



HAL
open science

Saccades and Eye–Head Coordination in Ataxia with Oculomotor Apraxia Type 2

Muriel Panouillères, Solène Frismand, Olivier Sillan, Christian Urquizar, Alain Vighetto, Denis Pelisson, Caroline Tilikete

► **To cite this version:**

Muriel Panouillères, Solène Frismand, Olivier Sillan, Christian Urquizar, Alain Vighetto, et al.. Saccades and Eye–Head Coordination in Ataxia with Oculomotor Apraxia Type 2. *The Cerebellum*, 2013, 12 (4), pp.557-567. 10.1007/s12311-013-0463-1 . hal-02196702

HAL Id: hal-02196702

<https://hal.science/hal-02196702>

Submitted on 26 Apr 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

The Cerebellum

Saccades and eye-head coordination in ataxia with oculomotor apraxia type 2

--Manuscript Draft--

Manuscript Number:	
Full Title:	Saccades and eye-head coordination in ataxia with oculomotor apraxia type 2
Article Type:	Original Article
Corresponding Author:	Muriel Panouilleres FRANCE
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	
Corresponding Author's Secondary Institution:	
First Author:	Muriel Panouilleres
First Author Secondary Information:	
Order of Authors:	Muriel Panouilleres Solène Frismand Olivier Sillan Christian Urquizar Alain Vighetto Denis Pélisson Caroline Tilikete
Order of Authors Secondary Information:	
Abstract:	<p>Ataxia with oculomotor apraxia type 2 (AOA2) is one of the most frequent autosomal recessive cerebellar ataxias. Oculomotor apraxia refers to horizontal gaze failure due to deficits in voluntary/reactive eye movements. These deficits can manifest as increased latency and/or hypometria of saccades with a stair-case pattern and are frequently associated with compensatory head thrust movements. Oculomotor disturbances associated with AOA2 have been poorly studied mainly because the diagnosis of oculomotor apraxia was based on the presence of compensatory head thrusts. The aim of this study was to characterize the nature of horizontal gaze failure in patients with AOA2 and to demonstrate oculomotor apraxia even in the absence of head thrusts. Five patients with AOA2, without head thrusts, were tested in saccadic tasks with the head restrained or free to move and their performance were compared to a group of six healthy participants. The most salient deficit of the patients was saccadic hypometria with a typical stair-case pattern. Saccade latency in the patients was longer than controls only for memory-guided saccades. In the head-free condition, head movements were delayed relative to the eye and their amplitude and velocity were strongly reduced compared to controls. Our study emphasizes that in AOA2, hypometric saccades with a stair-case pattern are a more reliable sign of oculomotor apraxia than head thrust movements. In addition, the variety of eye and head movements' deficits suggests that, although the main neural degeneration in AOA2 affects the cerebellum, this disease affects other structures.</p>
Suggested Reviewers:	

Saccades and eye-head coordination in ataxia with oculomotor apraxia type 2

Muriel Panouillères^{1,2}; Solène Frismand^{1,3}; Olivier Sillan¹; Christian Urquizar¹; Alain
Vighetto^{1,2,3}; Denis Péliçon^{1,2}; Caroline Tilikete^{1,2,3}

¹ INSERM U1028; CNRS UMR5292; Lyon Neuroscience Research Center, ImpAct Team,
Lyon, F-69000, France

² University Lyon 1, Lyon, F-69000, France

³ Hospices Civils de Lyon, Unité de Neuro-ophtalmologie and Service de Neurologie D,
Hôpital Neurologique, Bron F-69677, France

Corresponding author: M. Panouillères

Address: INSERM U1028; CNRS UMR5292; Lyon Neuroscience Research Center,
ImpAct Team
16 avenue du doyen Lépine
69676 Bron Cedex
FRANCE

Telephone: + 33 4 72 91 34 32

Fax: + 33 4 72 91 34 01

Conflict of interest statement

The authors declare that there is no conflict of interest

Abstract

Ataxia with oculomotor apraxia type 2 (AOA2) is one of the most frequent autosomal recessive cerebellar ataxias. Oculomotor apraxia refers to horizontal gaze failure due to deficits in voluntary/reactive eye movements. These deficits can manifest as increased latency and/or hypometria of saccades with a stair-case pattern and are frequently associated with compensatory head thrust movements. Oculomotor disturbances associated with AOA2 have been poorly studied mainly because the diagnosis of oculomotor apraxia was based on the presence of compensatory head thrusts. The aim of this study was to characterize the nature of horizontal gaze failure in patients with AOA2 and to demonstrate oculomotor apraxia even in the absence of head thrusts. Five patients with AOA2, without head thrusts, were tested in saccadic tasks with the head restrained or free to move and their performance were compared to a group of six healthy participants. The most salient deficit of the patients was saccadic hypometria with a typical stair-case pattern. Saccade latency in the patients was longer than controls only for memory-guided saccades. In the head-free condition, head movements were delayed relative to the eye and their amplitude and velocity were strongly reduced compared to controls. Our study emphasizes that in AOA2, hypometric saccades with a stair-case pattern are a more reliable sign of oculomotor apraxia than head thrust movements. In addition, the variety of eye and head movements' deficits suggests that, although the main neural degeneration in AOA2 affects the cerebellum, this disease affects other structures.

Keywords: AOA2, Oculomotor apraxia, Stair-case saccade, Eye-head coordination, Cerebellum

Introduction

Ataxia with oculomotor apraxia type 2 (AOA2) belongs to the autosomal recessive cerebellar ataxias, which are rare and early-disabling neurodegenerative diseases. AOA2 was first described in a Japanese family [1] and the defective gene, the Senataxin [2, 3] has been mapped on chromosome 9q34 [4]. The typical clinical presentation of AOA2 associates an age of onset around 10-22 years, a progressive cerebellar ataxia, a sensory-motor axonal neuropathy, an elevated level of serum alpha-feto-protein (AFP) and an oculomotor apraxia [5, 6].

Oculomotor apraxia is a term that has been used loosely to describe difficulty changing gaze, often associated with abnormal patterns of eye-head coordination including conspicuous overshooting, thrusting head movements. The head thrusts are a compensatory mechanism to facilitate changes in gaze [7-9]. While the head thrusts in patients with oculomotor apraxia have sometimes been used as the main diagnostic criterion for the condition, it is the precise characteristics of the ocular motor disturbances that should be used to define the condition and to clarify the underlying pathophysiology.

The gaze abnormality in oculomotor apraxia might primarily be characterized by a deficit of voluntary/reactive saccades and smooth pursuit while quick phases of nystagmus in response to vestibular or optokinetic stimulation are relatively preserved [7-9]. This relative specificity of the deficits indicates that the brain regions responsible for the oculomotor apraxia are located upstream from the saccadic premotor nuclei in the brainstem [10], and would possibly include the fronto-parietal cortical areas, the basal ganglia, the cerebellum and/or the superior colliculus. Deficits in voluntary/reactive eye movements can manifest as increased latency and/or hypometria of saccades and jerky smooth pursuit [11]. When saccades are hypometric, multiple small saccades are sometimes required to reach the target.

