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Reach and grasp deficits following damage to the dorsal pulvinar

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ABSTRACT

Expansion of the dorsal pulvinar in humans and its anatomical connectivity suggests its involvement in higher-order cognitive and visuomotor functions. We investigated visuomotor performance in a 31 year old patient (M.B.) with a lesion centered on the medial portion of the dorsal pulvinar (left > right) due to an atypical Sarcoidosis manifestation. Unlike lesions with a vascular etiology, the lesion of M.B. did not include primary sensory or motor thalamic nuclei. Thus, this patient gave us the exceedingly rare opportunity to study the contribution of the dorsal pulvinar to visuomotor behavior in a human without confounding losses in primary sensory or motor domains. We investigated reaching, saccade and visual decision making performance. Patient data in each task was compared to at least seven age matched healthy controls. While saccades were hypometric towards both hemifields, the patient did not show any spatial choice bias or perceptual deficits. At the same time, he exhibited reach and grasp difficulties, which shared features with both, parietal and cerebellar damage. In particular, he had problems to form a precision grip and exhibited reach deficits expressed in decreased accuracy, delayed initiation and prolonged movement durations. Reach deficits were similar in foveal and extrafoveal viewing conditions and in both visual hemifields but were stronger with the right hand. These results suggest that dorsal pulvinar function in humans goes beyond its subscribed role in visual cognition and is critical for the programming of voluntary actions with the hands.

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1. Introduction

Evolutionary history and ontogenetic development together with fronto-parietal connectivity of the dorsal pulvinar suggest its contribution to higher cognitive functions and in particular to primate-specific abilities such as complex visuomotor transformations that require the integration of visual with eye and hand position information (Grieve, Acuna, & Cudeiro, 2000; Preuss, 2007). The pulvinar is a typical association nucleus with strong reciprocal connections to a multitude of modality specific and multimodal cortical areas (Benarroch, 2015; Gutierrez, Cola, Seltzer, & Cusick, 2000). The pulvinar is a heterogeneous structure for which different parcellations schemes have been proposed, depending on the anatomical techniques that were used such as cyto-, myelo- or chemoarchitecture (Jones, 2007). However, most authors agree on at least four major subdivisions in human and non-human primates, consisting of anterior pulvinar (PuA), medial pulvinar (PuM), lateral pulvinar (PuL) and inferior pulvinar (PuI). Together, the medial pulvinar and the dorsal portion of the lateral pulvinar form the so called 'dorsal pulvinar', which roughly occupies the region dorsal to the level of the brachium of the superior colliculus (BSc) (Gutierrez et al., 2000; Kaas & Lyon, 2007). The majority of pulvinar studies have investigated its ventral aspect, which is retinotopically organized and is connected with striate and extrastriate visual cortices in monkeys and humans (Arcaro, Pinsk, & Kastner, 2015; Saalmann & Kastner, 2011). In contrast to the ventral pulvinar, the dorsal pulvinar portion does not contain an orderly retinotopic or visuomotor topography (Benevento & Port, 1995) and is reciprocally interconnected with cortical regions that underlie the coordination of visually-guided movements, such as posterior parietal and prefrontal cortices (Arcaro et al., 2015; Barron, Eickhoff, Clos, & Fox, 2015; Gutierrez et al., 2000; Jones, 2007; Rosenberg, Mauguiere, Catenoix, Faillenot, & Magnin, 2009). Response properties of dorsal pulvinar neurons resemble the complexity found in fronto-parietal cortices, i.e., neuronal firing correlates with visual attention, subjective perception, decision confidence as well as the planning and execution of eye- and hand movements (Bender & Youakim, 2001; Benevento & Port, 1995; Dominguez-Vargas, Schneider, Wilke, & Kagan, 2017; Komura, Nikkuni, Hirashima, Uetake, & Miyamoto, 2013; Magarinos-Ascone, Buno, & Garcia-Austt, 1988; Wilke, Mueller, & Leopold, 2009; Yirmiya & Hocherman, 1987). There is also evidence from pulvinar lesion studies in monkeys (Komura et al., 2013; Robinson & Petersen, 1992; Wilke, Kagan, & Andersen, 2013; Wilke, Turchi, Smith, Mishkin, & Leopold, 2010; Zhou, Schafer, & Desimone, 2016) and humans (Arend, Rafal, & Ward, 2008; Karnath, Himmelbach, & Rorden, 2002; Rafal, McGrath, Machado, & Hindle, 2004; Snow, Allen, Rafal, & Humphreys, 2009; Van der Stigchel, Arend, van Koningsbruggen, & Rafal, 2010; Ward, Danziger, & Bamford, 2005; Zihl & von Cramon, 1979) that the pulvinar is a critical contributor to a wide range of higher-order visual and oculomotor functions including attentional orienting, visual search, emotion recognition and saccadic decision making. At the same time, although an initial dorsal pulvinar inactivation study in monkeys suggests its critical contribution to the programming of reach and grasp movements (Wilke et al., 2010), there is a marked paucity of studies that tested basic visuomotor functions involving hand usage in humans (Benarroch, 2015; Bridge, Leopold, & Bourne, 2016).

This is particularly surprising given that multimodal signals from a wide range of well-studied cortical visuomotor areas converge in the dorsal pulvinar and it has thus been proposed to facilitate cortico-spinal control over movements and possibly better parietal-premotor integration for the flexible control of goal-directed movements (Cappe, Morel, Barone, & Rouiller, 2009; Grieve et al., 2000; Guillery & Sherman, 2002). In the present study, we investigated visuomotor functions with a focus on reach performance in a patient with a circumscribed lesion centered on the medial portion of the dorsal pulvinar. This patient provided the unique opportunity to unravel the contribution of the pulvinar to proper visuomotor behavior without lesions in functionally pertinent first-order thalamic nuclei (Sherman, 2016), and without primary sensory or motor deficits. Based on our previous dorsal pulvinar inactivation study in monkeys (Wilke et al., 2010), we hypothesized that the patient would show reach inaccuracies and initiation delays, possibly with a stronger effect for the (right) hand and space located opposite to the more pronounced pulvinar lesion (left). From an optic ataxia we expected reaching errors to be stronger in extrafoveal as compared to foveal reaches (Andersen, Andersen, Hwang, & Hauschild, 2014; Perenin & Vighetto, 1988), a comparison not available from pulvinar lesion studies in monkeys.

2. Material and methods

2.1. Participants

2.1.1. Patient M.B.

Patient M.B. is a right-handed 31 year old male with an atypical cerebral manifestation of a systemic Sarcoidosis (Hoitsma, Drent, & Sharma, 2010). Sarcoidosis is a rare disorder that shows CNS manifestations in 2–26% of the cases with many atypical lesion locations (Fritz, van de Beek, & Brouwer, 2016). In patient M.B. the neural manifestation of the sarcoidosis affected the thalamic pulvinar on both sides. The patient's symptoms started with walking problems, headache and loss of appetite. These symptoms improved after an initial high dose corticosteroid therapy. Several weeks later, his symptoms relapsed and he was referred to our hospital. The diagnosis of Sarcoidosis was secured by thoracic biopsies together with pathological CD4/CD8 ratio in the bronchoalveolar-lavage and histopathological documentation of epithelioid-cell granulomas that followed the detection of suspicious lymph nodes in the abdominal-CT and FDG-PET-CT (Fritz et al., 2016). All examinations described in this paper were done in February 2016, within the two weeks when the disease cause was just diagnosed.

2.1.1.1. Localization of the lesion. The pulvinar lesion was larger on the left side than on the right and included large portions of the medial pulvinar as well as a small portion of the anterior pulvinar. On the right side, initially only a small portion of the medial pulvinar was affected (Fig. 1). This right

pulvinar hyperintensity (on T2-weighted FLAIR images) was faint in February 2016 (the first admission to the hospital and the period in which all our reported behavioral testing was done), but was repeatedly detected. Routine diagnostic MR examinations based on T1-weighted contrast (with and without contrast agent) and contrast agent-based brain perfusion did not show any other alteration. A bilateral (and stable circumscribed) pulvinar lesion was then visible in all repeated scans from May–November 2016. This supported our interpretation that the right pulvinar lesion has been already present in February. Lesions did not involve the ventral pulvinar or surrounding primary sensory or motor thalamic nuclei (e.g., ventral anterior or lateral thalamic nuclei). Brainstem nuclei, cerebellum and cortex were structurally intact as evidenced by MRI (Fig. 1, Supplementary Figs. S1 and S2).

