

1 **Stimulus Unpredictability in Time, Magnitude, and Direction on Accommodation**

2 Carles Otero, PhD,^{1,2*} Mikel Aldaba, PhD,² Fernando Díaz-Doutón, PhD,² Fuensanta A.
3 Vera-Diaz, PhD, FAAO,³ and Jaume Pujol, PhD²

4

5 Author Affiliations:

6 1. Vision and Eye Research Unit, School of Medicine, Anglia Ruskin University,
7 Cambridge, United Kingdom

8 2. Center for Sensors, Instruments and Systems Development, Universitat
9 Politècnica de Catalunya, Terrassa, Spain

10 3. New England College of Optometry, Boston, Massachusetts

11 *carles.otero@anglia.ac.uk

12

13 INTRODUCTION

14 The accommodative system can respond reasonably quickly and accurately to a
15 variety of dynamically changing stimuli, either using stimuli modulated in step,
16 sinusoidal or ramp changes in defocus or near vision demands.¹⁻⁴ A square wave or a
17 sinusoidally modulated stimuli may be predictable to observers if the accommodative
18 demand is changed following a repetitive and well-defined pattern in magnitude (the
19 dioptric change between two accommodative states), direction (either accommodation
20 or disaccommodation) and time (the period of time that the fixation target remains in
21 each accommodative demand).

22 More than 50 years ago, some authors⁵⁻⁷ mentioned the possibility that the human
23 accommodative system is able to anticipate future accommodation stimulus changes,
24 i.e., there might exist a prediction operator that reduces response latency in
25 predictable, compared to random, accommodative stimulus. This concept was further
26 investigated by Phillips *et al.*² in 1972. They measured monocular accommodative
27 responses to square wave modulated stimuli for four subjects and found a mean
28 reduction in response latency of 204 ms when using a square wave stimulus instead of
29 a non-predictable stimulus. The mean reduction in response latency was highly
30 skewed, when the mode difference was computed, the reduction was of only 49 ms. In
31 the following two years, Krishnan *et al.*¹ and Van der Wildt *et al.*³ investigated the
32 presence of the prediction operator in repeatable sinusoidally modulated stimuli and
33 concluded that the effect of prediction is small but not negligible. Interestingly, one
34 subject studied by Van der Wildt *et al.*³ was not able to follow the accommodation
35 stimulus despite its predictability.

36 It is important to note that all these studies were each limited in sample size and
37 difficult to reproduce due to the lack of information about the participants' age,
38 refractive error, or the explicit task instructions. As shown in previous studies, the

39 accommodative response and some parameters of its dynamics (e.g., latency) are
40 significantly affected by age,^{8,9} refractive error,^{10,11} and the instructions given to
41 participants.¹² When these factors are not controlled, they could mask or bias the
42 findings. In addition, most of the subjects in these studies were presumably the authors
43 themselves, with consequent biases associated to the knowledge of the nature of the
44 study and extensive training in similar studies. After the aforementioned studies,
45 carried out approximately 40 years ago, little has been investigated in relation to a
46 possible prediction operator in accommodation.

47 Most subsequent accommodation dynamic studies have used predictable stimuli, either
48 sinusoidal or square wave, and have assumed the presence of anticipation
49 effects.^{8,10,13} A few studies considered random stimuli either in time^{9,14,15} or magnitude¹⁶
50 to avoid the possible effect of prediction. To our knowledge, there is a question related
51 to a possible prediction operator in accommodation that is not yet answered: Is
52 prediction affected by the interactions between the factors that define a predictable
53 stimulus (i.e., time, magnitude and direction)?

54 The effect of each of these factors, time, magnitude and direction, in isolation has not
55 been studied previously. The answer to this question would provide a deeper
56 understanding, at a fundamental level, of the role that the prediction operator has in the
57 models of oculomotor control.¹⁷ Moreover, the investigation of the effect of time,
58 magnitude and direction in accommodation responses would also provide insights into
59 the effect that anticipation has in clinical tests such as accommodative facility.^{10,18} In
60 this test, predictable stimuli are used to evaluate visual fatigue to focus changes.¹⁹ The
61 purpose of this study is, therefore, to investigate the effect of stimulus' predictability in
62 time, magnitude and direction, as well as their interactions, on reflex and voluntary
63 accommodation latency and response magnitude.

64 **METHODS**

65 **Subjects**

66 The research was performed according to institutionally approved human subject's
67 protocols with full informed consent provided by each subject, and it followed the tenets
68 of the Declaration of Helsinki. Criteria for inclusion were: 1) best-corrected visual acuity
69 of 0.00 logMAR (20/20 Snellen equivalent) or better in each eye; 2) between 21 and 28
70 years of age; 3) spherical equivalent error in each eye, as measured with subjective
71 refraction, between -6.50 and +0.50 D; 4) amplitude of accommodation above the
72 value given by Hofstetter's average formula for accommodation²⁰ (Amplitude = 15 –
73 0.25 * Age); 5) no strabismus, amblyopia, binocular or accommodative anomalies; and
74 6) no history of any ocular disease, surgery and/or pharmacological treatment that may
75 have affected vision at the time of the study. Subjects with myopia wore their own
76 disposable soft contact lenses during the study. All contact lens prescriptions were
77 within ± 0.50 D of the subject's best corrected spherical equivalent, determined by
78 subjective refraction, as explained below. A total of 12 subjects (with some experience
79 in accommodation studies) that met the inclusion criteria were tested and included in
80 the analyses.

81 **Instrumentation and Stimuli**

82 A binocular open field autorefractor, PowerRef II (Plusoptix Inc., USA), was used to
83 measure accommodation responses. This autorefractor is based on the principle of
84 dynamic infrared retinoscopy and it measures spherical equivalent, pupil size and gaze
85 position at a sampling frequency of 25 Hz.^{21,22} The PowerRef II refractor was calibrated
86 for each subject. In short, 6 different trial lenses (from +4.00 to -1.00 D, in 1-D steps)
87 were randomly placed in a trial frame fitted to each subject. For each trial lens, subjects
88 monocularly fixated a far distance stimulus during a period of 4 seconds while the
89 contralateral eye was eye patched. During this period of time, objective refraction was
90 obtained with the PowerRef II in the open eye. From each recording, the mean

91 refraction was computed and compared to that expected from the trial lenses. A linear
92 regression was obtained comparing the 6 measured refractions with the expected
93 refraction given by each trial lens. The slope and intercept of the linear fitting obtained
94 from this calibration was used as a correction factor for each subject's measurements,
95 in all experimental conditions. The linear correlation coefficient values obtained in all
96 subjects were greater than 0.75. Although this calibration procedure is not optimal
97 since subjects are likely to accommodate over the top of the -1 D lens and also for high
98 blur (+4 D), the same calibration is used for all study conditions.