1 This pattern, called stair-case saccades, has been described in the congenital forms of
2 oculomotor apraxia [11].
3

4 The presence and frequency of occurrence of oculomotor apraxia in AOA2 are probably
5 under-estimated. Indeed, some studies claiming that oculomotor apraxia is rare in this
6 pathology have provided a poor description of the deficits without mentioning whether
7 voluntary/reactive saccades were impaired and quick phases preserved [1, 5, 12]. Moreover,
8 other recent studies restricted the definition of oculomotor apraxia to the head thrust as the
9 main criterion, and reported a 20% to 100% of incidence [6, 13-16]. The only team that
10 investigated the saccadic disturbances associated with AOA2 [15] reported that patients'
11 saccades had normal latency but were hypometric. Moreover, the authors also noted that, in
12 contrast to AOA1 [17], these patients with AOA2 did not show stair-case saccades [15].
13 Whether true oculomotor apraxia without head thrust can occur in AOA2 has never been
14 asked in previous studies.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30

31 The aim of the present study was to characterize the nature of horizontal gaze failure in
32 five patients with AOA2 and to demonstrate oculomotor apraxia in the absence of
33 compensatory head thrust. We recorded eye and head movements while the AOA2 patients
34 performed horizontal reactive saccades and voluntary saccades (scanning saccades, memory-
35 guided saccades and anti-saccades) with their head restrained or free to move.
36
37
38
39
40
41
42
43
44
45
46
47

48 **Materials and Methods**

49 **Subjects**

50
51 Five patients were recruited (mean age at examination: 31.2 ± 7.6 years). Their genetic and
52 clinical features are summarised in Table 1. The patients presented a similar clinical
53 oculomotor phenotype including stair-case hypometria of horizontal and vertical saccades,
54
55
56
57
58
59
60
61
62
63
64
65

1 gaze-evoked nystagmus, saccadic smooth pursuit and absent visual suppression of vestibulo-
2 ocular reflex. None of them was using head thrust to change his line of sight.. Patients I-1 and
3
4 I-2 also presented exophoria and convergence insufficiency and Patient II-1 had right
5
6 hypertropia in far vision, without any limitation. Three siblings patients (family I) also
7
8 presented positional vestibular nystagmus, and high gain of the vestibulo-ocular reflex
9
10 (VOR). Six healthy subjects with no history of neurological disease served as the control
11
12 group (two males, mean age: 32.5 ± 7.0 years).
13
14
15

16 Approval was received from the National French ethical committee on human
17
18 experimentation, in agreement with French law (March 4, 2002) and the Declaration of
19
20 Helsinki (2003-036B). Written informed consents were obtained from all participants.
21
22
23
24
25

26 **Experimental set-up**

27
28 Participants were seated at a distance of 57 cm from a computer screen (refresh rate: 60 Hz –
29
30 visual angle: $60^\circ \times 34^\circ$). Movements of both eyes were recorded at 250 Hz with helmet-
31
32 mounted infrared eye trackers (Eyelink 2, SR-Research, Canada). In the head-restrained
33
34 condition, head movements were restrained with a chin and cheekbone rests. In the head-free
35
36 condition, the position of three infrared emitting diodes placed on the helmet was recorded at
37
38 200 Hz (Optotrak 3020, Northern Digital Inc., Ontario, Canada). In-house software controlled
39
40 the stimuli presentation (black circles, cross or arrows of 6 mm diameter on a grey
41
42 background) and recorded eye and head movements for off-line analysis.
43
44
45
46
47
48
49
50

51 **Experimental paradigms in the head-restrained condition**

52
53 Reactive, scanning and memory-guided saccades toward targets located $\pm 10^\circ$ or $\pm 20^\circ$ along
54
55 the horizontal meridian, as well as anti-saccades in response to $\pm 10^\circ$ targets, were elicited in
56
57 paradigms described in supplementary material 1A. In all tasks, leftward-saccades trials were
58
59
60
61
62
63
64
65

1 randomly intermingled with rightward-saccades trials. Fifteen trials for each direction and for
2 each target eccentricity were recorded in all tasks.
3
4
5
6

7 **Experimental paradigms in the head-free condition**

8
9 For the eye-head coordination tasks, patients and control subjects were instructed to move
10 their head as naturally as possible. However, because patients produced small head
11 movements, they were encouraged to mobilize their head more while changing gaze direction.
12
13 In separate reactive and scanning tasks, eye-head movements were elicited *from an eccentric*
14 fixation point ($\pm 25^\circ$) toward a target presented in the opposite hemifield at 5° or 25° (i.e. at a
15 distance of 30° or 50° from fixation, respectively). In both tasks, ten trials with a fixation
16 located at $+25^\circ$ (leftward movements) alternated with ten trials with a fixation at -25°
17 (rightward movements), until 60 trials were recorded. The paradigms are detailed in
18 supplementary material 1B.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33

34 **Data analysis**

35
36 In the head-restrained condition, the primary saccade and all subsequent corrective saccades
37 directed toward the target were analysed. The latency, gain and velocity peak of the primary
38 saccade and the total displacement gain were computed (see supplementary material 1C)
39
40

41
42 In the head-free condition, the latency and amplitude of the primary eye saccade, the
43 amplitude, duration and velocity peak of the head movement, the eye-head delay, the gain and
44 duration of the gaze displacement were calculated as described in the supplementary method
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

66 **Statistical analysis**

1 Non-parametric statistical analyses were performed with the R software [18], using Kruskal-
2 Wallis tests (“coin” package [19, 20]) and non-parametric ANOVA-type statistics (“nparLD”
3 package [21]). Significant ANOVAs were followed by nonparametric Behrens-Fisher
4 problem (“nparcomp” package [22]). Significance level was set at $p < 0.05$. Unless mentioned
5 otherwise, numeric values reported in the main text, tables and figures correspond to median
6 values.
7
8
9
10
11
12
13

14 **Results**

15 **Errors and anticipations**

16 Patients with AOA2 made significantly more anti-saccades direction errors (36% of trials)
17 than controls (3% of trials) (Kruskal-Wallis test: $p < 0.01$). Moreover, in the memory-guided
18 saccade task, patients anticipated the extinction of the fixation point in about 16% of the trials,
19 whereas healthy subjects anticipated in only 5% of the cases (Kruskal-Wallis test: $p < 0.05$).
20 Finally, in the scanning task of the head-free condition, patients anticipated the appearance of
21 the go signal in 20% of trials whereas healthy subjects never anticipated (Kruskal-Wallis test:
22 $p < 0.05$). In sum, patients with AOA2 had more difficulty than controls in inhibiting automatic
23 responses to the visual targets in these three tasks.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43

44 **Saccadic performance in the head-restrained condition**

45 A representative example of hypometria with stair-case pattern is illustrated in one patient for
46 leftward reactive response (Fig 1B – see for comparison the response of a control subject in
47 Fig 1A). This saccadic stair-case pattern was observed in all patients except in patient I-3 who
48 has the shortest disease duration (Table 1). In the following section, we first quantify the
49 parameters of the primary saccade performed by patients in the different tasks, and then
50 describe the characteristics of the secondary saccades.
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 No latency difference was observed between subjects groups for reactive saccades and
2 scanning saccades (Fig 2A –non-parametric ANOVA with saccade type, target eccentricity
3 and group factors, no group effect, nor any interaction: $p>0.07$) as well as for anti-saccades
4 (Kruskal-Wallis tests: $p>0.20$). In contrast, the latency of memory-guided saccades was
5 longer in patients than in controls (non-parametric ANOVA, group effect: $p<0.05$).
6
7
8
9
10

11 The gain of primary saccades was compared between controls and patients (Fig 2B). No
12 group difference was highlighted for anti-saccades (Kruskal-Wallis test: $p>0.58$). However,
13 for reactive and scanning saccades, the gain was significantly smaller in patients with AOA2
14 than in controls (non-parametric ANOVA with saccade type, eccentricity and group factors,
15 group effect: $p<0.001$). Similarly, memory-guided saccades directed toward the $\pm 20^\circ$ target
16 were significantly smaller in patients than in controls (non-parametric ANOVA, group \times
17 eccentricity interaction: $p<0.001$; nonparametric Behrens-Fisher problem: $p<0.01$).
18
19
20
21
22
23
24
25
26
27
28