To facilitate delineation of suspected lesion areas within the thalamus, these were mapped on the co-registered Morel atlas. While different pulvinar parcellation schemes exist (Benarroch, 2015; Jones, 2007), we here adopt the traditional terminology also used by the Morel atlas (Morel, Magnin, & Jeanmonod, 1997), subdividing the pulvinar into anterior or oral pulvinar (PuA), medial pulvinar (PuM), lateral pulvinar (PuL) and inferior pulvinar (PuI). In this scheme, the lesion of M.B. was centered on the medial pulvinar with an anterior extension into the anterior pulvinar on the left side and possibly also a small portion of the centromedian nucleus on the left side as well.

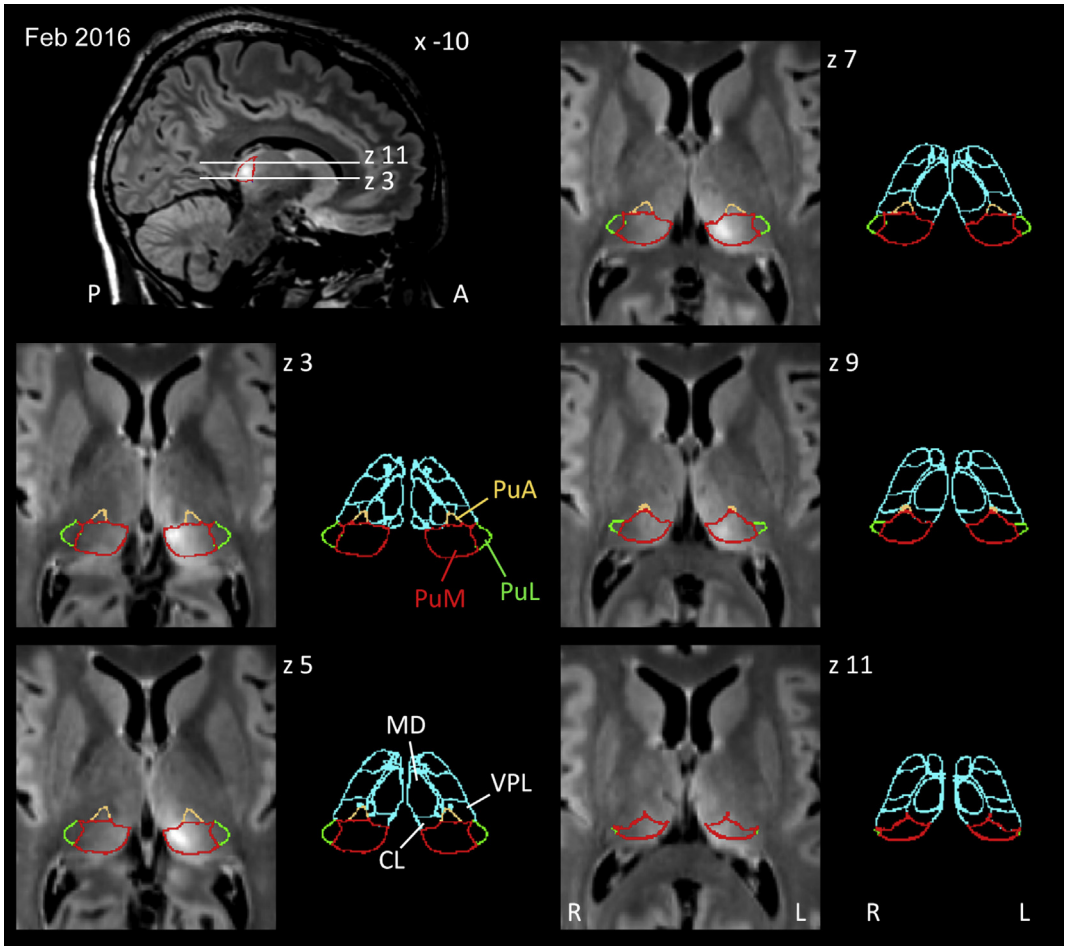

Fig. 1 – Lesion reconstruction of patient M.B. Magnified views of fluid-attenuated inversion recovery (FLAIR) MR images of patient M.B. in MNI-space, co-registered to the digital version of the Morel atlas. Images were acquired in February 2016 when the behavioral testing took place. The top left shows a sagittal section indicating the orientation of the axial cross-sections. FLAIR images show hyperintensity in the medial pulvinar on both sides, stronger in the left pulvinar (radiological convention with left hemisphere shown on the right side). Lesions spared the ventral pulvinar portions, anterior thalamus, brainstem, cerebellum and surrounding cortices. Cross-sections show the lesioned thalamic regions based on the overlaid pulvinar regions defined by the Morel atlas. Corresponding sections of the Morel atlas with all regions are shown on the right to the FLAIR images. The thalamic regions from the Morel atlas are outlined in light blue, except for medial pulvinar (PuM, red), lateral pulvinar (PuL, green), and anterior pulvinar (PuA, orange). A: anterior; CL: central lateral nucleus; L: left; MD: mediodorsal nucleus; P: posterior; R: right; VPL: ventral posterior lateral nucleus. x, z (in mm) denote the level of the cross-sections in MNI-space.

2.1.1.2. Neurological and neurophysiological examination. The corresponding neurological and neurophysiological examination took place within the first two weeks after hospital admission in February 2016. At that time, the patient's cranial nerve examinations were normal except for a slight posture-dependent down-beat nystagmus (while sitting upright but not while lying down in the horizontal position). His smooth pursuit was normal and there were no indications of gaze palsy. Further neurological and neurophysiological examinations showed normal vestibulo-ocular reflexes, no primary vestibular dysfunction with normal caloric tests, normal subjective visual vertical (SVV) and no visual impairment with normal visually evoked cortical potentials (VEP), visual acuity and visual field perimetry tests. The reflex-status, muscle tone and other sensory and muscle strength tests were normal. EEG, nerve conductance velocities, amplitudes and central motor conductance times were in the normal range. There was no indication of primary somatosensory or proprioceptive deficits with normal position and vibration sense and equal temperature and pain sensation on both sides. He did not display gait ataxia, wide-based stance and gait or other classical signs of cerebellar lesions such as impaired finger-to-nose test, heel-to-shin test, checking response or rebound phenomenon. Nevertheless, the patient had severe problems with upright stance and walking resembling an unusual form of (thalamic) astasia (Masdeu & Gorelick, 1988).

Over the course of several months after February, he developed a hand tremor with an unusual (dyskinetic-dystonic) hand posture as previously described as a delayed consequence of posterior thalamic lesions (Ghika, Bogousslavsky, Henderson, Maeder, & Regli, 1994; Kim, 2001; Miwa, Hatori, Kondo, Imai, & Mizuno, 1996). The development of dystonia, defined by sustained or repetitive muscle contractions resulting in twisting and repetitive movements or abnormal fixed postures (Albanese et al., 2013) with severe tremor prevented further (interpretable) testing of reach and grasp functions. Thus, all behavioral data presented in this paper were collected within two weeks in February 2016 when tremor and dystonia were not interfering with task performance.

2.1.2. *Neuropsychological testing of patient M.B*

Neuropsychological assessment revealed normal executive, memory and language functions apart from mild attentional impairments (Supplementary Table S1). Attentional functions were tested with the German equivalents of the Test of Attentional Performance (TAP) (Zimmermann & Fimm, 2002). Executive functions were tested with the Stroop color and word test (FWIT) (Bäumler & Stroop, 1985) and the Regensburger word fluency test (RWT) (Aschenbrenner, Tucha, & Lange, 2000). Learning and memory were tested with the forward and backward span of the Wechsler Memory Scale-Revised (WMS-R) (Härting et al., 2000) and the verbal learning and memory test (VLMT) (Helmstaedter, Lendt, & Lux, 2001). Based on the neuropsychological assessment, he exhibited normal executive, memory and language functions apart from a slight dysarthria. He showed mild attentional impairments in the subtests intrinsic and phasic alertness of the attentional performance battery (TAP) (Supplementary Table S1). There was no indication of spatial neglect or extinction, which was tested with the clinical confrontation method for visual auditory and somatosensory stimuli as well as with standard paper and pencil tasks (line bisection, line and apple cancellation test) (Fels & Geissner, 1997; Manning, Halligan, & Marshall, 1990; Mesulam, 1985). He showed deficits in the visuo-constructive mosaic subtest of the Wechsler Adult Intelligence Scale [WAIS –III (von Aster, 2006)], mostly because of his reach and grasp difficulties described below. While he was able to correctly describe location, shape and orientation of objects verbally, he typically adopted an abnormal hand posture when asked to grasp objects. At the same time, M.B. was able to perform tool use pantomime and imitate actions according to the Tulia-test (Vanbellingen et al., 2011), thus did not exhibit limb apraxia according to recent definitions (Osiurak & Rossetti, 2017).

