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Intraocular cataract lens replacement and light exposure potentially impact procedural learning in older adults

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Abstract

Procedural learning declines with age and appropriately timed light exposure can improve cognitive performance in older individuals. Because cataract reduces light transmission and is associated with cognitive decline in older adults, we explored whether lens replacement (intraocular blue-blocking [BB] or UV-only blocking) in older patients with cataracts enhances the beneficial effects of light on procedural learning. Healthy older participants ($n = 16$) and older patients with post-cataract surgery ($n = 13$ with BB or UV lens replacement) underwent a randomized within-subject crossover laboratory design with three protocols. In each protocol, 3.5 hr dim-dark adaptation was followed by 2 hr evening blue-enriched (6,500K) or non-blue-enriched light exposure (3,000K or 2,500K), 30 min dim post-light, ~8 hr sleep and 2 hr morning dim light. Procedural learning was assessed by the alternating serial reaction time task (ASRT), as part of a larger test battery. Here, ASRT performance was indexed by type of trial (random or sequence) and sequence-specific (high or low probability) measures. During evening light exposure, we observed a significant effect of the interaction of "group" versus "light condition" on the type of trial ($p = .04$; $p = .16$; unadjusted and adjusted p -values, respectively) and sequence-specific learning ($p = .04$; $p = .16$; unadjusted and adjusted p -values, respectively), whereby patients with UV lens replacement performed better than patients with BB lens or non-cataract controls, during blue-enriched light exposure. Lens replacement in patients with cataracts may potentially be associated with beneficial effects of blue light on procedural learning. Thus, optimizing spectral lens transmission in patients with cataracts may help improve specific aspects of cognitive function, such as procedural learning.

KEYWORDS

ageing, cataract, cognitive function, light, sequence learning

1 | INTRODUCTION

A key aspect of optimal cognitive function in sighted people is visual acuity, with a strong association between the rate of cognitive decline and decreased visual acuity, particularly in older patients with cataract (Clemons, Rankin, & McBee, 2006; Jefferis, Mosimann, & Clarke, 2011). Cataract is currently worldwide the major cause of blindness in individuals above 60 years (Bourne et al., 2017), and is associated with an attenuation in light transmitted to the retina, particularly in the short blue-light wavelength range (Xu, Pokorny, & Smith, 1997). In older adults, exposure to light, particularly blue-enriched light, can have acute beneficial effects on alertness (Gabel et al., 2017) and cognitive function, as indexed by the digit-symbol substitution test to assess working memory (Scheuermaier, Munch, Ronda, & Duffy, 2018) and the Mini-Mental State test (Riemersma-van der Lek et al., 2008). Although evidence for the beneficial effects of light exposure on cognitive function in ageing is limited, it may provide a potential behavioural intervention for age-related cognitive impairment. Although cataract has been associated with cognitive decline (Clemons et al., 2006) and cataract surgery may improve global cognitive function (i.e., Mattis Organic Mental Syndrome Screening scores) (Hall, McGwin, & Owsley, 2005) and episodic memory scores (Maharani, Dawes, Nazroo, Tampubolon, & Pendleton, 2018), it remains to be fully established whether surgical intraocular lens (IOL) replacement in this clinical population may improve cognitive function. The two most commonly implanted IOLs are ultraviolet (UV-only blocking) and blue-blocking (BB) only, as a means to prevent macular degeneration (Bronsted et al., 2015). We recently showed that IOLs may impact cognitive performance, as indexed by the improved psychomotor vigilance task performance (to assess sustained attention) in patients with UV-only lens replacement (Chellappa et al., 2019).

One aspect of cognitive function that can be adversely impacted by aging is procedural learning, which is a type of learning that occurs without an individual's intention and is often implicit (i.e., outside of awareness) (Zwart, Vissers, Kessels, & Maes, 2017). Implicit learning is essential to healthy functioning with the advancement of age in a plethora of everyday behaviours that require appropriate sequences, including typing, arithmetic operations, social interactions, reading and motor skills, and so forth (Janacsek et al., 2019). Procedural learning shows age-related decline (Nemeth & Janacsek, 2011; Nemeth et al., 2011, 2013; Zwart et al., 2017), which may reflect (a) cognitive slowing in older adults from having multiple representations simultaneously activated, (b) associative binding deficits between multiple stimuli or stimulus features and binding these associations into long-term memory traces; and (c) increased sensitivity to interference (Nemeth & Janacsek, 2011). Despite the well-established effects of ageing on procedural learning and its relevance to daily functioning, potential behavioural interventions to help improve procedural learning in older patients with cataract are yet to be established. Thus, we explored whether lens replacement (intraocular BB or UV) in older patients with cataracts enhances the acute beneficial light effects on cognitive function, as indexed

by procedural learning performance. Our assumptions are: (a) patients with UV, as compared to patients with BB lens replacement and non-cataract controls, show better procedural learning performance; and (b) the effects of the improved procedural learning performance in patients with UV lens replacement occur when they are acutely exposed to blue-enriched light. Because UV-only blocking IOLs do not reduce the amount of light transmittance in the short wavelength of light, exposure to blue-enriched light is expected to result in maximal beneficial effects on procedural learning.