99 In order to align the PowerRef with the subjects' eye while they viewed the target, a 50-
100 mm square IR hot mirror (transmits visible light and reflects infrared light) was placed at
101 40 mm from the subjects' pupil plane. Subjects looked at the accommodative stimulus
102 through an optical system comprised of three lenses (figure 1A). The first lens (L1,
103 diameter of 50 mm, focal length of 100 mm) was placed 200 mm from the subject's
104 pupil (twice f_{L1}). In this way, a pupil conjugate plane was created 200 mm away from
105 the lens, without magnification. The active module that performed the accommodation
106 stimulation was placed in that plane and was composed of an electro-optical lens²³
107 (EOL, EL-16-40-TC, Optotune Switzerland AG, Switzerland) and a second lens
108 (ophthalmic type) attached to it (L2, diameter of 25 mm, power of +3 D). The EOL had
109 a spherical power range from -10 to +10 D, with a reproducibility of ± 0.05 D and a
110 settling time of 25 ms (according to manufacturer's specifications).

111 The target was placed at 6 meters from the EOL. This design ensured both the linearity
112 and the 1:1 relationship between the power applied by the EOL and the
113 accommodation stimulus to the subject, as well as a constant stimulus size despite
114 changes in accommodative demand. The lens L2 shifted 3 D the working range of the
115 EOL in order to avoid its operation limits (far vision corresponds to an EOL power of +7
116 D, instead of +10 D), thus guaranteeing its best performance. The overall system can
117 accurately measure an accommodative range up to 10.00 D. The field of view was

118 constant with a diameter of 14.25°. The response time for each step change of
119 accommodative demand was approximately 40 ms (response time of the electronics +
120 settling time of the EOL). The EOL power was controlled by a driver connected to a PC
121 by means of a software application specifically developed for this study that
122 synchronized the accommodative demand changes with the PowerRef II. In each
123 change of accommodative demand, the EOL power was set before a pulse was send
124 to the PowerRef II. In order to avoid possible thermal drifts on the EOL response, the
125 lens was heated to 28°C before the beginning of the sessions, and kept of that
126 temperature throughout the procedures. Moreover, the EOL response at that
127 temperature was calibrated before its integration into the system by means of a digital
128 lensometer CL-300 (Topcon, Japan), including the calibration curve in the software
129 application.

130 The accommodative target used for all conditions was a 2° high-contrast black Maltese
131 cross on a white uniform background (figure 1B), with an average luminance of 3.7
132 cd/m² and 56.2 cd/m² for the black and white regions, respectively. Even though this
133 stimulus does not have peripheral depth cues, which could have improved the
134 accommodative response,^{24,25} it is the most frequently used stimulus for
135 accommodation studies due to its wide frequency spectrum²⁶ and it is easily
136 reproducible. The use of this stimulus allows direct comparisons of our results with
137 previous studies of dynamic accommodation.^{9,27,28}

138 **Examination protocol**

139 Monocular subjective refraction with endpoint criteria of maximum plus power that
140 provides best visual acuity followed by binocular balance was performed to determine
141 each subject's best optical correction. The dominant sensory eye (resistance to +1.50
142 D blur)²⁹ was chosen for the measurements while the fellow eye was occluded with an
143 eye patch. Subjects' pupil size was not controlled nor artificially limited during the

144 experiment and monocular subjective amplitude of accommodation was evaluated by
145 averaging the values of two push-up and two push-down trials.³⁰

146 Monocular accommodative responses were measured for nine randomly presented
147 conditions where the accommodative demand changed several times in a step-like
148 fashion for a total time period of 120 seconds. Subjects were instructed to clear the
149 target naturally and they were not asked to comment on the clarity of the target under
150 any of the experimental conditions. Each change in accommodative demand (i.e., trial)
151 could have different: time duration (1, 2 or 3 seconds), magnitude (1, 2 or 3 D) and/or
152 direction (accommodation or disaccommodation). All conditions were created
153 permuting the factors of time, magnitude and direction in a random or not random
154 fashion. The default values for not random factors of time and magnitude were 2
155 seconds and 2 D, respectively. For direction, the default value was accommodation
156 until the demand reached 4 D, at that moment the direction was reversed to
157 disaccommodation until it reached 0 D accommodation demand. Figure 2 shows the
158 nine testing conditions used in the study.

159 Notice that when time, magnitude and direction were not random, the input signal
160 followed a well-defined step function going from 0 to 4 D and from 4 to 0 D in steps of 2
161 D and staying a period of 2 seconds in each accommodative demand (figure 2, panel
162 2). This condition with three accommodative states was considered a baseline
163 reference for the analyses. This baseline condition was different to the signals used in
164 other dynamic accommodation studies, in which only two accommodative states were
165 considered.^{10,13,22,31} To extrapolate our results to other dynamic accommodation studies
166 such as those cited in the introduction, we included one extra baseline condition: a
167 square wave signal going from 0 to 2 D in steps of 2 D and staying a period of 2
168 seconds in both accommodative demands (figure 2, panel 1). This condition will
169 constitute the most predictable condition in this study.

170 Following each trial, the subject was asked to rank on a 5-point scale their subjective
171 perception of predictability for that condition, with level “1” indicating that the
172 accommodation level was fully predictable and level “5” indicating that it was totally
173 unpredictable. The examiner recorded these subjective responses. All subjects were
174 naïve to the purpose of the study, but they were trained at the beginning on what
175 constitutes a predictable condition. Subjects were trained using the far distance
176 accommodative facility test, consisting on repeatedly changing the accommodative
177 demand between 0 D and 2 D during a period of 60 seconds. For this training, the
178 fixation target was at 6 m distance and the 2 D accommodative demand was lens-
179 induced with an accommodation flipper held by the operator that had an ophthalmic
180 lens of -2.00 D. Subjects were informed that this would be a fully predictable condition
181 (i.e., score value of 1).

182 All conditions were measured once in one session that took approximately 30 minutes,
183 including breaks. Subjects were allowed to take breaks as needed, although there was
184 no systematic method to provide rests during the measurements. Randomization of
185 configurations was rigorously applied to minimize potential learning or fatigue biases.

186 **Data analyses**

187 Data was processed and analyzed using Matlab R2015b (MathWorks, Inc., USA).
188 Since the dynamics of accommodation and disaccommodation are dependent on
189 amplitude,³² the main analysis considered the accommodative changes (‘transitions’)
190 from 0 to 2 D (accommodation) and from 2 to 0 D (disaccommodation) only, although
191 for comparison purposes a secondary analysis also included the transitions 2/4 D. In
192 each transition both accommodative latency and response magnitude were computed.
193 Subsequently, a repeated measures ANOVA was computed for both latency and
194 accommodative response magnitude with two within-subjects’ factors: *condition* (with
195 nine levels) and *direction of accommodation* (with two levels).