2.1.3. *Healthy control subjects*

For each of the behavioral tasks we compared M.B. with a group of 7–8 healthy, age-matched subjects. Details of each group are given in the subject description within the respective method section. Normal controls were recruited from the local community and entailed mostly university students and employees.

2.2. MR-imaging

2.2.1. *MRI acquisition*

MRI was performed in the same week as the behavioral tests using a 3 T MR system (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) with a standard 32-channel phased-array head coil. Three-dimensional (3D) anatomical datasets at 1 mm^3 resolution were acquired with T1-weighting (turbo fast low angle shot (tFLASH), repetition time (TR): 2300 ms, inversion time (TI): 900 ms, echo time (TE): 2.96 ms, flip angle 9°) and with T2-weighting (fluid-attenuated inversion recovery (FLAIR), TR: 5000 ms, TI: 1800 ms, TE: 394 ms, integrated parallel acquisition technique: factor 2).

2.2.2. *Lesion mapping*

Anatomical data were analyzed using the FMRIB software library (FSL 5.0.7, Center for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, UK www.fmrib.ox.ac.uk/fsl). The T1-weighted tFLASH dataset was skull stripped (brain extraction tool BET) and registered to the standard brain template of the Montreal Neurologic Institute at 1 mm isotropic resolution (MNI152, provided with FSL), using the FMRIB's linear registration tool (FLIRT: 12 parameter affine transformation). The resulting transformation matrix was applied to the whole-head tFLASH dataset (without skull stripping) and the T2-weighted FLAIR dataset as well. In a second step, the linearly co-registered, whole-head tFLASH dataset was non-linearly registered to the MNI152 template using the FMRIB's non-linear registration tool (FNIRT). Again, the resulting transformation values were applied to the FLAIR dataset. Finally, FLIRT was used to sample the data to .5 mm isotropic resolution using the MNI152 template at .5 mm resolution. A digitalized version of the Morel atlas of the thalamus (Morel et al., 1997) provided by Krauth et al. (2010), registered to the high-resolution MNI 152 template allowed the visualization of the thalamic lesions in respect to the thalamic substructures detailed in the atlas.

2.3. Assessment of grasping performance

Grasping was assessed qualitatively by scoring movies (at normal and reduced replay speed) recorded in a task that involved reaching to and picking up small objects from a table (two near (central) and two far (more peripheral left and right) positions), similar to our previous pulvinar inactivation experiments in monkeys (Wilke et al., 2010). For each trial, we separately evaluated the occurrence of 1) reach errors (i.e., first contact with the table noticeably off target) and 2) grasp errors (inappropriate wrist angle, lack of precision grip, or too wide grip aperture).

2.4. Reaching experiments

2.4.1. Subjects

Apart from patient M.B., seven neurologically intact and age-matched subjects were tested (three males, mean age: 32.2 years, range: 26–39, SD = 4.5). None of the subjects had a history of psychiatric illness and all had normal or corrected-to-normal visual acuity.

2.4.2. Experimental setup and stimulus presentation

Subjects were sitting in a darkened room on a chair that was aligned to the center of the monitor with head and eyes facing straight ahead and with an eye-to-screen distance of 30 cm. Their head was stabilized by a chin rest and locked tight into the position with bars pressing against both sides of the head (HeadLock™ Ultra Precision Head Positioner ™, ViewPoint, Arrington Research, USA). Task controller and stimuli were programmed in MATLAB (The MathWorks, Inc. USA) using the Psychophysics Toolbox (Brainard, 1997). Stimuli were presented on a 27″ LED display (60 Hz refresh rate, model HN274H, Acer Inc. USA). Reaches were performed to a translucent surface acoustic wave touchscreen (IntelliTouch SCN-IT-FLT27.8-001-006, ELO Touch Solutions Inc. USA) placed in front of the monitor. After a custom-made digital to analog conversion, horizontal and vertical finger touch coordinates were recorded at 100 Hz with an external data acquisition card (USB-1208FS, Measurement Computing Corporation, USA). Real-time eye tracking was performed with a ViewPoint system (Arrington Research Inc. USA) running on a separate PC, where a mini-IR sensitive camera placed below subjects' right eye continuously sampled their gaze position at 60 Hz. The gaze position was then transferred to the task controlling PC using an Ethernet interface. Before the start of each experiment, the eye tracker was calibrated using the 4 × 5 point matrix from the ViewPoint software. An additional linear calibration implemented in the task controller guaranteed fast offset correction and gain refinement in case of slight head movements.

2.4.3. Visually-guided delayed reaching tasks

Before the start of the session and each block, the task and hand contingencies were explained to the subjects. M.B. and the control subjects performed the reach tasks in blocks in the same order. Task and hand varied as a function of block, which consisted of 20 successful trials. Each trial started with the onset of two dim fixation spots in the middle of the screen: a small .5° radius red circle (for eye fixation) and a larger 2° radius green circle (for the hand). Subjects were required to look at the red circle and to touch the green circle. The circles would then brighten up and subjects would have to maintain fixation for .5 sec to start the contingency-specific part of the trial. A peripheral 2° radius target stimulus at either 12° or 24° to the right or left of the central fixation circles cued the location of the movement. Subjects were instructed to start the reach when either one or both central circles disappeared after a delay of 1.28 sec. If only the central green circle disappeared, subjects had to make a reach while keeping their gaze at the red fixation spot (extrafoveal reaches). If both spots disappeared, subjects had to make a reach and were able to freely look for the remaining of the trial (foveal reaches). Once the hand was registered within a 5° window around the target center, the targets would brighten up and subjects would have to maintain their gaze/hand position for .5 sec on the target. Subjects had 4 sec to complete the movement and after each trial there was a 2 sec inter-trial interval.

2.4.4. Reach definitions and statistical analysis

Reach latency was defined as the time between fixation spot(s) offset and the moment when the hand lost contact with the touchscreen (reach onset). Reach duration was defined as the time from the reach onset to target acquisition. Reach endpoint was taken as the position of the first touchscreen contact after reach onset inside a 5° (radius) window around the target center. For horizontal and vertical axes, the inaccuracy was calculated as mean (across trials) signed offset between the reach position and the target center, for each target. The horizontal and vertical inaccuracy values are reported in Supplementary Table S2. Note that for both hemifields, negative values for the horizontal inaccuracy denote undershooting. Additionally, we calculated the absolute (Euclidean distance) inaccuracy defined as the square root of the sum of squared offsets for each axis, reported in Supplementary Table S2 and in Fig. 3E and F. Similarly, reach imprecision (endpoint scatter) was defined as the square root of the sum of squared standard deviations (across trials) of the signed reach offsets for each axis. Unless noted otherwise, we analyzed successful trials as a function of hemifield and hand while combining the 12° and 24° target eccentricities (to increase statistical power since both eccentricities yielded similar results). All data analysis was performed using MATLAB R2012b and the Statistics Toolbox (The MathWorks, Inc. USA). M.B.'s data were analyzed by using univariate analyses of variance (ANOVA) with the factors Task (foveal reach *vs.* extrafoveal reach), Space (left *vs.* right hemifield) and Hand (left *vs.* right hand). Statistical comparisons between M.B. and healthy controls were performed based on averaged data using Crawford's modified *t*-test for single case studies (Crawford & Garthwaite, 2002). Means as well as *t*- and *p*-values for the comparisons of interest are reported in the text and listed in Supplementary Table S2.