29 To determine if the stereotyped relationship between saccade amplitude and saccade peak
30 velocity was altered in patients with AOA2, we compared between groups the peak velocity
31 of reactive, scanning and memory-guided saccades with matched amplitude (8° - 12°). We
32 found that whereas the velocity of memory-guided saccades was similar between the two
33 groups (Kruskal-Wallis test: $p>0.39$), reactive and scanning saccades of similar amplitudes
34 were slower in patients than in controls (Table 2 – non-parametric ANOVA, group effect:
35 $p<0.05$).
36
37
38
39
40
41
42
43
44
45

46 In the example presented in Figure 1B, patient II-2 was able to compensate for his primary
47 saccade hypometria by making multiple corrective saccades. We found that in the group of
48 patients, this compensation was complete, as total eye gain (primary and corrective saccades)
49 was close to 1. This last parameter was similar to control values (Fig 2C) for reactive and
50 scanning saccades (non-parametric ANOVA, $p=0.08$) and for anti-saccades (Kruskal-Wallis
51 tests: $p=0.27$) or, for memory-guided saccades toward the 10° target, it was even slightly
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 larger than in controls (non-parametric ANOVA, group \times eccentricity interaction: $p < 0.001$;
2 nonparametric Behrens-Fisher problem: $p < 0.01$). The number of corrective saccades required
3
4 to reach the target (Fig 2D) was significantly larger in patients than in controls, for reactive,
5
6 scanning and memory-guided saccades (non-parametric ANOVA, group effect: $p < 0.01$), but
7
8 not for anti-saccades (Kruskal-Wallis test: $p > 0.41$).
9

10
11
12 In summary, latencies were similar between groups for reactive saccades, scanning saccades
13
14 and anti-saccades while they were longer for memory-guided saccades in patients compared
15
16 to controls. Patients made hypometric primary saccades followed by stair-case corrective
17
18 saccades. Saccade dynamics were slightly affected in patients and characterised by slower
19
20 reactive and scanning saccades compared to controls.
21
22
23
24
25

26 **Eye-head coordination**

27
28
29 Representative examples of eye-head coordination impairments are illustrated in two patients
30
31 for a rightward reactive response (Fig 3B, 3C – see for comparison the response of a control
32
33 subject in Fig 3A). Several parameters were calculated to compare eye-head coordination in
34
35 patients relative to the controls. First, we found that, as in head-restrained tasks, eye latency
36
37 did not differ between groups of subjects (Table 3 – non-parametric ANOVA: $p > 0.16$) and
38
39 that the amplitude of eye movements was smaller in patients than in controls (non-parametric
40
41 ANOVA, group effect: $p < 0.001$).
42
43
44

45
46 Second, the head movements' characteristics were scrutinized. Patients with AOA2 started
47
48 moving their head more than 100 ms after eye movement initiation (Fig 4A). This delay
49
50 between head and eye movement initiation was significantly larger than in healthy
51
52 participants (non-parametric ANOVA, group effect: $p < 0.001$). The amplitude of head
53
54 movements was significantly smaller than in control subjects (Fig 4B – non-parametric
55
56 ANOVA, group effect: $p < 0.001$). Despite this hypometria, head movements lasted longer in
57
58
59
60
61
62
63
64
65

1 patients than in controls, a difference that reached significance in the scanning task for the 50°
2 target (Fig 4C – non-parametric ANOVA, group × movement type interaction: $p < 0.01$).
3
4 Patients always had slower head displacements than controls (Fig 4D – non-parametric
5 ANOVA, group factor: $p < 0.001$; nonparametric Behrens-Fisher problem: $p < 0.001$).
6
7

8
9 Lastly, we analysed the gaze displacement resulting from combined eye-head movements.
10 We first estimated the gaze accuracy at the end of the primary saccade (Fig 5A). In controls,
11 gaze landed on target (gain around 1) for the small target eccentricity (30°) and close to the
12 target for the large eccentricity (50°). In contrast, gaze gain was only around 0.4-0.6 in
13 patients. This gaze hypometria in patients relative to controls was larger for the 50° than for
14 the 30° eccentricity (non-parametric ANOVA, group and eccentricity interaction: $p < 0.001$;
15 nonparametric Behrens-Fisher problem: $p < 0.001$). Contrary to controls (Fig 5B), the gaze of
16 patients had still not reached the target at the end of head movement and gaze gain (0.8-0.9)
17 was still significantly smaller than in controls (non-parametric ANOVA, group effect:
18 $p < 0.001$). Finally, when stabilised, gaze was on target both in controls and patients (Fig 5C),
19 as revealed by gain values close to 1 in all participants and by the lack of significant
20 difference between groups (non-parametric ANOVA: $p > 0.07$). Interestingly, the total gaze
21 shift duration (Fig 5D) in AOA2 patients (exceeding 1500 ms) significantly differed from that
22 of control subjects (200 to 400 ms – non-parametric ANOVA, group effect: $p < 0.001$).
23
24

25 To summarize, eye-head coordination was severely impaired in our patients with AOA2.
26 The head movement was delayed by around 100 ms relative to the eye movement. The
27 amplitudes of the eye and head movements were smaller in patients than in controls, leading
28 to a marked gaze hypometria. The head velocity was decreased in all patients. Finally the
29 duration of the head displacement was unaffected for reactive movements but larger for
30 scanning movements in patients compared to controls. Because of all these deficits, the
31 patients required highly longer times than controls to reach the target.
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Discussion

Saccade inhibition

Patients with AOA2 made more anticipatory errors than controls in the memory-guided task and more directional errors in the anti-saccade task. These errors reflect a deficiency of a saccade inhibition process common to both tasks, classically associated with an impairment of the dorsolateral prefrontal cortex [23-25]. Poor performance in the anti-saccade task has been reported earlier in patients with AOA2 [15] and in patients with AOA1 [17]. Moreover, an increased error frequency in the anti-saccade and memory-guided saccade tasks has also been described in patients with Friedreich ataxia [26], in spinocerebellar ataxia type 17 [27] and in patients with cerebellar atrophy [28]. Finally, an increased percentage of errors in anti-saccades was also found in spinocerebellar ataxia type 1, 2 and 3 [29]. Fielding et al [26] suggested that: “Given that the primary site of pathology in FDRA is within the cerebellum, it is conceivable that disruption to cerebro-ponto-cerebello-thalamo-cerebral circuitry may be involved in the manifestation of these deficits”. Thus, poor performance in anti-saccades and memory-guided saccades observed in these various cerebellar ataxic syndromes, as well as in our AOA2 patients, may be taken as evidence of dysfunction at the level of the cerebello-frontal neural network. Dysfunction outside of the cerebellum in AOA2 is further strengthened by dystonic movements and mild cognitive defects observed in some patients with AOA2 [5].

Saccade dynamics

We found that the dynamics of reactive and scanning saccades were slightly altered in patients with AOA2. Indeed, for saccades of matched amplitude, peak velocity was about 10% lower than in healthy participants. This observation contrasts with a previous study which reported normal saccade velocity in patients with AOA2 [15]. However, this lack of

1 velocity deficits might be linked to the limited impairment of saccadic accuracy found in this
2 previous study. Disturbance of saccadic dynamics is a sensitive marker of brainstem
3 involvement in neurodegenerative diseases [30]. Thus, our results suggest a partial brainstem
4 dysfunction in patients with AOA2.
5
6
7
8
9

10 11 **Saccade accuracy**

12 The most striking oculomotor deficit found in patients with AOA2 was a saccadic
13 hypometria, which increased with target distance, and which was observed regardless of
14 whether the head was restrained or free to move. Hypometria in patients with AOA2 was
15 reported in a previous study, but to a smaller extent [15]. This study has additionally
16 suggested that saccadic stair-case specifically characterizes AOA1 but not AOA2 [15]. Our
17 results instead suggest for the first time that stair-case saccades are a common feature of
18 AOA1 and AOA2. The observation of saccadic hypometria and stair-case saccades is
19 consistent with a cerebellar impairment in such patients [31]. However, both deficits of the
20 superior colliculus [32, 33] and of the basal ganglia [34-36] can also lead to saccadic stair-
21 cases. Thus, a dysfunction at the level of one of these two areas cannot be ruled out in patients
22 with AOA2.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42