2 | METHODS

2.1 | Participants

The protocol, advertisements, screening questionnaires and consent form were approved by the local Ethical Committee (EKBB/Ethikkommission beider Basel, Switzerland) and in agreement with the Declaration of Helsinki (as described in Chellappa et al., 2019). All participants provided written informed consent. We screened ~1,200 patients with previous cataract to recruit a total of 60 patients who underwent bilateral cataract surgery. Of these 60 patients, 44 were excluded for one of the following reasons: (a) inability to follow a regular sleep-wake schedule; (b) inadequate sleep quality, as indicated by a Pittsburgh sleep quality index score >5; and (c) extreme morning/evening chronotype ratings. Three participants with cataract either did not complete all laboratory protocols or dropped out of the study immediately prior to the laboratory protocols. The control group was enrolled using similar inclusion/exclusion criteria (except for the specific cataract-related participant criteria), and 16 out of 60 participants were enrolled for this study (for detailed inclusion/exclusion criteria, see Chellappa et al., 2019). Sixteen healthy older control participants (63.6 ± 5.6 years; 8 women) and 13 older patients with post-bilateral cataract surgery (69.9 ± 5.2 years; 10 women) with either BB lens ($n = 8$; 69.8 ± 6.2 years; seven women) or UV lens replacement ($n = 5$; 70.8 ± 4 years; four women) underwent a stringently controlled randomized within-subject crossover design with three in-laboratory protocols, separated by 1 week.

All older patients with cataract had bilateral IOLs replacement using standard techniques through limbal or clear corneal incision for implanting UV-only IOLs (SA60 WF IOL; Alcon) or BB IOLs (SN60 WF IOL; Alcon). Second-eye IOL implantation was performed using the same implant as in the first eye within 4–6 weeks of the first cataract surgery (Chellappa et al., 2019; Steinemann et al., 2019; the latter publication demonstrated that IOLs may impact subjective visual perception of light and subjective mental effort in the same patients as reported here, and did not include any cognitive tasks). The UV lens blocked light transmission from 300–360 nm but not from other light wavelengths. The BB lens blocked ~100% of 300–400 nm and ~50% of light transmission between 410 and 480 nm (Chellappa et al., 2019; Steinemann et al., 2019). Patients with cataract had their bilateral sequential cataract surgery within 4–8 weeks before the laboratory study, and underwent an eye examination including

visual acuity measurement, intraocular pressure measurement with non-contact air-puff tonometer or Goldmann applanation tonometer, and split lamp examination of the anterior and posterior segment of the eyeball. The fundus was examined under dilated pupils.

2.2 | Study design

The study consisted of a within-subject cross-sectional observational design with three laboratory protocols, separated by 1-week (Figure 1). Because evening light exposure has been shown to beneficially impact cognitive performance (Cajochen et al., 2011; Chellappa et al., 2011), the study design was planned to occur during the evening hours, and commenced ~10 hr after the individually scheduled wake-time of each participant. The first part of each laboratory protocol comprised 3.5 hr of prior light control (1.5 hr dim-light < 8 lux, and subsequently 2.5 hr dark adaptation at 0 lux). The extended controlled prior light history exposure (practice in dim light; baseline in dark) allowed adequate assessment of the effects of the subsequent 2 hr of evening light exposure, as light effects are heavily dependent on light properties, which include duration, timing, spectral composition and dynamics (Cajochen, Chellappa, & Schmidt, 2010), as well as prior light history (Chang, Scheer, Czeisler, & Aeschbach, 2013; Chellappa et al., 2014). Subsequently, each participant underwent a 2-hr test session with light exposure (illuminance at horizontal gaze was between 38 and 40 lux), during which they were exposed to light from either a compact fluorescent light (CFL) source with 6,500K or non-blue-enriched light exposure (CFL at 2,500K or incandescent light source at 3,000K). The use of two different non-blue-enriched light sources (2,500K and 3,000K) was due to the naturalistic design of this study: light at 2,500K (albeit not a widely used light source) contains a lower irradiance at the

short wavelength in comparison with light at 6,500K, whereas light at 3,000K is a broadband polychromatic incandescent white light source, which was often used in Switzerland (before the introduction of its ban). After light exposure, participants had 30 min in post-light exposure (under dim light, <8 lux), 8 hr of sleep opportunity and a 2-hr test session, which corresponds to morning dim light exposure (<8 lux) after sleep (see Chellappa et al., 2013, for details on intensity and spectral composition). During the entire protocol (practice in dim light; baseline in dark and light exposure), participants were monitored by trained study staff and performed salivary melatonin assessments every 30 min, a waking electroencephalogram (EEG) measure every hour, and analogue scales to assess subjective sleepiness, mood, motivation, visual comfort and mental effort once per study segment (Chellappa et al., 2019; Steinemann et al., 2019).