2.5. Visual spatial decisions

2.5.1. Subjects

Apart from the patient M.B., eight neurologically intact subjects were tested (four males, mean age: 25.6 years, range: 20–30, SD = 1.8).

2.5.2. *Visual stimuli*

The stimuli consisted of trains of stereo flickers of 3 sec duration that were presented on the horizontal plane of the screen at a horizontal eccentricity of 16°. Stimuli were drawn from a Poisson distribution. Each train had 6 flickers per second; each flicker duration was 16.7 ms. Consecutive flickers had a minimum inter-pulse interval of 120 ms to minimize adaptation (Brunton, Botvinick, & Brody, 2013). First and last flickers were presented bilaterally to prevent bias towards the side of the first or the last flicker presented. Stimuli were generated using MATLAB, version R2011b using custom scripts.

2.5.3. *Perceptual decision task*

Subjects were asked to perform a visual evidence accumulation task with two alternative forced choices, adapted from (Brunton et al., 2013) (Fig. 5A). Subjects had to determine whether more flickers were presented to the left or to the right side of the fixation spot. Each trial started with the presentation of a central red fixation cross, followed by a variable delay of 1–4 sec. The color of the fixation cross changed to green indicating the beginning of the trial. After a mandatory stable fixation period of 1 sec, stimuli were presented for 1–4 sec. Subjects were asked to respond with their right hand using the index finger to press key '1' for indicating that the trial had more stimuli on the left and key '2' with the middle finger when a trial had more stimuli on the right. No feedback was given to the subjects. The interval between trials was varied between 1 and 4 sec. Participants were asked to use the whole information presented to them in each trial to form their decision. Each participant completed one run with 48 trials.

2.5.4. *Behavioral data analysis*

We plotted the probability of a rightward choice as a function of number of flickers presented to the right minus the number of flickers presented to the left. We fit a 4-parameter sigmoidal function for each subject as follows:

$$y(x) = y_0 + \frac{a}{1 + \exp\left(\frac{-(x-x_0)}{b}\right)}$$

where y_0 is the left endpoint, $(y_0 + a)$ is the right endpoint, x_0 is the bias, and a/4b is the slope. Bias represents the inflection point of the sigmoidal curve in each subject. Fits were nonlinear least-square regressions calculated using the nlinfit function from MATLAB. Significant differences between M.B. and the healthy controls values of bias and slope were assessed with the Crawford modified *t*-test for single case studies.

3. Results

One apparent deficit of M.B. in daily life situations was an impairment in reach-grasp behavior, which appeared slowed and effortful. Fig. 2 illustrates his typical reach-grasp behavior under unconstrained viewing conditions. With the left hand, wrist rotation during the arm transport phase appeared abnormal and instead of a precision grip with the distal part of the fingers, he used the middle part of the index finger and the thumb to lift the object (Fig. 2A), or performed an even less accurate palm scooping movement with an abducted thumb (Fig. 2B). When he attempted a precision grip (mostly with the right hand), his initial contact with the surface was typically off the target, and thumb-index finger aperture was too wide (Fig. 2C). The slowness of the grasp is indicated by the fact that he needed on average 3–4 sec to complete a given grasp as compared to typical <1 sec durations in healthy controls. Example reach-grasp movie sequences of patient M.B. are provided in the Supplementary Material.

Although it was not always possible to clearly dissociate misreaching from grasping deficits as in studies that specifically aimed to answer this question (Cavina-Pratesi, Ietswaart, Humphreys, Lestou, & Milner, 2010), we estimated that 45% of trials contained only grasp impairments while the remaining contained reach as well as grasp errors. Impaired grip scaling was observed at closer and further table positions and with both hands.

3.1. *Reach performance*

The experiments described below aimed to quantify the reach aspect and to compare it with optic ataxia symptoms arising from parietal cortex lesions (Andersen et al., 2014; Perenin & Vighetto, 1988). The reach data of M.B. were compared to a group of seven healthy subjects. We performed two types of reach tasks, measuring reach accuracy and timing. In the first (foveal reach) task, subjects were allowed to move their eyes to the target (Fig. 3A), while in the second (extrafoveal reach) task, subjects were not allowed to look at the target and were required to continue to fixate in the middle of the screen during the reach (Fig. 3B). From an optic ataxia we expected reach errors to be stronger in extrafoveal as compared to foveal reaches (Andersen et al., 2014; Perenin & Vighetto, 1988).

3.1.1. *Reach endpoint accuracy and variability*

We first evaluated reach errors and their trial-by-trial endpoint variability as a function of hand usage and viewing condition. Fig. 3C and D displays the distribution of reach endpoints for the foveal and extrafoveal reach task in M.B. and the healthy controls. As compared with the average error of the healthy subjects, M.B's reach performance was less accurate and also more variable across trials with the left and right hand and to both sides of space (Supplementary Table S2). In the horizontal dimension, reaches were dysmetric (hypometric or hypermetric) without a systematic pattern. A more systematic pattern was revealed in respect to reach accuracy in the vertical dimension. Specifically, with the right hand M.B. misreached below the target in the left hemifield and above the target in the right hemifield, with similar reach errors for the foveal and extrafoveal reach condition (Fig. 3C–D). For statistical purposes, reach endpoint errors (inaccuracy) and variability (endpoint scatter) were grouped by hemifield, and data of M.B. were statistically compared with the healthy control (HC) group by the adjusted *t*-test (Crawford & Garthwaite, 2002). In comparison to the healthy controls, M.B. exhibited significantly larger reaching errors when he used the right hand and the reach was toward the right hemifield (Fig. 3E–F). This higher magnitude of reach inaccuracy in M.B. was observed for both, the foveal and extrafoveal reach conditions [HC *vs.* M.B., Foveal reach; R_{hand}-RVF: .7° *vs.* 2.2° ($t_{(6)} = 3.7$, $p < .01$); Extrafoveal reach; R_{hand}-RVF: .6° *vs.* 1.9°