43 **Eye-head coordination**

44 Patients with AOA2 tested in the present study did not exhibit head thrusts, but their eye-head
45 coordination was strongly impaired. First, a marked increase of head movement latency led to
46 an abnormally long delay (~100 ms) between eye and head, disrupting the normal eye-head
47 coordination. Second, head movements in patients were markedly smaller and slower than in
48 control subjects. Consequently, the head contributed very little to the overall gaze shift.
49
50
51
52
53
54
55
56
57
58 Because of this altered eye-head coupling and of the marked hypometria of eye and head
59
60
61
62
63
64
65

1 movements, patients needed more time than controls to shift their gaze onto the targets. Note
2 that in family I, the high gain of the VOR further interfered with orientation and stabilisation
3 of gaze.
4
5

6
7 The observed deficits of eye-head coordination could directly result from a role of the
8 cerebellum in head-orienting movements, according to lesion data in the cat [37]. Note that a
9 similar pattern of head movements' deficits (i.e. increased latency, reduced size and velocity)
10 has been identified earlier in patients with Parkinson's disease [35, 38]. These deficits might
11 originate from an alteration of the pathway from the basal ganglia to the superior colliculus,
12 as this structure is known as a key area for orienting head movements (for review see [39]).
13 Thus, in the case of patients with AOA2, and in addition to a direct cerebellar impairment,
14 deficits in head movements might also be linked to a dysfunction of the basal ganglia-superior
15 colliculus network.
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30

31 **Global brain deficits in AOA2**

32
33 In the previous parts of the discussion, we suggested that deficits in our patients could result
34 from dysfunction scattering in various brain areas. Indeed, cerebellar damages can be
35 responsible for the saccadic hypometria with a stair-case pattern and for the deficits in head
36 movements. However, dysfunction in the basal ganglia-superior colliculus network can result
37 in similar deficits. Moreover, alterations of saccade dynamics are classically attributed to
38 brainstem dysfunction whereas deficits in saccadic inhibition are usually characteristic of
39 lesion of the dorsolateral prefrontal cortex. Thus, the oculomotor and head movements
40 abnormalities reported in the present study suggest that patients with AOA2 suffer from
41 impairments involving a much wider network than the cerebellum. Because the cerebellum
42 sends direct or indirect projections to this network, and is primarily implicated by the
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2 pathological degeneration, all these ocular motor deficits might be due to an abnormal
3 cerebellar drive to this network.
4
5

6 7 **Oculomotor apraxia**

8
9 Our patients with AOA2 presented deficits of voluntary/reactive saccades (hypometria with
10 stair-case pattern, increased latency of memory-guided saccades) in agreement with the
11 definition of oculomotor apraxia. Instead of compensatory head thrusts, they showed strongly
12 altered head movements characterised by long latency, small amplitude and reduced velocity.
13
14 Under natural conditions, patients produced rare and small head movements, and none of
15 them made head thrusts movements. Our study therefore emphasizes that head thrust is not a
16 mandatory symptom of oculomotor apraxia and that instead, the eye movements' deficits best
17 characterize the pathology and are the most clinically relevant criteria to determine if patients
18 suffer from oculomotor apraxia. When the description of oculomotor performance is used as a
19 criterion, the prevalence of oculomotor apraxia in AOA2 is expected to be higher than what
20 has been reported in previous studies.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 **Conclusion**

42
43 This study showed for the first time that gaze disorder in patients with AOA2 mainly
44 originates from the production of stair-case saccades. This result emphasizes that in AOA2,
45 hypometric saccades with a stair-case pattern are a more reliable sign of oculomotor apraxia
46 than head thrust movements. A direct comparison of the oculomotor deficits of AOA2
47 patients with and without head thrust would be necessary to understand the origin of these
48 head thrusts. Moreover, the various saccadic and eye-head coordination deficits reported here
49 suggest dysfunctions of the different brain structures such as cerebellum, brainstem, superior
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 colliculus, basal ganglia and/or frontal lobe. Thus, although the main neural degeneration in
2 AOA2 affects the cerebellum, this disease seems to impact other structures indirectly,
3
4 probably through reduced input from the cerebellum.
5
6
7
8
9
10

11 **Acknowledgements**

12 The authors thank the patients and the healthy subjects for contributing to this study. The
13
14 authors thank Pr S. Thobois, Dr I. Rouillet-Solignac and Dr A. Poisson for referring the
15
16 patients. The authors are really grateful to Pr. D. Zee for a helpful discussion. This work was
17
18 promoted by the Hospices Civils de Lyon (2002-303).
19
20
21
22
23
24
25
26
27
28

29 **References**

- 30
31
32 1. Watanabe M, Sugai Y, Concannon P, Koenig M, Schmitt M, Sato M et al. Familial
33 spinocerebellar ataxia with cerebellar atrophy, peripheral neuropathy, and elevated
34 level of serum creatine kinase, gamma-globulin, and alpha-fetoprotein. *Ann Neurol*
35 1998;44:265-9.
36
37
- 38
39 2. Bomont P, Watanabe M, Gershoni-Barush R, Shizuka M, Tanaka M, Sugano J et al.
40 Homozygosity mapping of spinocerebellar ataxia with cerebellar atrophy and
41 peripheral neuropathy to 9q33-34, and with hearing impairment and optic atrophy to
42 6p21-23. *Eur J Hum Genet* 2000;8:986-90.
43
44
- 45
46 3. Nemeth AH, Bochukova E, Dunne E, Huson SM, Elston J, Hannan MA et al.
47 Autosomal recessive cerebellar ataxia with oculomotor apraxia (ataxia-telangiectasia-
48 like syndrome) is linked to chromosome 9q34. *Am J Hum Genet* 2000;67:1320-6.
49
50
- 51
52 4. Moreira MC, Klur S, Watanabe M, Nemeth AH, Le Ber I, Moniz JC et al. Senataxin,
53 the ortholog of a yeast RNA helicase, is mutant in ataxia-ocular apraxia 2. *Nat Genet*
54 2004;36:225-7.
55
56
- 57
58 5. Anheim M, Fleury MC, Franques J, Moreira MC, Delaunoy JP, Stoppa-Lyonnet D et
59 al. Clinical and molecular findings of ataxia with oculomotor apraxia type 2 in 4
60 families. *Arch Neurol* 2008;65:958-62.
61
62
63
64
65

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
6. Anheim M, Monga B, Fleury M, Charles P, Barbot C, Salih M et al. Ataxia with oculomotor apraxia type 2: clinical, biological and genotype/phenotype correlation study of a cohort of 90 patients. *Brain* 2009;132:2688-98.
7. Cogan DG. A type of congenital ocular motor apraxia presenting jerky head movements. *Trans Am Acad Ophthalmol Otolaryngol* 1952;56:853-62.
8. Cogan DG. A type of congenital ocular motor apraxia presenting jerky head movements. *Am J Ophthalmol* 1953;36:433-41.
9. Cogan DG, Adams RD. A type of paralysis of conjugate gaze (ocular motor apraxia). *AMA Arch Ophthalmol* 1953;50:434-42.
10. Leigh RJ, Zee DS. *The Neurology of Eye Movements*. New-York: Oxford University Press, 2006.
11. Zee DS, Yee RD, Singer HS. Congenital ocular motor apraxia. *Brain* 1977;100:581-99.
12. Asaka T, Yokoji H, Ito J, Yamaguchi K, Matsushima A. Autosomal recessive ataxia with peripheral neuropathy and elevated AFP: novel mutations in SETX. *Neurology* 2006;63:1581.
13. Criscuolo C, Chessa L, Di Giandomenico S, Mancini P, Sacca F, Grieco GS et al. Ataxia with oculomotor apraxia type 2 - A clinical, pathologic, and genetic study. *Neurology* 2006;66:1207-10.
14. Gazulla J, Benavente I, Lopez-Fraile IP, Modrego P, Koenig M. Sensorimotor neuronopathy in ataxia with oculomotor apraxia type 2. *Muscle Nerve* 2009;40:485.
15. Le Ber I, Bouslam N, Rivaud-Pechoux S, Guimaraes J, Benomar A, Chamayou C et al. Frequency and phenotypic spectrum of ataxia with oculomotor apraxia 2: a clinical and genetic study in 18 patients. *Brain* 2004;127:759-67.
16. Tazir M, Ali-Pacha L, M'Zahem A, Delaunoy JP, Fritsch M, Nouioua S et al. Ataxia with oculomotor apraxia type 2: A clinical and genetic study of 19 patients. *J Neurol Sci* 2009;278:77-81.
17. Le Ber I, Moreira MC, Rivaud-Pechoux S, Chamayou C, Ochsner F, Kuntzer T et al. Cerebellar ataxia with oculomotor apraxia type 1: clinical and genetic studies. *Brain* 2003;126:2761-72.