196 *Latency* was defined as the time period (in seconds) between the start of the
197 accommodative stimulus change and the start of the accommodative response by the
198 subject, computed as described by Kasthurirangan *et al.*³² To determine the start of the
199 accommodative response, a custom algorithm was created to search for three
200 consecutive increasing data values, followed by four consecutive data values in which
201 no two consecutive decreases occurred, the first data point in this sequence was
202 recorded as the start of the response. The inverse algorithm was used to determine the
203 start of the disaccommodative response. It should be noted that the algorithm used in
204 this study only considers latencies greater or equal to zero. In order to explore the
205 latency algorithm further, the algorithm was modified in such a way that negative
206 latencies could be detected up to -560 ms in steps of 40 ms. The proportion of times
207 where we found latencies < 40 ms for both the most predictable (#1) and the most
208 unpredictable (#9) conditions were very similar (figure A1 in the Appendix), which
209 suggests that the latency algorithm affects both the most predictable and unpredictable
210 conditions in the same way. However, other authors have used a velocity-criterion
211 algorithm to compute latency, which may be more accurate and more indicated when
212 using procedures with higher sampling rates (e.g., 200 Hz).^{14,27} The *accommodative*
213 *response magnitude* at each accommodative transition was computed as the difference
214 in diopters between the median response of the last four samples and the median
215 response of the first four samples of the interval. Missing data points (e.g., due to
216 blinks) were not interpolated and only those accommodative transitions in which there
217 were at least 8 valid data points during the accommodative interval were included in
218 the analysis. A valid data point was considered when pupil diameter was properly
219 detected and a refraction measure was given by the PowerRef II.

220 The perceived predictability scores given by the participants for each condition were
221 analyzed using Friedman tests and with Wilcoxon tests with Bonferroni correction, to
222 determine which pairwise comparisons were significant. Statistical power was

223 determined using free open source G*Power 3.0.10.³³ Data from a pilot study with four
224 subjects was used to compute the required sample size for a statistical power of 0.8.
225 Considering a significance of 0.05 and an Analysis of Variance model with nine
226 repetitions, the required sample size was seven subjects.

227 **RESULTS**

228 Subjects had a mean age \pm standard deviation of 25 ± 2 years, a mean monocular
229 subjective amplitude of accommodation of 11 ± 2 D, and a mean subjective spherical
230 equivalent of -1.45 ± 1.89 D.

231 **Perceived predictability analysis**

232 The Friedman test conducted on the perceived predictability of each condition resulted
233 in statistically significant differences between the conditions ($\chi^2=56.57$, $p<0.01$).
234 However, Bonferroni post-hoc tests did not show statistically significant differences for
235 any pairwise comparison (all p-values were above 0.05/36, being 36 the number of
236 possible pairwise comparisons). Descriptive statistics of each condition are shown in
237 figure 3.

238 **Accommodative latency analysis**

239 Repeated measures ANOVA applied to latency for the nine conditions tested (figure
240 4A) did not show significant effects for either direction of accommodation
241 (accommodation or disaccommodation, $F=3.15$, $p=0.10$), condition ($F=0.94$, $p=0.49$),
242 nor the interaction direction x condition ($F=1.20$, $p=0.31$). The median latency for each
243 subject and condition is shown in Table A1 (Appendix).

244 The Spearman correlations (ρ , p-value) between the perceived predictability scores
245 and latency responses for the most predictable condition (#1) and the less predictable

246 condition (#9) are shown in figures 5A and 5B, respectively, with the corresponding
247 regression coefficients.

248 Analogously, the Spearman correlations between the latency responses obtained
249 versus time are also shown in figures 6A and 6B, respectively, for the most predictable
250 and less predictable conditions, and for both accommodation and disaccommodation.
251 In all regressions the slope is less than 0.01 and the regression coefficients go from
252 0.02 in the worst case to 0.16 in the best case. None of the correlations are statistically
253 significant ($p > 0.05$).

254 **Accommodative response magnitude analysis**

255 Repeated measures ANOVA applied to accommodative response magnitude for the
256 nine conditions tested (figure 4B) did not show significant effects for either direction of
257 accommodation ($F=0.37$, $p=0.56$), condition ($F=0.48$, $p=0.75$), nor the interaction
258 direction x condition ($F=1.39$, $p=0.25$). The median accommodative response for each
259 subject and condition is shown in Table A2 (Appendix).

260 Analogously to latency analysis, the Spearman correlations and regression coefficients
261 between the perceived predictability scores and accommodative response magnitudes
262 for the most predictable condition (#1) and the less predictable condition (#9) are
263 shown in figures 5C and 5D, respectively. The Spearman correlations between the
264 accommodative response magnitudes and time of the most predictable condition and
265 the less predictable condition are also shown in figures 6A and 6B, respectively.

266 Finally, to gain insight on whether the prediction operator in accommodation depends
267 on its starting point, we compared the latency and accommodative response magnitude
268 values obtained for two different starting points: transition in accommodative demand
269 between 0 and 2 D, and between 2 and 4 D. The results are shown in figure 7. Note

270 that data points of this figure were exclusively obtained from condition #2, i.e., a double
271 step wave modulated stimuli that is predictable in time, direction and magnitude.

272 **DISCUSSION**

273 Some authors⁵⁻⁷ suggested that observers might be able to anticipate subsequent
274 changes in accommodation demand. This idea was further tested by Krishnan,¹
275 Phillips,² and Van der Wildt.³ The conclusion from these studies is that, when using
276 repeatable stimuli (e.g., sinusoids), accommodative latency can be reduced and the
277 accommodative response accuracy can be enhanced. In this study, we investigated the
278 effects of accommodation predictability factors such as time, magnitude and direction
279 of the accommodative change, as well as the interactions between these factors, on
280 the accommodation response latency and magnitude.

281 Our results indicate no significant effect of stimuli predictability on either the
282 accommodation latency or its magnitude when using two different types of analysis. No
283 statistically significant differences were found when comparing the average latency and
284 accommodative response magnitude across all conditions (figure 4). In addition, the
285 individual data scatterplots shown in figure 6 did not reveal any systematic increase or
286 decrease for both variables over the 120 seconds that lasted each condition. Based on
287 previous studies, and considering that there exists a prediction effect in certain ocular
288 movements (i.e., saccades)³⁴ for repetitive stimuli, we initially expected that
289 accommodation latency would be larger for unpredictable stimuli. However, no
290 statistically significant effect was found for accommodative latency, at least no effect
291 larger than the 40 milliseconds detectable by the PowerRef II autorefractor. The limited
292 sampling rate of the device does not preclude the prediction operator to exist for values
293 below 40 milliseconds. In order to analyze how this limitation affected our results, the
294 proportion of times where we found latencies of 0 milliseconds for both the most
295 predictable (#1) and the most unpredictable (#9) conditions were computed. For

296 condition #1, there were 14% and 17% of the cases for accommodation and
297 disaccommodation, respectively. Analogously, for condition #9, 18% and 16% of the
298 cases were found, respectively, for accommodation and disaccommodation. These
299 results indicate that in both conditions equal or more than 82% of the cases latencies
300 were larger than the sampling resolution of the instrument, thus, there is an uncertainty
301 in 18% of the cases or less in which it is not exactly known if there was a prediction
302 effect (of less than 40 ms). As shown in figure A1 (Appendix), these results can be
303 affected by the way latency is obtained. Alternative algorithms to compute latency exist
304 in the literature^{14,27} although it is not clear yet what is the most appropriate one.