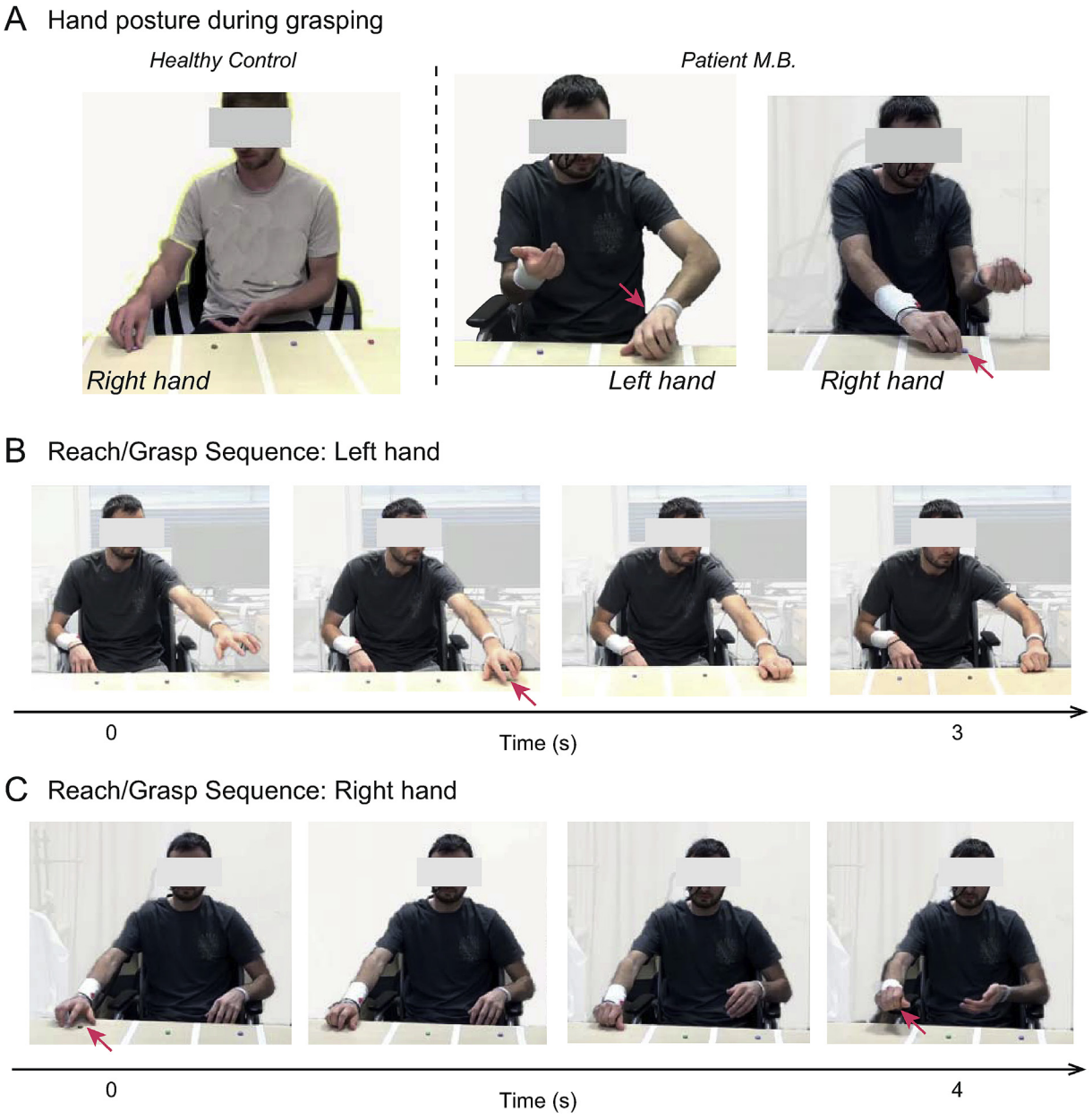

Fig. 2 – Reach-grasp deficits of M.B. (A) Typical grasp postures. Healthy control (left) and M.B. (right). Left hand: note the abnormal wrist angle (red arrow) and the absence of a precision grip. Right hand: note the attempted precision grip with the right hand, but off the target (red arrow). Also note that the non-acting hand is not dystonic but is used to hold the collected objects. (B) Typical reach-grasp sequence of M.B. with the left hand under unconstrained viewing conditions. Note the abduction of the thumb, absence of a precision grip (red arrow) and scooping movement for picking up the object. (C) Typical reach-grasp sequence of M.B. with the right hand. Note that scaling of the grip was too wide at the contact with the table and the object was squeezed between the index finger and the base of the abducted thumb (red arrows).

($t_{(6)} = 5.3$, $p < .01$)] (Fig. 3E–F, Supplementary Table S2). None of the other comparisons with left hand and left visual field reached statistical significance with errors ranging between .7° and 1.5° (all $p > .1$).

3.1.2. *Reach latencies and movement durations*

Next, we tested whether reaching deficits in M.B. would also be reflected in increased initiation times and movement durations, as has been observed in the recorded movies of unconstrained reach-to-grasp trials. To this end we compared reach initiation (lift of the hand after go-cue, central hand fixation offset) and reach durations (lift of the hand to target touch) between M.B. and the healthy controls. M.B.'s reach latencies towards both hemifields were delayed by 80–350 ms in comparison with the controls to either hemifield, with the longest latencies for right hand reaches (Fig. 4A

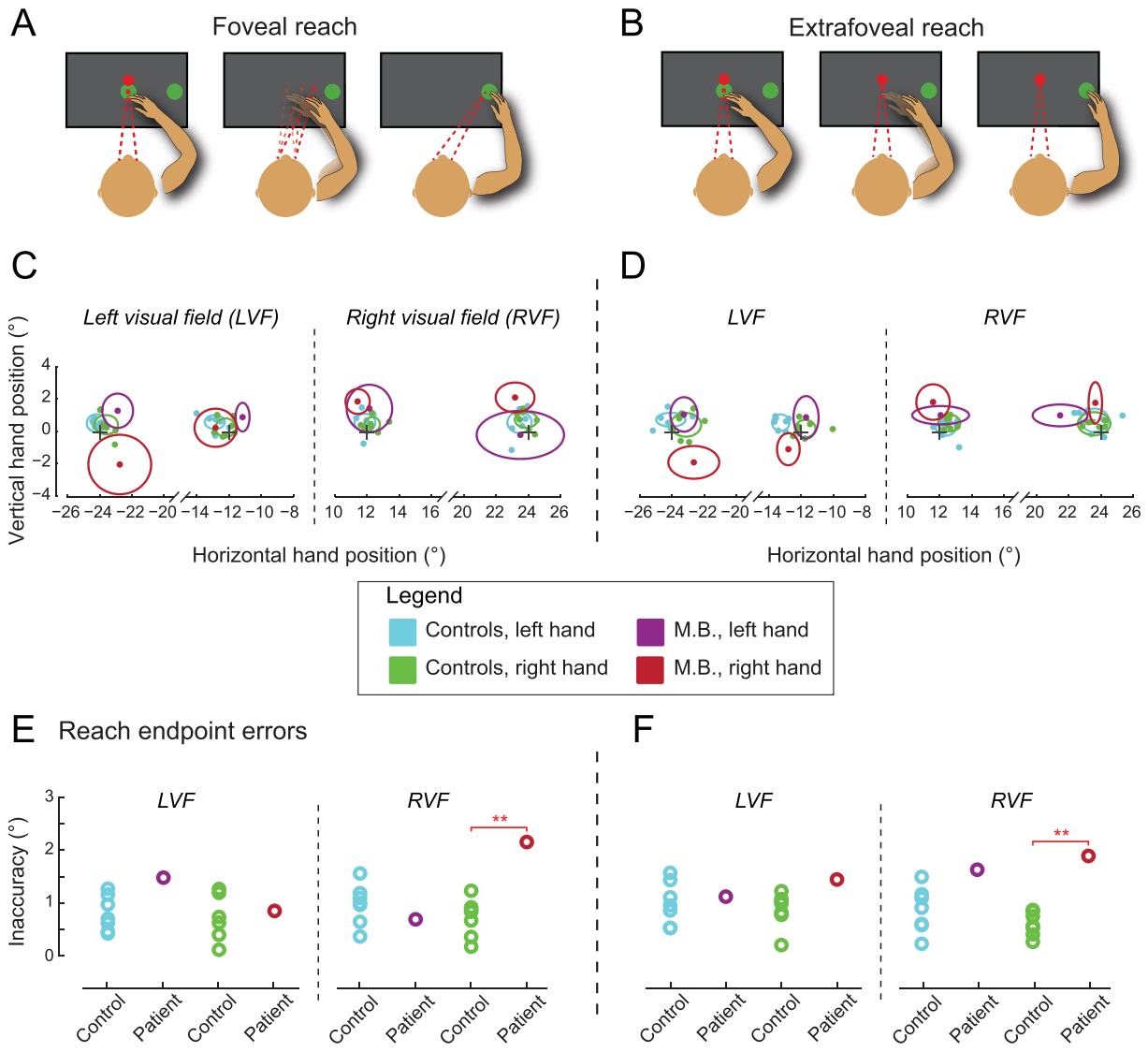

Fig. 3 – Reaching performance with foveal and extrafoveal viewing of the target. (A) Foveal reach task. (B) Extrafoveal reach task. (C,D) Endpoints of reaching movements in the foveal (left) and extrafoveal (right) reach tasks. Data are separated by visual hemifield (LVF and RVF) and hand (see Legend). Ellipses represent the horizontal and the vertical standard deviation over trials in M.B. and the mean standard deviation of the seven age-matched healthy control subjects. Note the larger endpoint variability in M.B. as compared to the healthy subjects, for reaches with both hands. (E,F) Absolute reaching inaccuracy (mean Euclidian distance from the reach target) for patient M.B. and controls as a function of hemifield, hand and reach task. Each dot represents the mean of a single subject, red connection lines indicate statistical significance of differences between M.B. and controls computed with the Crawford modified t-test, $^{**}p < .01$. LVF: left visual hemifield, RVF: right visual hemifield.

and B). This hand effect is also underlined by the ANOVA across trials in M.B., which revealed a main effect for hand ($F(1,72) = 19.96$, $p < .0001$), but not for space, hemifield or any interaction. M.B. not only started the reach movements later, but depending on the exact condition, he also needed between 500 and 1400 ms longer to complete the reach after initiation. In comparison with the healthy controls, this prolonged movement duration was statistically significant for both hands, hemifields as well as for foveal and extrafoveal reaches (two-tailed modified t-test, all $p < .05$, Fig. 4C and D; Supplementary Table S2). However, reach delays in M.B. were most pronounced with the right hand, which is also expressed in the ANOVA, revealing a significant main effect of hand ($F(1,72) = 26.6$, $p < .0001$). The stronger reach deficit with the right hand might be explained by the more extensive lesion in his left pulvinar.