18. R Development Core Team. R: A Language and Environment for Statistical Computing. 2012. Vienna, Austria, R Foundation for Statistical Computing.
19. Hothorn T, Hornik K, van de Wiel MA, Zeilis A. A Lego system for conditional inference. *The Am Stat* 2006;60:257-63.
20. Hothorn, T., Hornik, K., van de Wiel, M. A, and Zeilis, A. Implementing a class of permutation tests: The coin package. *J.of Stat.Soft.* 28(8), 1-23. 2008.
21. Brunner, E., Domhof, S., and Langer, F. *Nonparametric Analysis of Longitudinal Data in Factorial Experiments.* Wiley(New-York). 2002.
22. Brunner, E. and Munzel, U. The Nonparametric Behrens-Fisher Problem: Asymptotic Theory and a Small Sample Approximation. *Biomed.Jour.* 42, 17-25. 2000.
23. DeSouza JF, Menon RS, Everling S. Preparatory set associated with pro-saccades and anti-saccades in humans investigated with event-related FMRI. *J Neurophysiol* 2003;89:1016-23.
24. Guitton D, Buchtel HA, Douglas RM. Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp Brain Res* 1985;58:455-72.
25. Pierrot-Deseilligny C, Muri RM, Ploner CJ, Gaymard B, Demeret S, Rivaud-Pechoux S. Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. *Brain* 2003;126:1460-73.
26. Fielding J, Corben L, Cremer P, Millist L, White O, Delatycki M. Disruption to higher order processes in Friedreich ataxia. *Neuropsychologia* 2010;48:235-42.
27. Hubner J, Sprenger A, Klein C, Hagenah J, Rambold H, Zuhlke C et al. Eye movement abnormalities in spinocerebellar ataxia type 17 (SCA17). *Neurology* 2007;69:1160-8.
28. Filippopoulos, F., Eggert, T., and Straube, A. Deficits of cortical oculomotor mechanisms in cerebellar atrophy patients. *Exp.Brain Res.* 224(4), 541-550. 2013.
29. Rivaud-Pechoux S, Durr A, Gaymard B, Cancel G, Ploner CJ, Agid Y et al. Eye movement abnormalities correlate with genotype in autosomal dominant cerebellar ataxia type I. *Ann Neurol* 1998;43:297-302.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
30. Ramat S, Leigh RJ, Zee DS, Optican LM. What clinical disorders tell us about the neural control of saccadic eye movements. *Brain* 2007;130:10-35.
31. Solomon D, Ramat S, Leigh RJ, Zee D. A quick look at slow saccades after cardiac surgery: where is the lesion? Using Eye Movements As An Experimental Probe of Brain Function - A Symposium in Honor of Jean Buttner-Ennever 2008;171:587-90.
32. Robinson DA. Eye movements evoked by collicular stimulation in the alert monkey. *Vision Res* 1972;12:1795-808.
33. Schiller PH, Stryker M. Single-unit recording and stimulation in superior colliculus of the alert rhesus monkey. *J Neurophysiol* 1972;35:915-24.
34. Sauleau P, Pollak P, Krack P, Pelisson D, Vighetto A, Benabid AL. Contraversive eye deviation during stimulation of the subthalamic region. *Movement Disord* 2007;22:1810-3.
35. Sauleau P, Pollak P, Krack P, Courjon JH, Vighetto A, Benabid AL et al. Subthalamic stimulation improves orienting gaze movements in Parkinson's disease. *Clin Neurophysiol* 2008;119:1857-63.
36. Shaikh AG, Xu-Wilson M, Grill S, Zee DS. 'Staircase' square-wave jerks in early Parkinson's disease. *B J Ophthalmol* 2011;95:705-9.
37. Pelisson D, Goffart L, Guillaume A. Contribution of the rostral fastigial nucleus to the control of orienting gaze shifts in the head-unrestrained cat. *J Neurophysiol* 1998;80:1180-96.
38. White OB, Saint-Cyr JA, Tomlinson RD, Sharpe JA. Ocular motor deficits in Parkinson's disease. III. Coordination of eye and head movements. *Brain* 1988;111:115-29.
39. Gandhi NJ, Katnani HA. Motor Functions of the Superior Colliculus. *Annu Rev Neurosci* 2011;34:205-31.

Tables

Table 1: *Characteristics of the AOA2 patients*

Family	Mutation	Patient	Sex	Age at onset (yrs)	Disease Duration (in yrs)	Initial symptom	Funct score	Tendon reflexes	Deep sensory loss	MMSE (/30)	FAB (/18)	Chorea/ Dystonia	ICAR S total (/100)	AFP level (µg/L)	HIT-VOR (gain)
F1*	homozygous for missense mutation 5413C→T (P1805S)	I-1	F	18	10	Gait ataxia Writing ataxia Dysarthria	5	Absent	Present	29	18	Absent	69	60	1.39
		I-2	M	12	14	Dysarthria	4	Absent	Present	29	17 (Luria)	Chorea left hand	50	45.9	1.26
		I-3	F	20	3	Gait ataxia	3	Absent	Present	29	18	Absent	39	78.6	1.49
F2*	homozygous for missense mutation 7267G→A (G2423R)	II-1	F	10	27	Gait ataxia	6	Absent	Present	24/28	13	Absent	69	15.1	NA
		II-2	M	17	24	Gait ataxia	6	Absent	Present	24	18	Absent	68	22.5	0.69

* = known consanguinity; Motor disability was assessed by a seven-stage functional scale (Funct. Score): 0 = normal; 1 = mild modifications at examination; 2, mild functional disability, able to walk and run; 3 = able to walk without help up to 500 m, unable to run; 4 = needs unilateral help to walk; 5 = needs bilateral help to walk; 6 = wheelchair-bound ; 7, bedridden. MMSE= mini mental state examination. FAB= Frontal Assessment Battery. ICARS= International Cerebellar Ataxia Rating Scale. AFP=alpha feto-protein (Normal < 10 µg/L). HIT-VOR= Head-Impulse Test - Vestibulo-Ocular Reflex (viewing distance > 100 cm).

Table 2: *Main sequence for saccades with amplitude comprised between 8° and 12°*

	Reactive saccades		Scanning saccades		Memory-guided saccades	
	Ctrl	Patients	Ctrl	Patients	Ctrl	Patients
Amplitude (°)	10.0	10.2	10.2	10.3	9.4	10.0
Peak vel (°/s)	375	336*	357	313*	297	318

Median values are presented. Asterisks indicate significant differences of velocity (Vel) between controls (Ctrl) and patients (non-parametric ANOVA, group factor: $p < 0.05$).