2.3 | Cognitive performance

Cognitive test sessions were conducted twice before light exposure, once during light exposure and once in the morning after sleep. To investigate procedural (sequence) learning performance, all participants performed the alternating serial reaction time (ASRT) task (Nemeth & Janacek, 2011), which lasted approximately 20 min per cognitive session (Figure 1). In the ASRT task, the participants responded as fast as possible to a series of stimuli, which were presented alternatively at a random (random trials) or a predictable (sequence trials) location on the display. Predictability was induced by recurring patterns of four display locations for sequence trials (Figure 1). Because this pattern is better hidden than that in other implicit learning paradigms, such as the finger-tapping task, it heavily depends on implicit learning (Song, Howard, & Howard, 2007). Each ASRT task consisted of 15 blocks, comprising 85 trials each,

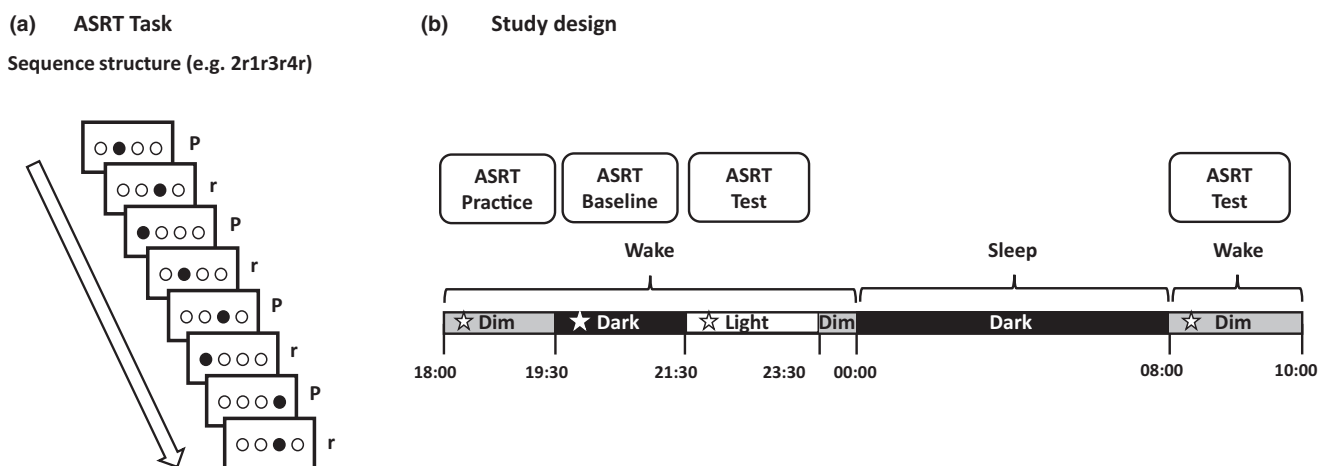


FIGURE 1 Alternating serial reaction time (ASRT) task and study design. (a) In the ASRT task, a stimulus appears in one of four empty circles on a computer screen. Participants are asked to react as fast and accurately as possible to the stimulus by pressing one of four corresponding keys. Stimulus presentation has an eight-element pattern, with alternating predetermined (*P*, sequence) and random (*r*) trials; Arrow represents time. (b) Randomized within-subject observational study, whereby each participant underwent this study design on three separate visits (interspaced by 1 week). Light exposure was at 6,500K, 2,500K or 3,000K per study visit (see text for details on study design). White stars correspond to the timing of the ASRT task (~19:00 hr for the practice session, ~20 hr for the baseline session, ~22:00 hr for the test session during light exposure, and ~09:00 hr for the test session during the morning after sleep)

of which the first five trials were random for practice purposes. Per ASRT, one sequence was presented 150 times. The used sequences were pseudo-randomized and were not repeatedly presented within a participant. In our analyses, we focused on RTs during correct trials only and classified runs of three successive stimuli (triplets) as either high probability (sequence-random-sequence triplets) or low probability (random-sequence-random triplets) (Howard & Howard, 2013). Here, we indexed the procedural learning performance as the difference in reaction times between types of trials (difference between sequence and random trials) and triplets (difference between low and high probability triplets, i.e., sequence-specific learning) (Howard & Howard, 2013; Nemeth & Janacek, 2011).