3.2. *Saccades and perceptual decision making*

The hand-specific effect in the reaching task and the generalization of his deficits across viewing conditions already suggests that M.B.'s reach difficulties cannot be solely due to deficient eye movements or perceptual impairments. Nonetheless, we conducted two additional control tasks that aimed

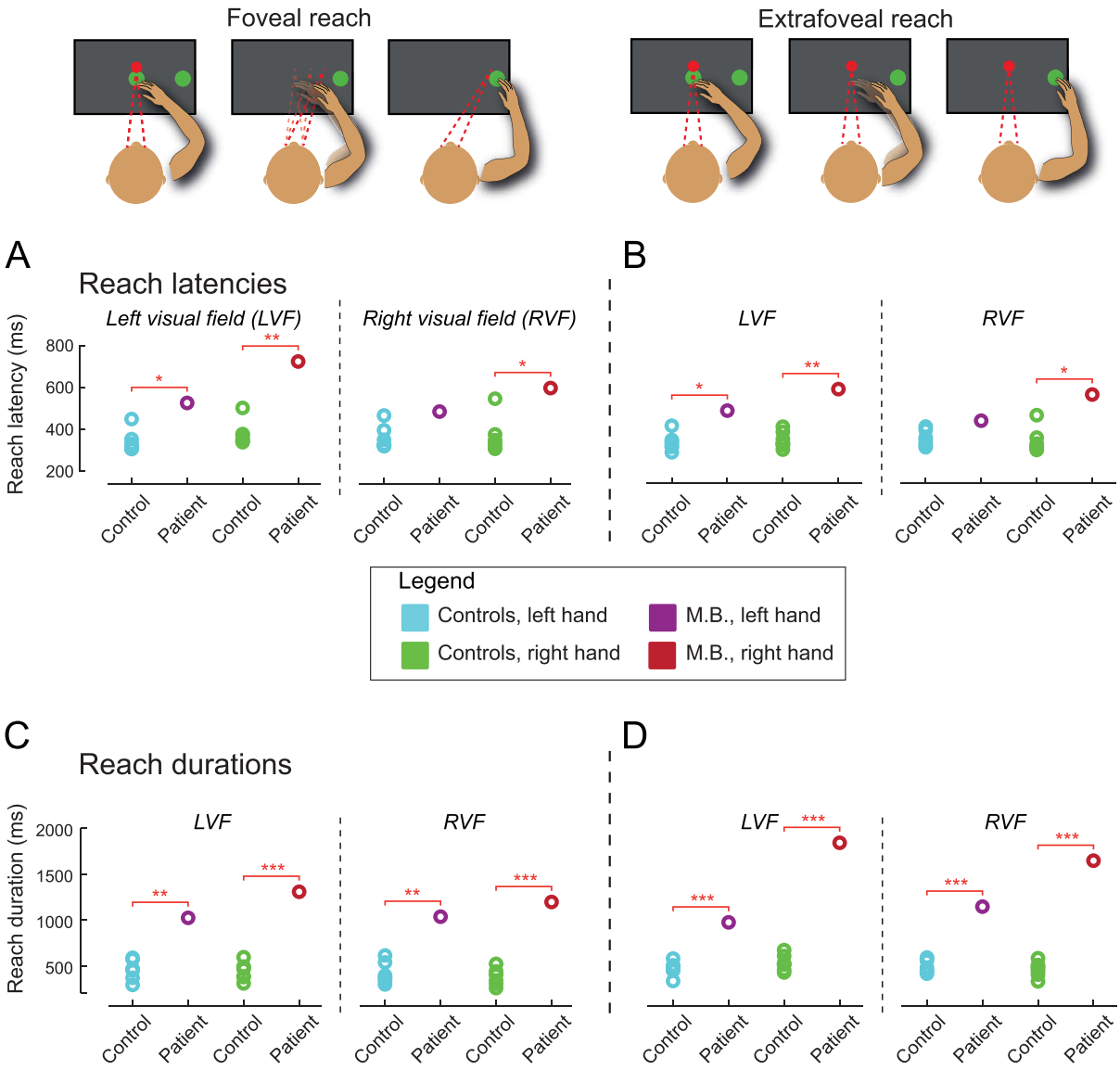

Fig. 4 – Reach latencies and durations in the foveal and extrafoveal reach task. (A,B) Reach latencies denoting the time between offset of the hand fixation spot and lift of the finger from the screen for correct trials, as a function of hand and hemifield, in the foveal (A) and extrafoveal (B) reach tasks. (C,D) Mean movement duration as a function of hand and hemifield in the foveal (C) and extrafoveal (D) reach tasks. Duration was computed from movement onset (lift of the finger from the touch screen) until target acquisition within the 5° success window around the target. In (A–D) each dot represents the mean of a single subject, red connection lines indicate statistical significance of differences between M.B. and the controls computed with the Crawford modified *t*-test, $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$. LVF: left visual hemifield, RVF: right visual hemifield.

to investigate saccade and perceptual performance without accompanying reaches.

3.2.1. *Saccades*

In order to assess eye movement performance, we tested M.B. in a visually-guided saccade task towards instructed and freely chosen targets at eccentricities of 10°, 12.5° or 15° (Supplementary Material, Fig. S3A). Target locations were randomized across trials. In the *instructed* condition only one target was presented; in the *choice* condition two targets were presented at corresponding positions: one in the left and one in the right visual hemifield. In *choice* trials, subjects were asked to choose on every trial whether they wanted to perform a saccade to the left or to the right target (Supplementary Fig. S3A). In choice trials, M.B. selected in 39% of trials the right target and did thus not exhibit a significant spatial choice

bias in comparison to the healthy controls ($t_{(7)} = -.68$, $p = .52$). This measure also confirms the neurological and neuropsychological assessment that M.B. did not exhibit spatial neglect or extinction (Supplementary Fig. S3B). Unlike the reaches described above, saccade latencies and durations did not significantly differ between M.B. and the healthy controls (all $p > .2$, Supplementary Fig. S3C and Table S3). A consistent impairment however was observed in saccade endpoints: in comparison to the healthy controls, M.B. exhibited hypometric saccades towards both hemifields and in both instructed and choice trials (all $p < .01$; Supplementary Fig. S3D). The saccade hypometria was demonstrated by a significantly lower gain of M.B's. saccades for both left and right targets as well as by the saccade endpoint inaccuracy (undershooting) as compared to the healthy control group (Supplementary Table S3; Supplementary Fig. S3E; saccade gain instructed: LVF: $t_{(7)} = -7.7$, $p < .001$; RVF: $t_{(7)} = -3.9$, $p < .01$; choice: LVF: $t_{(7)} = -6.1$, $p < .001$; RVF: $t_{(7)} = -5.8$, $p < .001$). Since our target array was predominantly horizontal and did not contain purely vertical locations, we cannot independently evaluate the vertical saccade component, but the pattern of the endpoints with undershooting in both the horizontal and the vertical dimensions suggest hypometria along the target vector without a vertical tilt.

