant hemisphere [6,14].

One limitation of this study is the restricted sample size, which allows only analyses uncorrected for multiple testing in the present cross-sectional, exploratory study. Furthermore, only patients in a chronic stage of disease were included. Since major processes of vestibular compensation are known to occur during the early phase of the disease, one might speculate that compensatory changes in the cerebral dopamine transmission may match the temporal dynamics of clinical adaptation. Therefore, investigation of vestibular plasticity at earlier time points and its relationship with the dopamine $D_{2/3}$-receptors is desirable in future longitudinal studies.

5. Conclusion

The observed changes in $D_{2/3}$-receptor availability in BVF-patients give first evidence for an involvement of the dopaminergic system in synaptic plasticity of the multisensory vestibular and motion-sensitive visual cortical network in humans. The association of vestibular and visual symptoms with reduced $D_{2/3}$-receptor availability in the multisensory vestibular cortical areas as well as the motion-sensitive area MT/MST and the midbrain tectum might indicate relevance for pathophysiology. Dependent on the stage of disease dopaminergic treatment might improve vestibular handicap as well as oscillopsia.

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