305 A number of factors may account for the differences between our data and previous
306 studies. Unsurprisingly, we found large inter-subjects standard deviations, which could,
307 to some extent, explain the lack of statistical significance found in all analyses.
308 However, the statistical power was above 0.8 for all response variables in this study
309 and it has been reported by Schaeffel *et al.*²¹ and Heron *et al.*³⁵ that the dynamics of
310 accommodative responses exhibit significant inter-subject variability. Another possibility
311 is that the prediction operator in accommodation depends on its starting point.
312 Bharadwaj and Schor^{14,36} comprehensively analyzed the dynamics of ocular
313 accommodation and disaccommodation and reported that the peak velocity and peak
314 acceleration of disaccommodation increased with the proximity of starting position.
315 However, for a given starting position, these authors found accommodation magnitude
316 responses to be invariant to the starting level. To gain insight on this question, figure 7
317 compares the latency and accommodative response magnitude values obtained for two
318 different starting points. This figure shows that disaccommodation is more affected by
319 the starting level than accommodation, which is consistent with the results obtained by
320 Bharadwaj and Schor,^{14,36} but overall, latency is not significantly affected by the starting
321 level, and there is not a significant systematic bias in the accommodative response.
322 These results indicate that changes in accommodation latency and response

323 magnitude with predictable stimuli do not depend on the starting level, at least for naïve
324 subjects.

325 Another consideration to differences with previous studies is that we used a step wave
326 modulated stimuli for all conditions, not sinusoidal as used in the studies described in
327 the introduction. This procedural difference should not have an effect because when
328 Heron *et al.*^{35,37} compared latency and accommodation response magnitude between
329 step and sinusoidally modulated stimuli, they concluded that the responses were
330 broadly comparable. Nevertheless, they did note that accommodation latencies at
331 frequencies up to 1 Hz were greater for step wave modulated stimuli than those found
332 by other investigators using sinusoidally modulated stimuli, whereas other authors
333 suggested that a sinusoidally moving target may not have much effect on the
334 anticipation of accommodative response when blur is the only stimulus.³⁸

335 More important than the type of modulation stimuli are subjected to, may be the task
336 instructed to the observers and whether they are naïve or not. After a thorough review
337 of previous studies that found an effect of stimulus predictability on accommodation,¹⁻³
338 it came to light that their results were obtained using limited sample sizes (4 subjects²
339 or 1 subject^{1,3}), they did not report whether participants were naïve or not, and did not
340 describe the specific task observers were instructed to perform. It is therefore difficult to
341 compare our results with these studies since accommodation dynamics are affected by
342 age,^{8,9} refractive error^{10,11} and instructions.¹² We speculate that we did not find an effect
343 of predictability in our study because: 1) every observer was instructed to “clear the
344 target” naturally, and 2) none of the participants were trained to perform voluntary
345 accommodation and all of them were naïve to the purpose of the study. In our study,
346 we did not control for the subjects’ ability to perform voluntary accommodation. Kruger
347 and Pola³⁹ suggested that voluntary control in the form of prediction and anticipation of
348 accommodation may be a natural mode of the accommodative system. On the other
349 hand, negative accommodation latencies found under predictable stimulus conditions

350 in previous studies could be attributed to voluntary accommodation.⁴⁰ Our hypothesis is
351 that anticipation affects accommodation only in experienced subjects that are
352 instructed to purposely use voluntary accommodation in addition to reflex
353 accommodation. This hypothesis is consistent with reports by Heron, Charman and
354 Schor³⁵ who suggested that accommodative latencies obtained with predictable stimuli
355 may tell us more about the training and alertness of the subjects than about the
356 temporal abilities of the accommodation system.

357 Additionally, the lack of appropriate accommodation cues can significantly alter the
358 overall accommodative response when stimulated optically.²⁴ This may become
359 relevant in the clinical monocular accommodation facility flipper test, where there are
360 no disparity cues and blur cues do not match vergence, i.e., blur changes while the
361 size-distance cue does not.⁴¹ The neural cross-linkages between vergence and
362 accommodation, that are subject to adaptive regulation,⁴² may have played a role in the
363 results of our study, as disparity is an important cue for distance.⁴³ However, it has
364 been shown that voluntary efforts appear to primarily affect accommodation rather than
365 vergence in the near response.⁴⁴ According to our results, the monocular
366 accommodation facility clinical test would not be influenced by the predictability of the
367 stimulus. Further studies should specifically address this question, unpredictable stimuli
368 may give a better indication of dynamic accommodation performance under real-life
369 conditions,³⁵ and increased accommodation facility with flippers may be more related to
370 learning to accommodate in an unusual visual situation.⁴¹

371 Another interesting finding of our study is that subjects seemed to perceptually notice
372 whether the stimulus was predictable or not, even though accommodation responses
373 and latency were not statistically significantly related with predictability. Despite that the
374 differences between the perceived scores of predictable and unpredictable conditions
375 were not statistically significant after the Bonferroni correction for multiple tests, non-
376 significance is probably obtained provided that the Bonferroni procedure ignores

377 dependencies among the data and is therefore much too conservative when the
378 number of tests is large,⁴⁵ as it occurs in our study with 36 pairwise comparisons. It
379 could be possible that the perceptual scores of predictability may not be necessarily
380 indicative of the degree of predictability of the stimuli, hence, the lack of significant
381 differences found in this study may also be caused by the unpredictable stimuli not
382 being sufficiently unpredictable. Even though the most unpredictable condition in this
383 study (#9) comprised up to 54 different changes of accommodative demand that were
384 randomly presented during 120 seconds in each subject, future studies could include
385 unpredictable conditions with more random accommodative states.

386 **CONCLUSIONS**

387 The effect of predictability in changes of time, magnitude and direction of the
388 accommodation demand on the accommodation response latency and its magnitude is
389 not significant. Our results did not find evidence for a strong prediction operator in a
390 repetitive accommodative task where voluntary accommodation was not controlled, this
391 suggests that the clinical accommodative facility test may not be influenced by potential
392 anticipation effects.