3.2.2. *Perceptual spatial decision making*

All tasks described above required a directed motor response. In order to assess perceptual performance in a more isolated manner, we tested the ability of M.B. to accumulate visual evidence from each hemifield without a directed motor response, i.e., reported with a button press. In this perceptual decision task (Brunton et al., 2013), different numbers of visual flickers were presented in each hemifield and subjects were required to accumulate the sensory evidence to decide which side contained more stimuli (Fig. 5A). As shown in the psychometric plots fitted with a four-parameter sigmoidal function to the rightward choices of each individual subject, performance of M.B. and the healthy subjects in this task was similar (Fig. 5B). Importantly, as compared to the healthy subjects, M.B. did not exhibit a significant decision bias towards either hemifield ($t_{(7)} = -.51$, $p = .62$) (Fig. 5C). We also did not find a significant perceptual accumulation deficit, indicated by the insignificant difference between slope estimates from patient data as compared to healthy controls ($t_{(7)} = .19$,

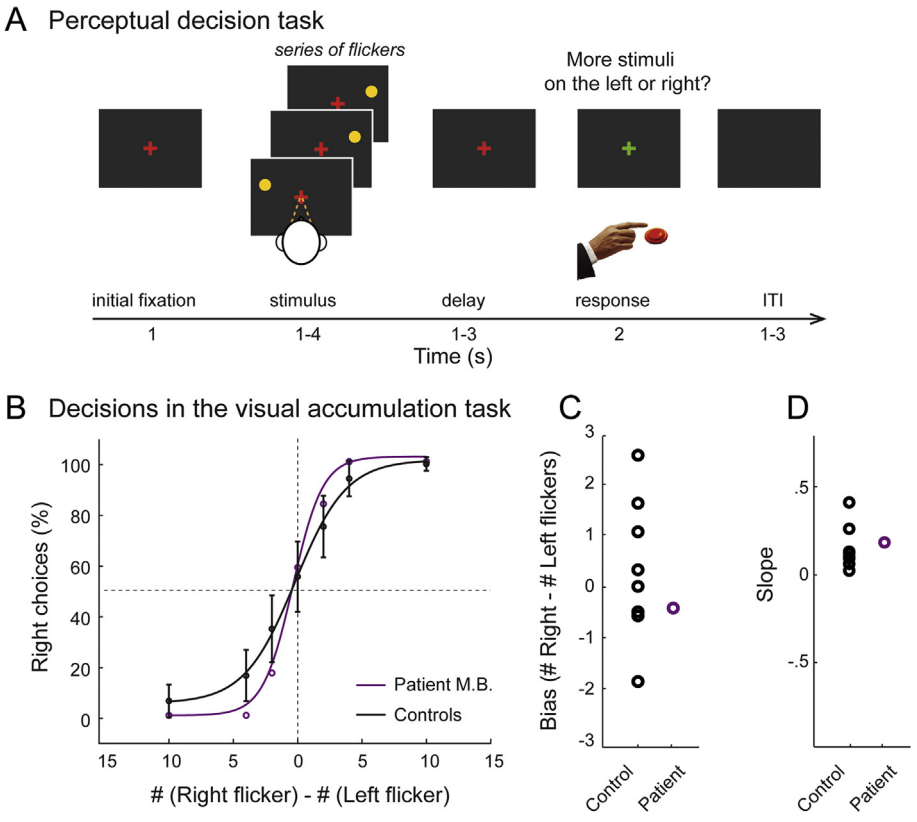

Fig. 5 – Perceptual evidence accumulation performance. (A) Visual decision task with two alternative forced choices. (B) Psychometric curves of % rightward choices as a function of number of flickers presented to the right minus number of flickers to the left. Curves represent fitting of a four parameters sigmoid function, dots the unfitted raw percentages (purple: patient M.B., black: healthy controls). Note the similarity of the curves, indicating that M.B. was able to accumulate perceptual evidence from both sides of space and to form a correct decision. (C,D) Each dot represents the spatial bias defined as the inflection point of the sigmoidal curve (C), or the slope of each individual subject (D). Note that spatial bias and slope of M.B. were in the range of the healthy subjects.

$p = .86$) (Fig. 5D). There were no reaction time differences between M.B. and controls (leftward: $t_{(7)} = .5$, $p = .63$; rightward: $t_{(7)} = -.17$, $p = .87$). Thus, data from the evidence accumulation task are in agreement with the free choice saccade task, indicating that M.B. did not suffer from a visual perception deficit.

4. Discussion

Taken together, our results indicate that the subcortical route through the medial pulvinar is critical for proper reach-grasp behavior. To our knowledge, this is the first study that systematically investigated reach behavior after a selective pulvinar lesion in humans. Possibly, this is because the known cases with thalamic lesions also affecting the pulvinar were of vascular etiology and thus entailed primary somatosensory and motor nuclei in the thalamus as well, resulting in respective deficits (Schmahmann, 2003; Schmahmann & Pandya, 2008). The symptoms seen in M.B. shared features of (parietal) cortex and cerebellar lesions, without being identical with either of them. While his grasping deficits were reminiscent of patients with parietal lesions, he did not show optic ataxia which is alleviated with central object viewing (Andersen et al., 2014; Perenin & Vighetto, 1988). In summary, our data indicate that the function of the human pulvinar goes well beyond its subscribed role in visual cognition and provide evidence that the medial pulvinar serves as an important hub for the control of limb movements.

4.1. *The pulvinar and reach-grasp behavior*

During object grasping under natural viewing conditions, M.B. often exhibited an abnormal wrist rotation during the arm movement, did not adapt a precision grasp, widened the grip aperture too much, and performed a scooping movement only after making contact with the object. In the quantified reaching task, M.B.'s reaching performance was less accurate and slower than in controls, in particular when he used the right hand and when the reach was towards the right hemifield.

Is it possible that the grasping deficit of M.B. reflected a secondary impairment due to positional insecurity and misreaching as has been previously reported in an optic ataxia patient with a posterior parietal lesion (Cavina-Pratesi et al., 2010)? Although we cannot exclude the possibility that some of the errors in the reach-to-grasp task might have been due to spatial mislocalization, this would not well account for the distorted hand posture, cumbersome approach trajectory, and the difficulty in picking up the object. Also, in contrast to the optic ataxia patient described in (Cavina-Pratesi et al., 2010) his grasp deficit occurred for close and peripheral object locations. Most importantly, grasp deficits were more pronounced with the left hand, while reach endpoint errors in the touchscreen task were more pronounced when he used the right hand and for reaches toward the right hemifield. It needs to be noted however that a clear limitation of our study is the absence of precise kinematic measurements to dissociate between proximal and distal components of the grasp movements (Jakobson, Archibald, Carey, & Goodale, 1991). Generally, the pattern of reach and grasp deficits resembled our previous observations with pharmacological inactivation of the dorsal pulvinar in monkeys, which also showed failures to form a precision grip and increased reach errors that were stronger for the contralesional hand and space (Wilke et al., 2010). In this monkey study however, reach behavior following pulvinar inactivation was only assessed under unconstrained viewing conditions. Thus, further monkey inactivation studies are needed to resolve whether the reach deficits in monkeys would be present for foveal as well as extrafoveal viewing conditions. To our knowledge, this is the first report examining reach and grasp deficits in a patient with a pulvinar lesion without accompanying lesions in any of the primary sensory or motor thalamic nuclei such as ventrolateral thalamus, lateral geniculate nucleus or white matter tracts running through the internal capsule. The sparing of those nuclei and tracts in our patient is most likely due to the fact that the lesion etiology of M.B. was a sarcoidosis and thus did not affect the vascular territories that are typically damaged by ischemia. Thus, the closest patient in the literature is the description of reach-grasping deficits in a patient with thalamic hemorrhage that was more extensive than in M.B. and entailed the right posterior thalamus (pulvinar, geniculate body), superior colliculus and adjacent fibers of the internal capsule as well as (Classen et al., 1995). In contrast to M.B. this patient had primary visual and somatosensory deficits as well. Similar to M.B. the patient described in this study (Classen et al., 1995) misreached with either hand and in both hemifields with and without central fixation and grasp kinematics were also impaired. The observed reach deficits of M.B. differed from optic ataxia observed following unilateral or bilateral parietal lesions in monkeys and humans as they were: 1) not alleviated when he was allowed to look at the target (foveal reach) and 2) the largest reach errors were observed in the vertical and not in the horizontal dimension (Battaglia-Mayer et al., 2013; Hwang, Hauschild, Wilke, & Andersen, 2012; Karnath & Perenin, 2005; Perenin & Vighetto, 1988). Interestingly, some symptoms of M.B. also overlapped with descriptions of lesions in deep cerebellar nuclei, including the bilateral reach imprecision and hypometric saccades. However, in contrast to patients with a cerebellar lesion (Bastian & Thach, 1995), movements of M.B. were not decomposed and appeared rather smooth. Some of the features such as the abnormal approach and object picking patterns, hand specificity and the fact that M.B. exhibited similar reach deficits whether he was allowed to look at the target and the hand or had to maintain central fixation, suggest that the problem was not 'just' on a cognitive or visuomotor transformation level. In this sense, one might consider at least part of the observed deficit as "motor". In the context of visuomotor tasks, dorsal pulvinar neurons show a variety of firing patterns ranging from purely visuospatial responses modulated by the task context to motor planning, execution, and post-execution signals, further modulated by postural effects (Acuna, Gonzalez, & Dominguez, 1983; Dominguez-Vargas et al., 2017). Therefore, it is unlikely that the deficits observed after dorsal pulvinar lesion would be readily classified into visuospatial, transformational, or motor-only domains. Generally, reach and grasping movements are dependent on neural activity in a widely distributed