Table 3: *Eye movement latency and amplitude in the head-free condition*

	Reactive saccade				Scanning saccades			
	30°		50°		30°		50°	
	Ctrl	Patients	Ctrl	Patients	Ctrl	Patients	Ctrl	Patients
Lat (ms)	290	249	307	267	464	465	468	513
Amp (°)	29.1	14.8***	39.1	19.4***	29.0	18.3***	38.4	20.7***

Median values are presented. Asterisks indicate significant differences of amplitudes between controls (Ctrl) and patients (post-hoc Behrens-Fisher comparisons: $p < 0.05$). Lat= latency, Amp= amplitude

Figure captions

Figure 1: Examples of saccadic recordings in the head-restrained condition for a representative control subject (A) and for a patient (B).

The horizontal eye position (black for control and dark grey for patient) during a reactive saccade trial is presented as a function of time and is aligned on target appearance (light grey). In these recordings, the target was presented at -20° . One single saccade of about 20° , initiated after a latency of approximately 200 ms, allows the control subject to accurately fixate the target. For the patient, the primary saccade is initiated after a similar latency, however this saccade is small ($<5^\circ$) and is followed by six other saccades (“stair-case”) directed toward the target.

Figure 2: Saccade parameters in the head-restrained condition.

The saccade latency (A), the gain of primary saccade (B), the total gain (C) and the number of corrective saccades per trial (B) are represented as a function of the different categories of saccades for control subjects (white boxes) and for the patients (gray boxes). On the left panel are depicted the saccades toward targets at an eccentricity of 10° and on the right panel are presented the saccades toward targets located at an eccentricity of 20° . The band in the whisker box is the median, the bottom and the top of the box are the lower and upper quartiles and the ends of the whiskers are the minimum and maximum values without outliers.

Asterisks indicate significant differences between controls and patients (see text for the statistical tests): * $p < 0.05$; ** $p < 0.01$ and *** $p < 0.0001$.

Figure 3: Examples of recordings of gaze shift in the head-free condition for a representative control subject (A), for a patient from family I (B) and for a patient from family II (C).

1 The eye (top), head (middle) and gaze (bottom) horizontal positions during a reactive eye-
2 head movements' trial are presented as a function of time. The vertical arrow indicates the
3
4 time of target appearance, corresponding to the go signal. In these recordings, the fixation
5
6 point was located at -25° and the target was presented at $+25^\circ$. The vertical dashed line
7
8 indicates the initiation of the eye movements.
9

10
11 For the control (Fig 3A), the eye (top panel) started moving slightly before the head (middle
12
13 panel) and a total saccadic eye movement of about 30° was produced. When the gaze
14
15 approached the target (bottom panel), it stabilised despite the continuing head movement
16
17 thanks to a counter-rotation of the eyes in the orbit resulting from the vestibulo-ocular reflex
18
19 (VOR). For the patients (Fig 3B and 3C), the latency of the first eye movement was similar to
20
21 that of the control subject, but the eye-head movements revealed a strong disruption of eye-
22
23 head coordination. For patient I-3 (Fig 3B), the latency of the head movement was slightly
24
25 longer, and its amplitude much smaller, compared to the control. Also, a high gain of the
26
27 VOR caused a marked instability of gaze, drifting in the direction opposite to the head. For
28
29 the patient II-1 (Fig 3C), the head started moving only after three eye saccades were
30
31 completed. The size of head movement was excessively small and thus barely contributed to
32
33 the gaze displacement.
34
35
36
37
38
39
40
41
42
43

44 **Figure 4: Head movements' parameters in the head-free condition**

45
46 The latency of the head relative to eye latency (A), the head amplitude (B), the head
47
48 movement duration (C) and the head velocity (D) are represented separately for the two
49
50 categories of movements (reactive and scanning) and for control subjects (white boxes) and
51
52 for patients (gray boxes). On the left panel are depicted the movements toward the targets at a
53
54 distance of 30° and on the right panel are presented the movements toward the targets at a
55
56 distance of 50° . The band in the whisker box is the median, the bottom and the top of the box
57
58
59
60
61
62
63
64
65

1 are the lower and upper quartiles and the ends of the whiskers are the minimum and
2 maximum values without outliers.
3

4 Asterisks indicate significant differences between controls and patients (see text for the
5 statistical tests): ** $p < 0.01$ and *** $p < 0.0001$.
6
7
8
9

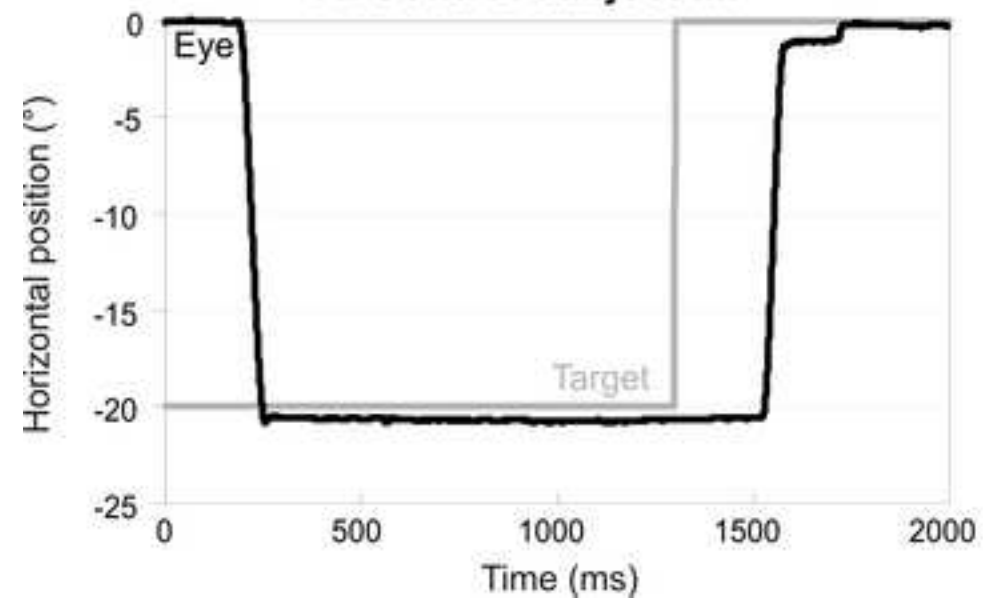
10 11 **Figure 5: Gaze shift parameters in the head-free condition.**

12 The gain of the gaze at the end of the primary saccade (A), at the end of the head movement
13 (B), and after its own stabilisation (C), as well as the total duration of gaze shift (D) are
14 represented separately for the two categories of movements (reactive and scanning), for
15 control subjects (white boxes) and for patients (gray boxes). On the left panel are depicted the
16 movements toward the targets at a distance of 30° and on the right panel are presented the
17 movements toward the targets at a distance of 50° . The band in the whisker box is the median,
18 the bottom and the top of the box are the lower and upper quartiles and the ends of the
19 whiskers are the minimum and maximum values without outliers.
20
21
22
23
24
25
26
27
28
29
30
31
32

33 Asterisks indicate significant differences between controls and patients (see text for the
34 statistical tests): *** $p < 0.0001$.
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Recordings of leftward reactive saccades