393 **CONFLICTS OF INTEREST**

394 The authors report no conflicts of interest and have no proprietary interest in any of the
395 materials mentioned in this article.

396 **FUNDING SUPPORT**

397 This research was supported by the Spanish Ministry of Economy and Competitiveness
398 under the grant DPI2014-56850-R, the European Union and by Davalor Salud, S.L.
399 None of the institutions had a role in the realization of this manuscript. Carles Otero
400 thanks the Generalitat de Catalunya for his awarded PhD studentship.

401 **APPENDIX**

402 **Figure A1.** Comparison between the most predictable (#1) and unpredictable
403 conditions (#9) for different inferior limits of the latency algorithm. The Y-axis is the
404 number of cases where latency is <40 ms. The X-axis is the inferior limit set in latency
405 algorithm, i.e., we have allowed the algorithm to compute latencies from 0 (0 ms), 1 (-
406 40 ms), 2 (-80 ms), ..., 14 samples (-560 ms) before the starting position of each
407 accommodative transition.

408 **Table A1.** Median latency obtained for each subject and experimental condition in
409 accommodation (0 to 2 D) and disaccommodation (2 to 0 D). Acc.: Accommodation.
410 Dis.: Disaccommodation.

411 **Table A2.** Median accommodative response obtained for each subject and
412 experimental condition in accommodation and disaccommodation. Acc.:
413 Accommodation. Dis.: Disaccommodation.

414 **REFERENCES**

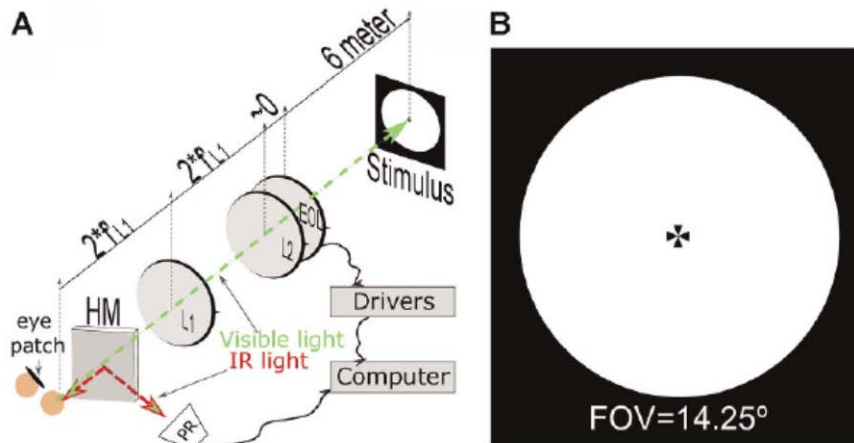
- 415 1. Krishnan V, Phillips S, Stark L. Frequency Analysis of Accommodation,
416 Accommodative Vergence and Disparity Vergence. *Vision Res* 1973;13:1545-
417 54.
- 418 2. Phillips S, Shirachi D, Stark L. Analysis of Accommodative Response Times
419 Using Histogram Information. *Am J Optom Arch Am Acad Optom* 1972;49:389-
420 401.
- 421 3. Van Der Wildt G, Bouman M, Van De Kraats J. The Effect of Anticipation on the
422 Transfer Function of the Human Lens System. *Opt Acta (Lond)* 1974;21:843-60.
- 423 4. Khosroyani M, Hung GK. A Dual-Mode Dynamic Model of the Human
424 Accommodation System. *Bull Math Biol* 2002;64:285-99.

- 425 5. Stark L, Takahashi Y. Absence of an Odd-Error Signal Mechanism in Human
426 Accommodation. *IEEE Trans Biomed Eng* 1965;BME-12(3&4):138-46.
- 427 6. Carter JH. A Servoanalysis of the Human Accommodative Mechanism. *Arch Soc*
428 *Am Ophth Opt* 1962;4.3-4:137-68.
- 429 7. Sun F, Brandt S, Nguyen A, et al. Frequency Analysis of Accommodation: Single
430 Sinusoids. *Ophthalmic Physiol Opt* 1989;9:392-7.
- 431 8. Mordi JA, Ciuffreda KJ. Dynamic Aspects of Accommodation: Age and
432 Presbyopia. *Vision Res* 2004;44:591-601.
- 433 9. Kasthurirangan S, Glasser A. Age Related Changes in Accommodative
434 Dynamics in Humans. *Vision Res* 2006;46:1507-19.
- 435 10. Radhakrishnan H, Allen PM, Charman WN. Dynamics of Accommodative Facility
436 in Myopes. *Invest Ophthalmol Vis Sci* 2007;48:4375-82.
- 437 11. Otero C, Aldaba M, Vera-Diaz F, et al. Effect of Experimental Conditions in the
438 Accommodation Response in Myopia. *Optom Vis Sci* 2017;94:1120-8.
- 439 12. Stark LR, Atchison DA. Subject Instructions and Methods of Target Presentation
440 in Accommodation Research. *Invest Ophthalmol Vis Sci* 1994;35:528-37.
- 441 13. Heron G, Charman WN. Accommodation as a Function of Age and the Linearity
442 of the Response Dynamics. *Vision Res* 2004;44:3119-30.
- 443 14. Bharadwaj SR, Schor CM. Dynamic Control of Ocular Disaccommodation: First
444 and Second-Order Dynamics. *Vision Res* 2006;46:1019-37.
- 445 15. Heron G, Charman WN, Gray LS. Accommodation Responses and Ageing.
446 *Invest Ophthalmol Vis Sci* 1999;40:2872-83.

- 447 16. Ciuffreda KJ, Kruger PB. Dynamics of Human Voluntary Accommodation. Am J
448 Optom Physiol Opt 1988;65:365-70.
- 449 17. Hung GK. Models of Oculomotor Control. 1st ed. Singapore: World Scientific
450 Publishing Co. Pte. Ltd.; 2001.
- 451 18. Otero C, Aldaba M, López S, et al. Random Changes of Accommodation
452 Stimuli : An Automated Extension of the Flippers Accommodative Facility Test.
453 Curr Eye Res 2018;43:788-95.
- 454 19. Thiagarajan P, Ciuffreda KJ. Visual Fatigue and Accommodative Dynamics in
455 Asymptomatic Individuals. Optom Vis Sci 2013;90:57-65.
- 456 20. Scheiman M, Wick B. Clinical Management of Binocular Vision. 4th ed.
457 Lippincott Williams & Wilkins; 2014.
- 458 21. Schaeffel F, Wilhelm H, Zrenner E. Inter-Individual Variability in the Dynamics of
459 Natural Accommodation in Humans: Relation to Age and Refractive errors. J
460 Physiol 1993;32:301-20.
- 461 22. Aldaba M, Gómez-López S, Vilaseca M, et al. Comparing Autorefractors for
462 Measurement of Accommodation. Optom Vis Sci 2015;92:1003-11.
- 463 23. Sanàbria F, Díaz-Doutón F, Aldaba M, Pujol J. Spherical Refractive Correction
464 with an Electro-Optical Liquid Lens in a Double-Pass System. J Eur Opt Soc
465 2013;8:7-10.
- 466 24. Otero C, Aldaba M, Martínez-Navarro B, Pujol J. Effect of Apparent Depth Cues
467 on Accommodation in a Badal Optometer. Clin Exp Optom 2017;100:649-55.
- 468 25. Aldaba M, Otero C, Pujol J, Atchison D. Does the Badal Optometer Stimulate
469 Accommodation Accurately? Ophthalmic Physiol Opt 2017;37:88-95.