network consisting of cortical regions such as motor, premotor, ventral supplementary motor area (SMA), superior parietal and dorsal occipital cortex as well as the cerebellum (Andersen et al., 2014; Castiello, 2005). All of those structures have reciprocal connections with the dorsal pulvinar as evidenced by anatomical tracer and microstimulation studies in monkeys (Baleydier & Mauguiere, 1985; Gutierrez et al., 2000; Romanski, Giguere, Bates, & Goldman-Rakic, 1997; Sultan et al., 2012; Trojanowski & Jacobson, 1974), and functional imaging and microstimulation studies in humans (Arcaro et al., 2015; Barron et al., 2015; Rosenberg et al., 2009). The unique combination of M.B.'s symptoms might thus either be explained by the loss of integrative pulvinar functions and/or by a functional disconnection with and between those regions.

4.2. *Effects on saccade metrics and spatial decision behavior*

M.B. had normal saccade latencies to all screen positions tested, which is consistent with a previous posterior thalamus lesion study in humans (Rafal et al., 2004). There is convergent evidence from lesion studies in humans (Rafal et al., 2004; Van der Stigchel et al., 2010) and monkeys (Wilke et al., 2013; Wilke et al., 2010) that the dorsal pulvinar, including its medial portion, is a critical contributor to the selection of goal-directed eye movements but is less critical for saccade execution itself. This notion is also consistent with electrophysiological and microstimulation studies in monkeys, showing a diversity of saccade-related neural activity without a clear retinotopic or saccade direction organization and relatively high current thresholds for evoking saccades, unlike in the connected superior colliculus, frontal eye fields or lateral intraparietal area (Benevento & Port, 1995; Dominguez-Vargas et al., 2017). Albeit investigated in only few studies, pulvinar lesions in humans or monkeys do typically not result in primary oculomotor deficits and when such deficits have been reported in either humans (Rafal et al., 2004) or in monkeys performing memory saccades (Wilke et al., 2013), effect sizes were relatively small. However, saccade metrics were affected in M.B. as he did exhibit hypometric saccades towards both hemifields. This undershooting was not easily predicted from the current pulvinar literature, unless one assumes a Balint-like syndrome that can be found following bilateral parietal lesions (Andersen et al., 2014). Indeed, attention-related impairments in distractor filtering, spatial exploration and decision-making have been repeatedly reported following (unilateral) pulvinar lesions in humans (Karnath et al., 2002; Rafal et al., 2004; Van der Stigchel et al., 2010) and monkeys (Robinson & Petersen, 1992; Wilke et al., 2013; Wilke et al., 2010; Zhou et al., 2016). Since the lesion in M.B. was more pronounced in the left pulvinar, we expected a saccade choice bias towards the left hemifield based on our monkey studies that used a similar task design (Wilke et al., 2013; Wilke et al., 2010). While M.B. did choose slightly more targets (61%) in the left visual hemifield, this bias was in the range of the normal subjects. The absence of neglect and extinction might be due to the fact that the pulvinar lesion was most pronounced in the left hemisphere or could be due to the fact that the lesion was bilateral to some extent (Rushmore, Valero-Cabre, Lomber, Hilgetag, & Payne, 2006). Since the patient with a left medial pulvinar lesion described by Ward et al. did also not exhibit spatial neglect symptoms, we favor the interpretation that left dorsal pulvinar lesions in humans might not lead to a spatial bias (Ward et al., 2005). It is also worth noting that spatial attention and higher-order saccade selection deficits following pulvinar lesions were typically interpreted to reflect functional disruption in fronto-parietal cortices (Arend, Machado, et al., 2008; Wilke et al., 2010). However, the pattern of intact saccade latencies in combination with hypometric saccade endpoints differ from left and right unilateral or bilateral parietal lesions in humans that cause deficits in both latencies and endpoints (Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991; Ptak & Muri, 2013). Also, the perceptual decisions reported by a button response were not impaired in M.B., which is consistent with recent dorsal pulvinar inactivation studies in monkeys, showing intact detection of large reward stimuli even in the contralesional hemifield (Wilke et al., 2013) and intact perceptual categorization performance (Komura et al., 2013). Since the error patterns in the reach tasks qualitatively differed from the saccade errors and since the perceptual task did not reveal deficits, we assume that the reach deficits might be related to an impaired integration of visual stimulus position, hand position and/or movement planning.

4.3. *Possible limitations*

Finally, we wondered whether the reaching deficits could be due to a lesion in structures other than the pulvinar. We have carefully assessed tracts and nuclei that could potentially lead to a similar picture as documented in our patient and discuss it together with the neurological assessment. The MR scans indicated that the lesion in M.B. did not involve those thalamic nuclei that are usually affected by ischemia-induced lesions: the posterior cerebral artery supplies not only the posterior thalamus but also the lateral nucleus and the ventral posterior nucleus. The posterior choroidal arteries supply not only the pulvinar but also the lateral and medial geniculate nucleus (Schmahmann, 2003; Schmahmann & Pandya, 2008). Theoretically, a lesion in the rubro-thalamic tract could result in a similar picture. However, the rubro-thalamic tract runs far more anterior and lateral than the lesion in M.B. (Kwon et al., 2011). Patients with affection of the paramedian territory usually show somnolence, gaze abnormalities, display memory problems or hemiparesis. If the thalamogeniculate area or the posterior choroidal artery territories are affected, one expects neurological symptoms that were not present in M.B. such as hemiataxia, pain sensations and hemianopia. Tuberothalamic lesions come with facial paresis and hemisymptoms. As stated above, M.B. did not have abnormalities in his primary sensory qualities (e.g., position sense, touch, vibration) nor in his vestibular or cerebellar tests. Nevertheless, he showed deficits with reaching and grasping. We think that this can only be explained by the lesion pattern due to the atypical sarcoidosis manifestation that spares vascular territories and is restricted to the medial pulvinar. Is it possible that the visuomotor deficits in M.B. are due to damage of fibers that originate in neighboring thalamic nuclei but travel through the pulvinar? This is unlikely since (unlike the lateral pulvinar portion) there is no clear

evidence for fiber tracts travelling through the core of the medial pulvinar (Rosenberg et al., 2009). Consideration must also be given to the fibers that travel within or along the posterior thalamus such as the posterior limb of the internal capsule and the brachium of the superior colliculus that connects the parietal cortex with the superior colliculus (Jones, 2007). However, no such damage was detected on the MRI. While the possibility remains that the patient had very small lesions that were below the spatial resolution of our structural imaging, we conclude based on his clinical symptoms, which clearly differed between lesions of the parietal cortex (optic ataxia) and from lesions of the posterior limb of the internal capsule (which lead to disturbances in primary sensory and motor functions), that the deficits observed in of M.B. are most parsimoniously explained by the pulvinar lesion.

4.4. Ethics

All subjects, including patient M.B. gave written informed consent to participate in the study and M.B. signed a video release form. The study was approved by the local Ethics Committee of the Georg-August-University Göttingen according to the Declaration of Helsinki.

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.cortex.2017.10.011.

Author contributions

M.W. and M.B. designed the study, M.W., I.K. and M.B. wrote the paper. M.B. supervised and/or performed the clinical assessment, neurophysiological and neuropsychological examinations of the patient, M.W. and I.K. planned and supervised data collection and analysis. L.S. and A.D. programmed, performed and analyzed the reaching experiments. K.M., H.S. and M.W. planned, performed and analyzed the grasping data. P.D., C.S., Y.C. performed the imaging data acquisition and P.D. analyzed the structural data for lesion mapping. C.S. programmed, performed and analyzed the saccade experiment. A.N. performed and analyzed the perceptual accumulation task. All authors contributed figures, methods and result sections and critique to the manuscript.

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Supplementary data

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