A. Control subject MP



B. Patient II-2

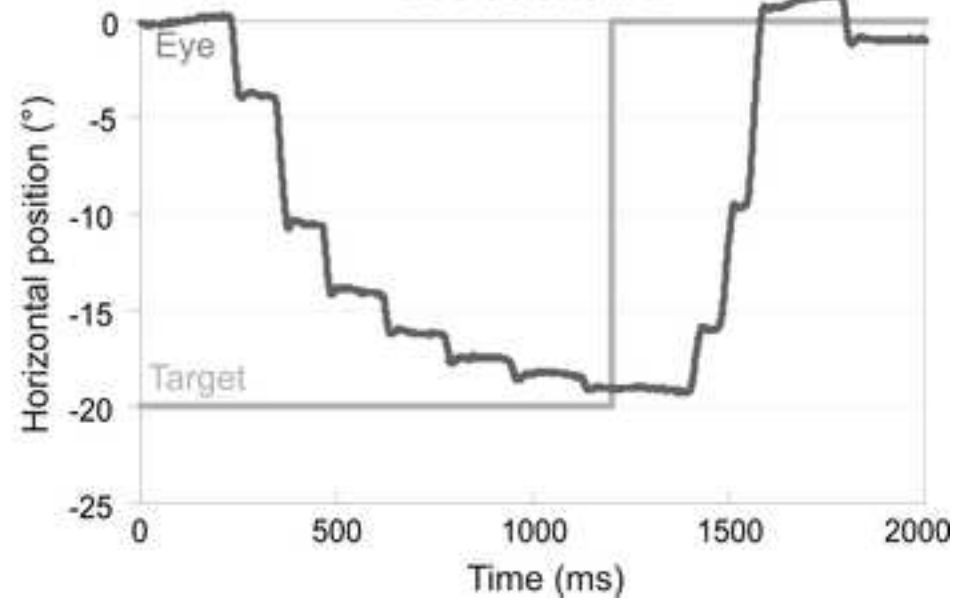
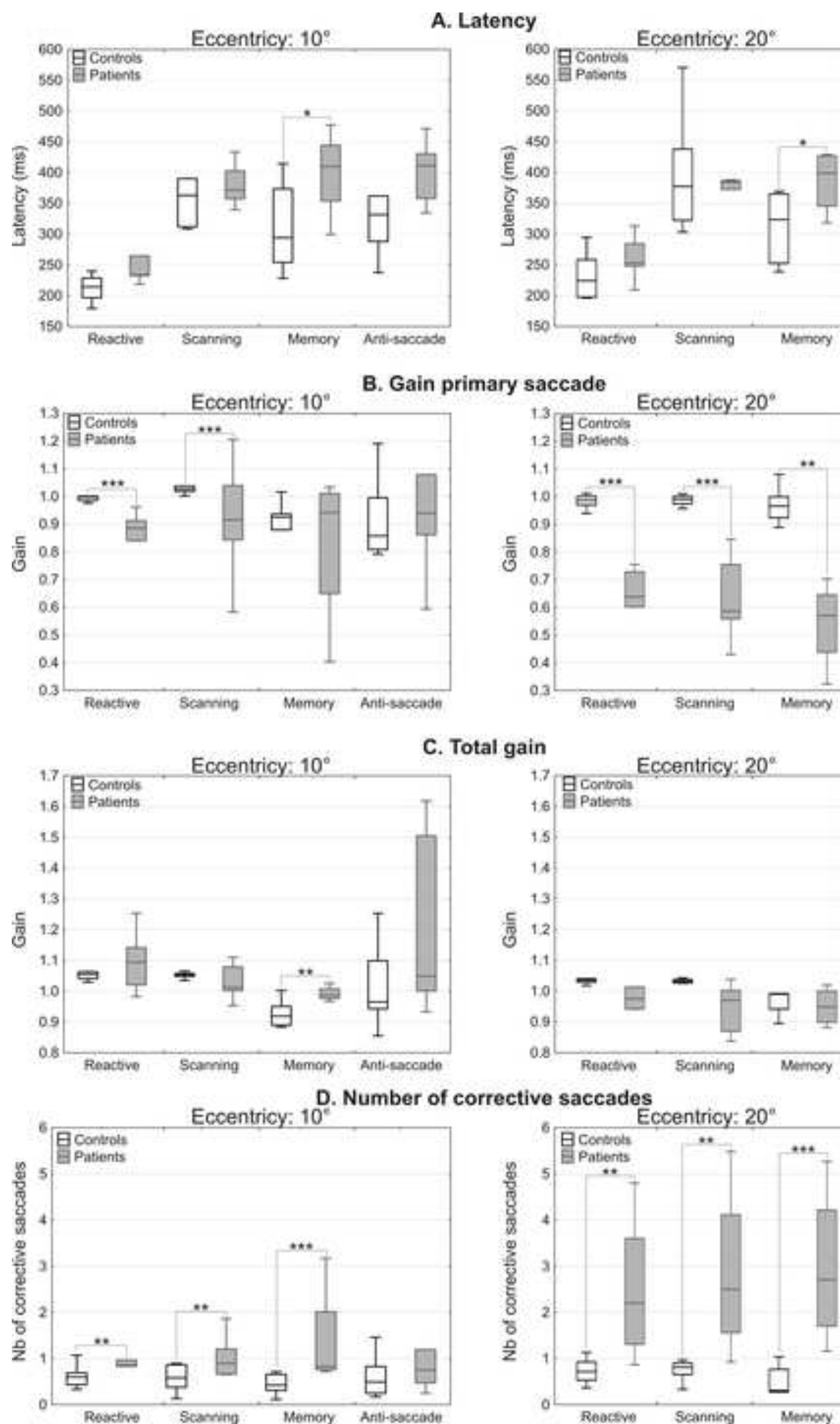


Figure 2

[Click here to download high resolution image](#)



Recordings of rightward gaze shift

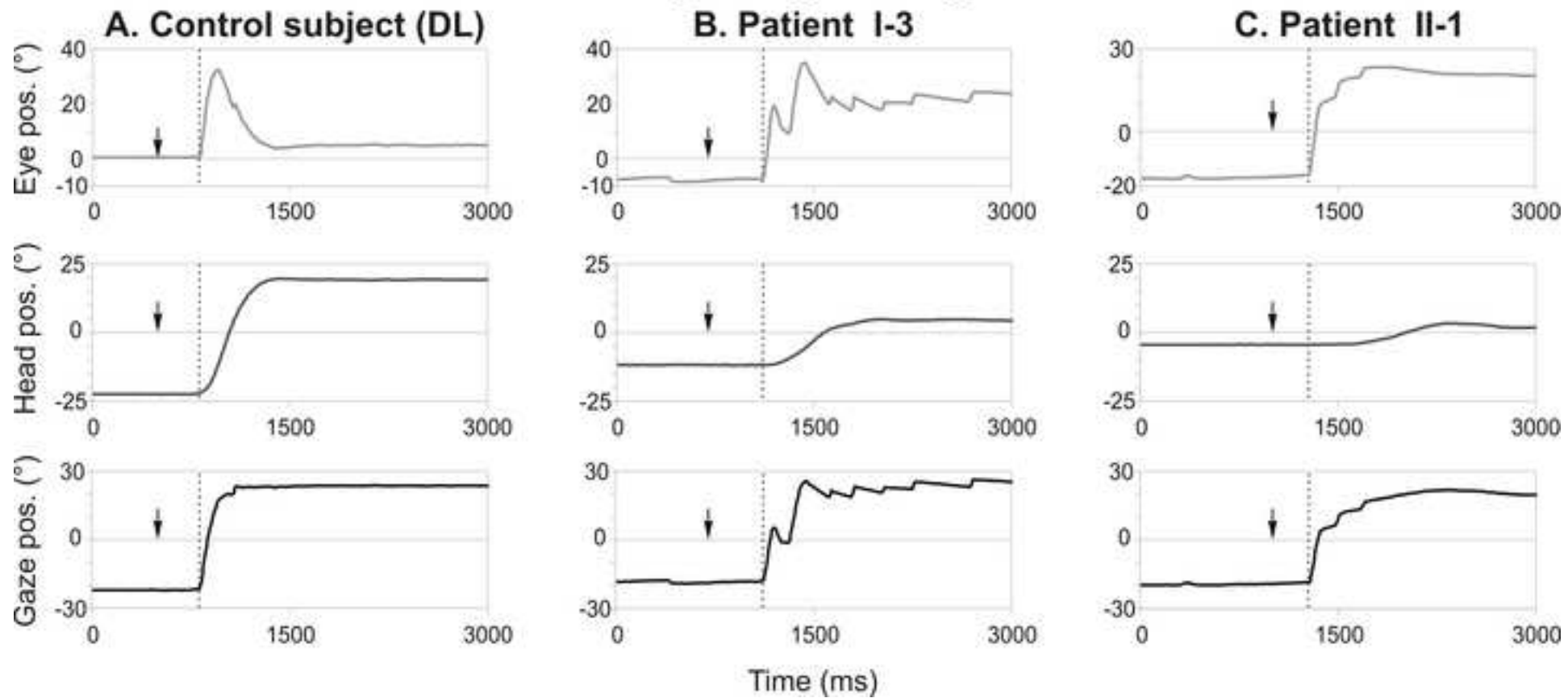


Figure 4
[Click here to download high resolution image](#)