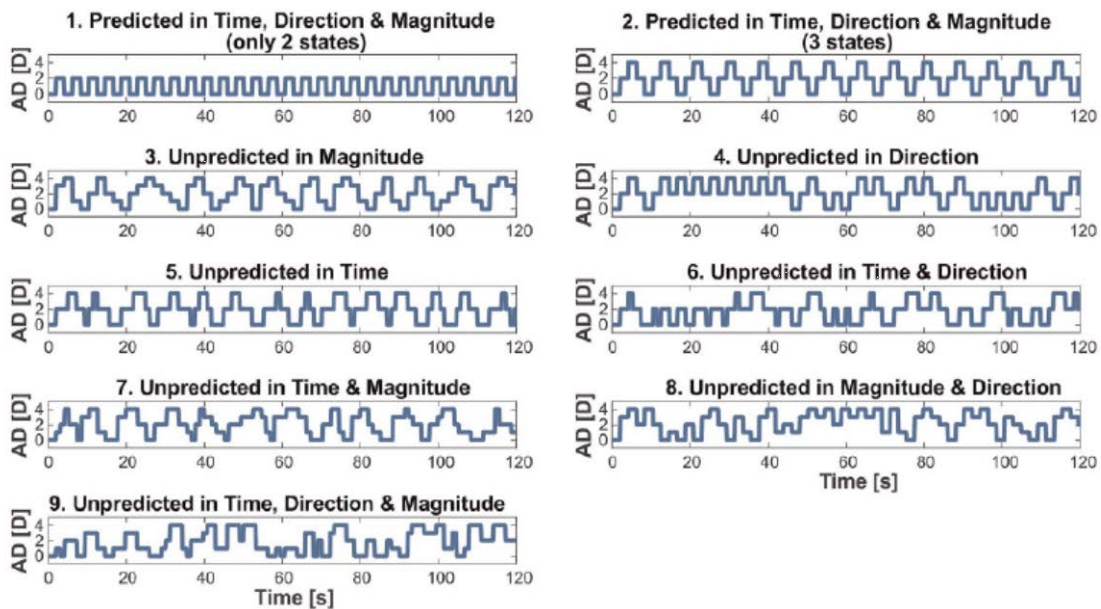
- 470 26. Charman WN, Tucker J. Dependence of the Accommodation Response on the
471 Spatial Frequency Spectrum of the Observed Object. *Vision Res* 1977;17:129-
472 39.
- 473 27. Bharadwaj SR, Schor CM. Acceleration Characteristics of Human Ocular
474 Accommodation. *Vision Res* 2005;45:17-28.
- 475 28. Bernal-Molina P, Marín-Franch I, Del Águila-Carrasco AJ, et al. Human Eyes Do
476 Not Need Monochromatic Aberrations for Dynamic Accommodation. *Ophthalmic*
477 *Physiol Opt* 2017;37:602-9.
- 478 29. Lopes-Ferreira D, Neves H, Queiros A, et al. Ocular Dominance and Visual
479 Function Testing. *Biomed Res Int* 2013;2013:7.
- 480 30. Momeni-moghaddam H, Kundart J, Askarizadeh F. Comparing Measurement
481 Techniques of Accommodative Amplitudes. *Indian J Ophthalmol* 2014;62:683-7.
- 482 31. Tondel GM, Candy TR. Human Infants' Accommodation Responses to Dynamic
483 Stimuli. *Invest Ophthalmol Vis Sci* 2007;48:949-56.
- 484 32. Kasthurirangan S, Vilupuru AS, Glasser A. Amplitude Dependent
485 Accommodative Dynamics in Humans. *Vision Res* 2003;43:2945-56.
- 486 33. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a Flexible Statistical
487 Power Analysis Program for the Social, Behavioral, and Biomedical Sciences.
488 *Behav Res Methods* 2007;39:175-91.
- 489 34. McLaughlin S. Parametric Adjustment in Saccadic Eye Movements'. *Percept*
490 *Psychophys* 1967;2:359-62.
- 491 35. Heron G, Charman WN, Schor C. Dynamics of the Accommodation Response to
492 Abrupt Changes in Target Vergence as a Function of Age. *Vision Res*

- 493 2001;41:507-19.
- 494 36. Bharadwaj SR, Schor CM. Initial Destination of the Disaccommodation Step
495 Response. *Vision Res* 2006;46:1959-72.
- 496 37. Charman WN, Heron G. On the Linearity of Accommodation Dynamics. *Vision*
497 *Res* 2000;40:2057-66.
- 498 38. Mathews S, Kruger P. Spatiotemporal Transfer Function of Human
499 Accommodation. *Vision Res* 1994;34:1965-80.
- 500 39. Kruger P, Pola J. Dioptric and Non-Dioptric Stimuli for Accommodation: Target
501 Size Alone and with Blur and Chromatic Aberration. *Vision Res* 1987;27:555-67.
- 502 40. Randle R, Murphy M. The Dynamic Response of Visual Accommodation Over a
503 Seven-Day Period. *Am J Optom Physiol Opt* 1974;51:530-44.
- 504 41. Maxwell J, Tong J, Schor CM. Short-Term Adaptation of Accommodation,
505 Accommodative Vergence and Disparity Vergence Facility. *Vision Res*
506 2012;62:93-101.
- 507 42. Miles F, Judge S, Optican L. Optically Induced Changes in the Couplings
508 Between Vergence and Accommodation. *J Neurosci* 1987;7:2576-89.
- 509 43. Gwiazda J, Thorn F, Held R. Accommodation, Accommodative Convergence,
510 and Response AC/A Ratios Before and at the Onset of Myopia in Children.
511 *Optom Vis Sci* 2005;82:273-8.
- 512 44. McLin LN, Schor CM. Voluntary Effort as a Stimulus to Accommodation and
513 Vergence. *Invest Ophthalmol Vis Sci* 1988;29:1739-46.
- 514 45. Bland J, Altman D. Multiple Significance Tests: the Bonferroni Method. *Br Med J*
515 1995;310:170.