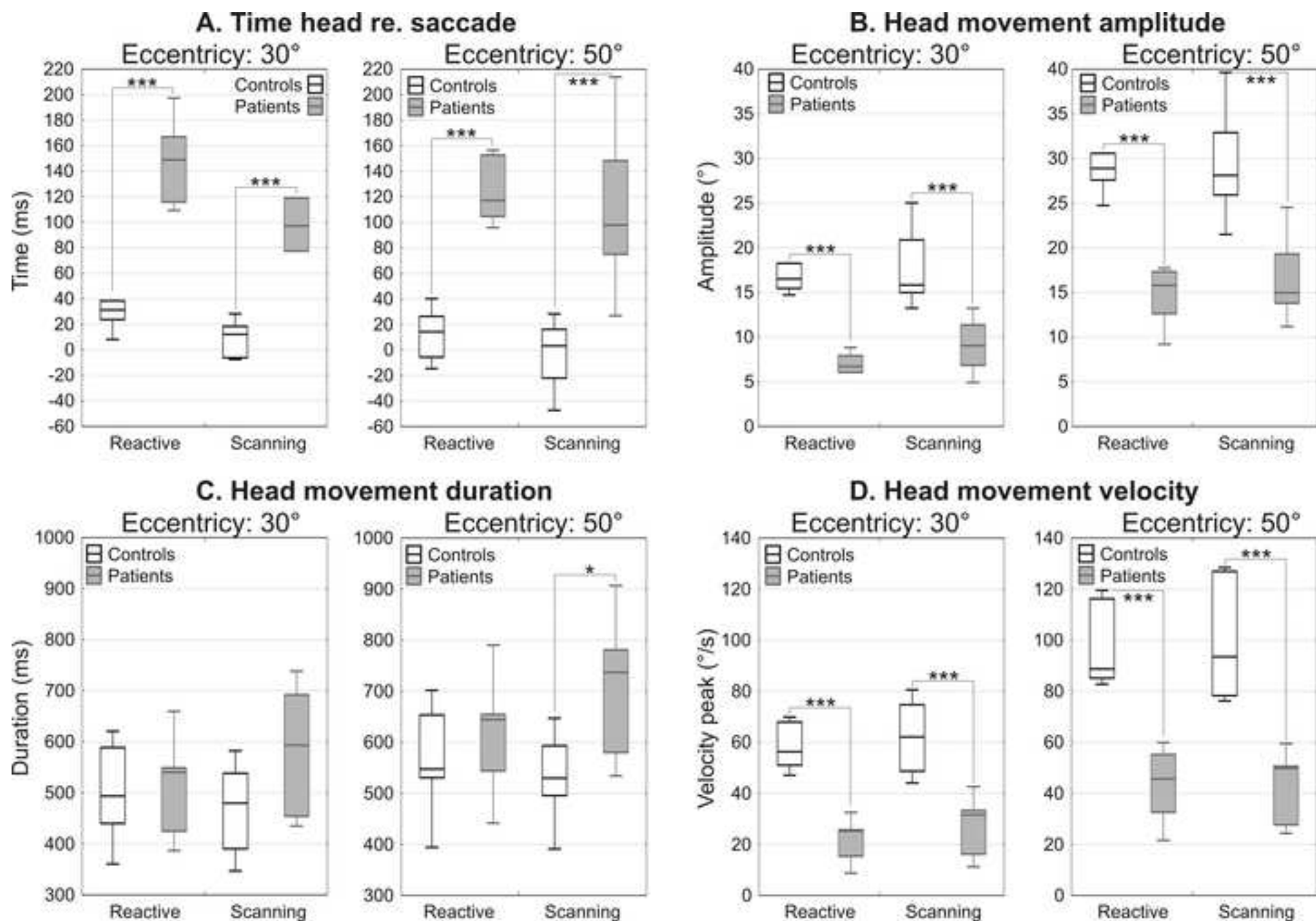
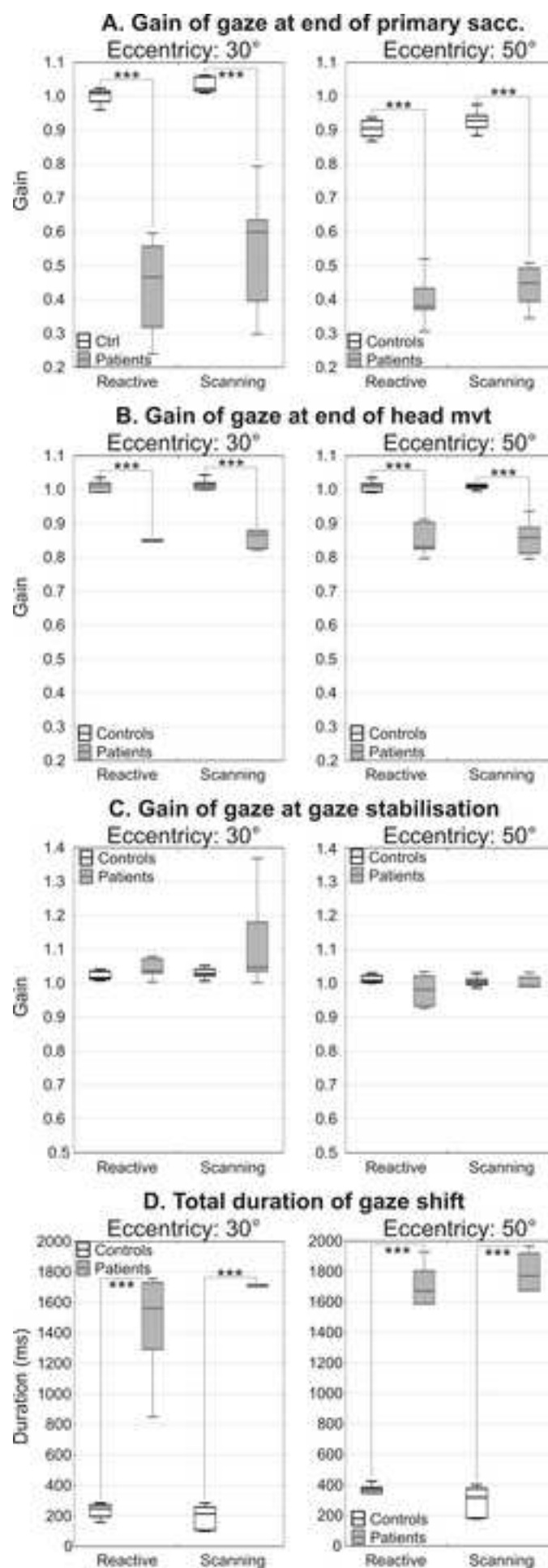


Figure 5

[Click here to download high resolution image](#)



Supplementary Material

[Click here to download Supplementary Material: 2013-02-13 Panouilleres_AOA2_SupplMat.doc](#)