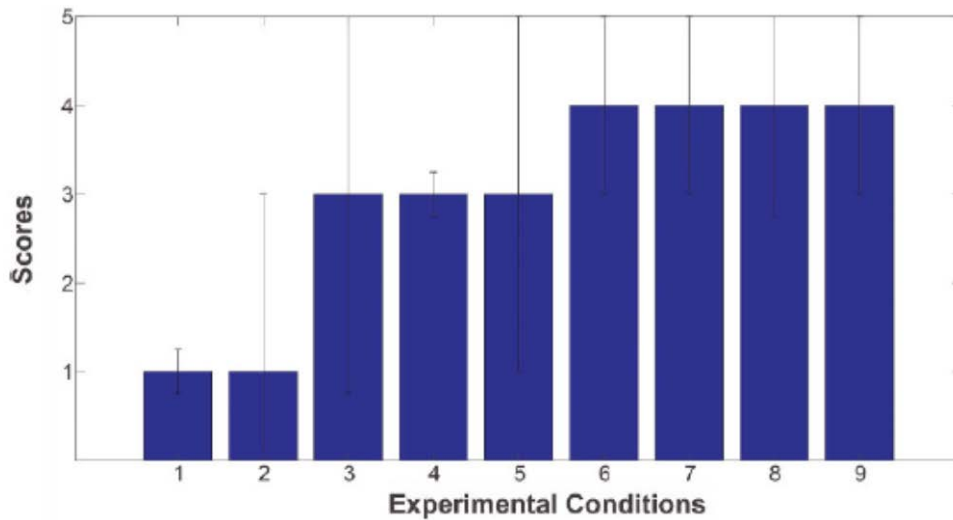
517

518 **Figure 1.** A: schematic view of the setup. B: accommodative stimulus used in the
 519 experiment. HM: Hot mirror. EOL: Electro-optical lens. PR: PowerRef II. f' : focal length.
 520 L1: first lens with a diameter of 50 mm and focal length of 100 mm. L2: second lens
 521 with a diameter of 25 mm and power of +3 D.



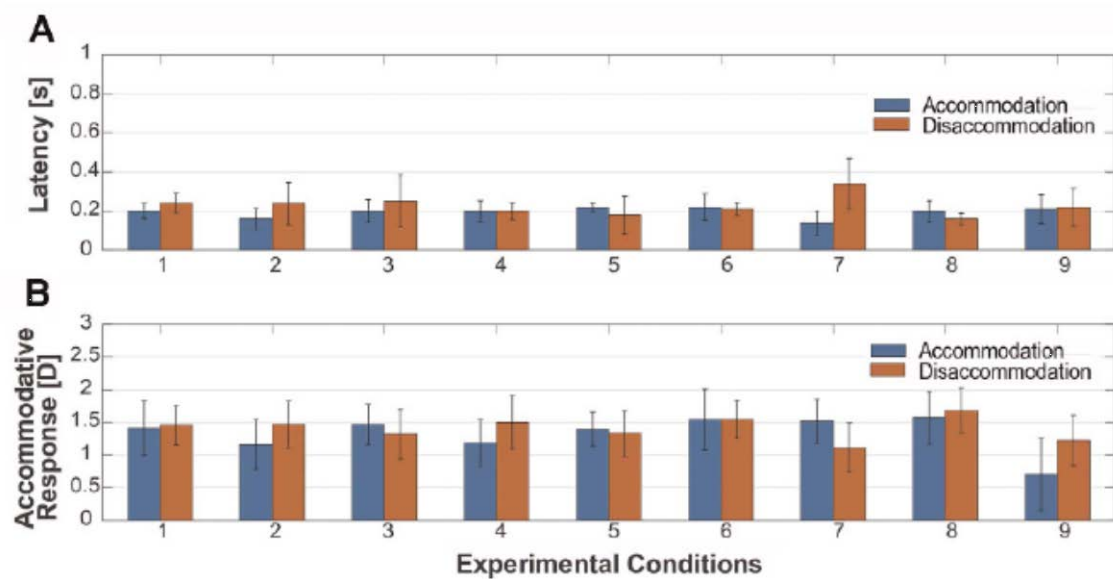
522

523 **Figure 2.** Examples of each accommodation step changes (nine conditions) tested in
 524 the experiment. AD: Accommodative Demand. A: the simplest and most predictable
 525 condition (baseline). I: the most unpredictable condition (totally unpredictable in time,
 526 direction and magnitude).



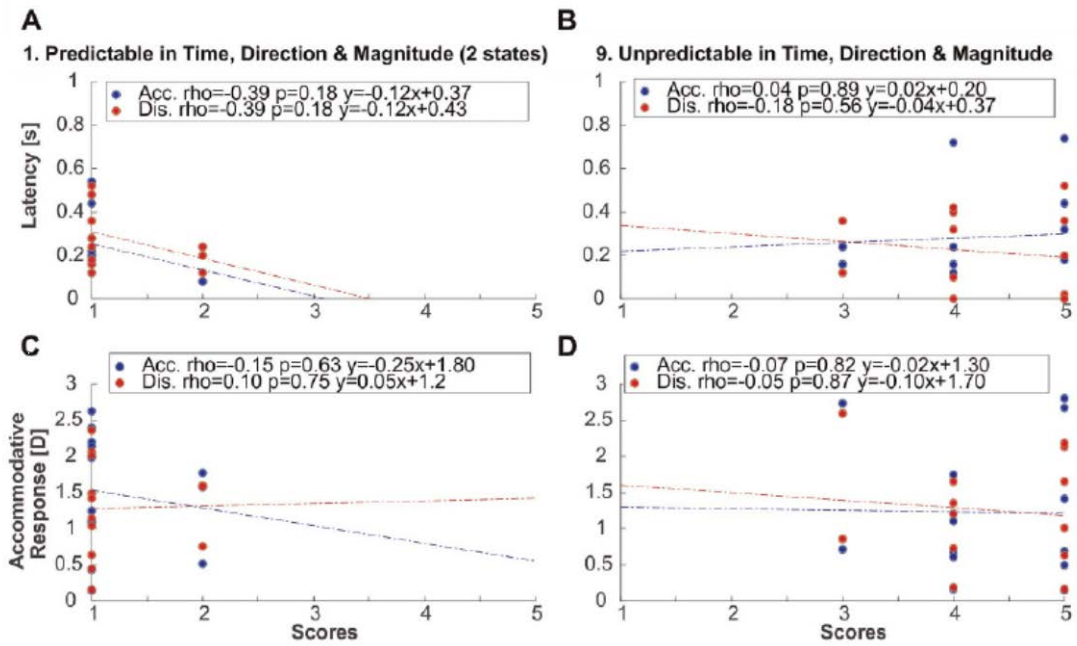
527

528 **Figure 3.** The median and interquartile range of the perceptual predictability scores
 529 given to each condition.



530

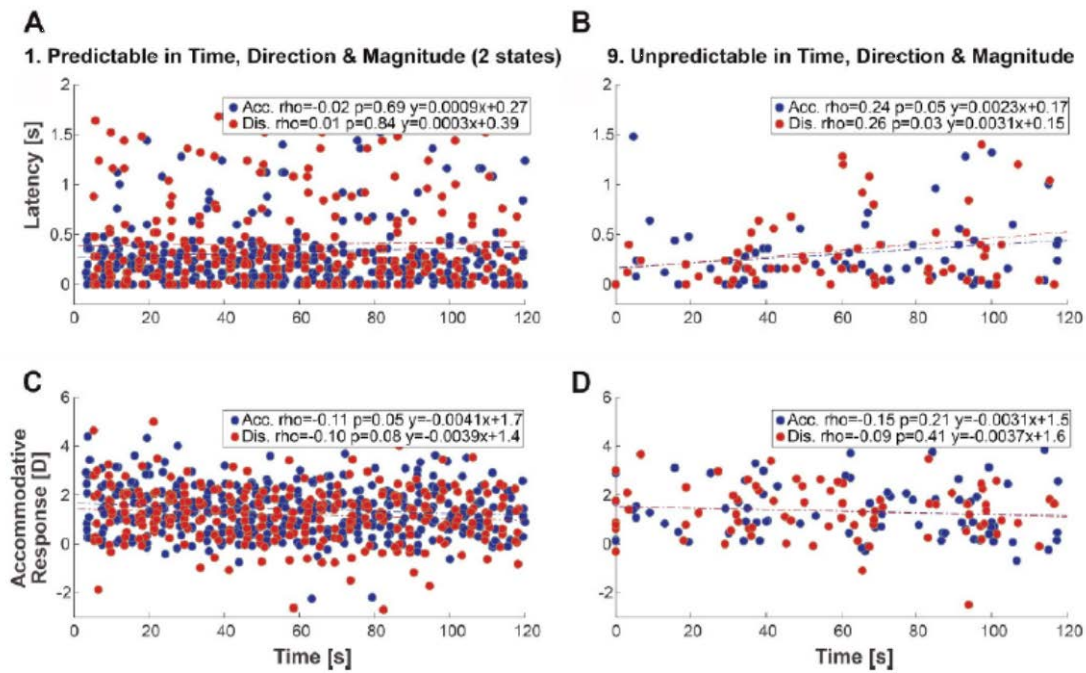
531 **Figure 4.** The median and interquartile range obtained for each testing condition and
 532 direction of accommodation for both variables: latency and accommodative response
 533 magnitude. Data obtained from the transitions between 0 and 2 D of accommodative
 534 demand only.



535

536 **Figure 5.** Scatter plots between latency or accommodative response magnitude and
 537 subjective predictability scores for conditions 1 (i.e., predictable in time, direction and
 538 magnitude) and 9 (i.e., unpredictable in time, direction and magnitude), and
 539 accommodation (Acc., blue circles) and disaccommodation (Dis., red circles). The
 540 Spearman correlation coefficient, the P -value for each correlation as well as the
 541 regression coefficients are shown in each plot's legend.

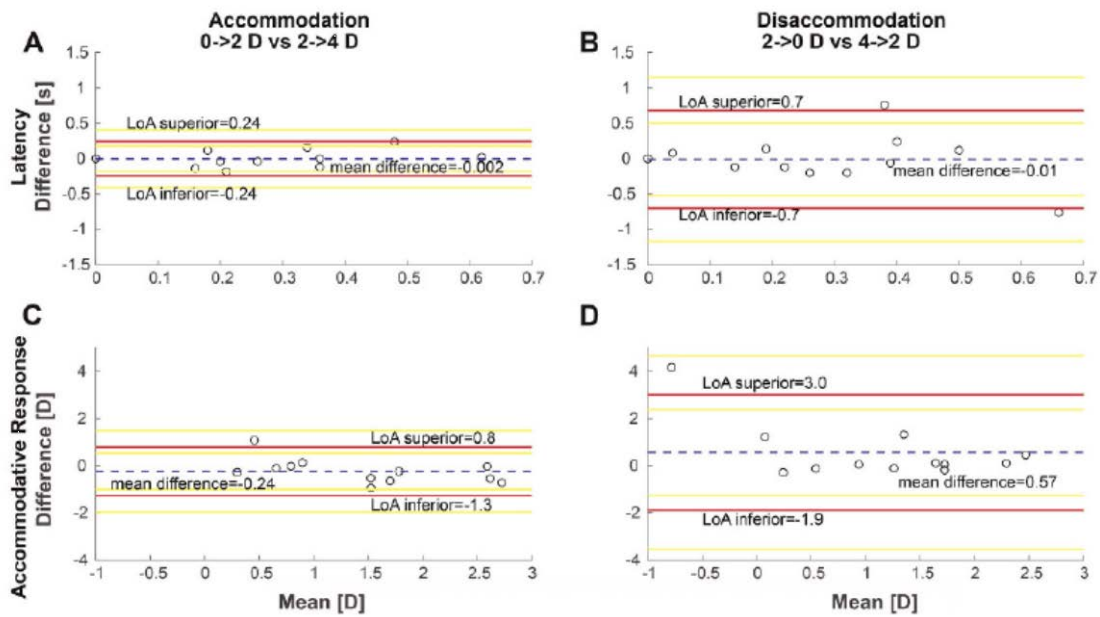
542



543

544 **Figure 6.** Scatter plots between latency or accommodative response magnitude and
 545 time for conditions 1 (i.e., predictable in time, direction and magnitude) and 9 (i.e.,
 546 unpredictable in time, direction and magnitude), and accommodation (Acc., blue
 547 circles) and disaccommodation (Dis., red circles). The Spearman correlation
 548 coefficient, the *P*-value for each correlation as well as the regression coefficients are
 549 shown in each plot's legend.

550



551

552 **Figure 7.** Bland and Altman plots comparing the latency and accommodative response
 553 magnitude values obtained for 2 different starting points of accommodative demand:
 554 the transition in accommodative demand between 0 and 2 D, and the transition
 555 between 2 and 4 D. Blue line: mean difference (value of the transition 0/2 D minus
 556 value of the transition 2/4 D). Red lines: 95% Limits of Agreement. Yellow lines: 95%
 557 Confidence Interval for both limits of agreement. Latencies and accommodative
 558 responses of both transitions are obtained from condition 2 (i.e., predictable in time,
 559 direction and magnitude with 3 accommodative states).