To index the effects of IOLs on cognitive function in patients with cataract, our laboratory protocols included, apart from the ASRT task, three other cognitive performance tasks: the psychomotor vigilance task (PVT) and two *n*-back tasks (0-back and 2-back). Within the cognitive test battery, the ASRT task was presented first, followed by the PVT, 0-back and 2-back tasks. This order was kept the same for all laboratory protocols and for all participants. These tasks allowed assessment of, respectively, procedural learning (the topic of our current work), as well as sustained attention and working memory, which were addressed in a separate publication (for details on the PVT and *n*-back tasks, see Chellappa et al., 2019).

2.4 | Statistical analyses

Statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, NC, USA). Procedural learning performance was assessed with mixed-model analyses of variance (PROC MIXED) using factors “group” (control, BB lens and UV lens), “light condition” (2,500K, 3,000K and 6,500K) and their interaction, separately for each time of testing. All *p*-values were based on Kenward–Rogers

corrected degrees of freedom (significance level: $p < .05$ prior to adjustments for multiple comparisons). For the statistical comparisons of age, sex, BMI and night time sleep measures across groups, see Chellappa et al. (2019). We also performed our mixed-model analyses with age, sex and BMI as covariates of interest, and none of these significantly affected our procedural learning outcomes. The Least Square means statement was used for post hoc tests and the Tukey–Kramer test was used for post hoc corrections. Lastly, as the present analyses represent follow-up analyses of a published dataset (Chellappa et al., 2019), we controlled for overall type I error in null hypothesis testing by adjusting *p*-values from the mixed-model analysis for the procedural learning outcomes (type of trial and sequence-specific learning) using false discovery rates (FDR) (PROC MULTTEST) across the cognitive tasks used in the laboratory protocols, with a corrected *p*-value threshold $p = .0125$. We also tested for potential order effects, and no significant effects were observed for the cognitive tasks used in the test battery.

3 | RESULTS

Given our main assumption that IOLs differentially impact procedural learning, data are presented for each group separately (controls, UV and BB lens groups; thus, a 3×3 design). As a first step, we assessed whether the groups differed with respect to their baseline performance (assessed during dim-light and dark adaptation), and no significant differences were observed among the three groups for the type of trial nor for the sequence-specific learning performance (Table 1). During the acute evening light exposure, we observed a significant “group” effect and an interaction of “group” versus “light condition” on the type of trial (respectively, $p < .001$ and $p = .04$; Table 1). Accordingly, patients with UV lens replacement performed better, particularly during the sequence trials, as compared to the

	Mixed-model analyses (fixed effects and interaction)		
	“Group”	“Light condition”	“Group” versus “light condition”
Baseline (dim–dark adaptation)			
Type of trial performance	$F_{2,25} = 0.6; p = .55$	$F_{2,222} = 0.76; p = .47$	$F_{4,222} = 0.31; p = .87$
Sequence-specific performance	$F_{2,25} = 0.62; p = .54$	$F_{2,220} = 1.25; p = .3$	$F_{4,220} = 0.79; p = .53$
Acute light exposure (6,500K, 2,500K and 3,000K)			
Type of trial performance	$F_{2,25} = 17.5; p < .001$	$F_{2,222} = 5.9; p = .001$	$F_{4,222} = 2.5; p = .04$
Sequence-specific performance	$F_{2,25} = 13.1; p = .001$	$F_{2,220} = 1.25; p = .08$	$F_{4,220} = 2.4; p = .04$
Morning after sleep (dim light)			
Type of trial performance	$F_{2,26} = 0.15; p = .85$	$F_{2,221} = 2.61; p = .07$	$F_{4,220} = 1.6; p = .17$
Sequence-specific performance	$F_{2,26} = 2.22; p = .14$	$F_{2,220} = 1.07; p = .34$	$F_{4,220} = 0.63; p = .64$

TABLE 1 Mixed-model analyses of variance results for procedural learning performance

non-cataract controls ($p = .005$; Bonferroni post hoc correction) (Figure 2a). Importantly, we observed that these group effects occurred only during blue-enriched light exposure ($p = .02$; Bonferroni post hoc correction) (Figure 2c). Furthermore, we observed a significant “group” effect and an interaction of “group” versus “light condition” on sequence-specific learning performance (respectively, $p = .001$ and $p = .04$) (Table 1). Patients with UV lens replacement performed better (particularly during the low probability trials) than patients with BB lens replacement and non-cataract controls ($p = .006$; Bonferroni post hoc correction) (Figure 2b), and these effects occurred only during blue-enriched light exposure ($p = .02$; Bonferroni post hoc correction) (Figure 2d). No significant differences were observed among the groups for type of trial or sequence-specific learning performance in the morning after sleep (Table 1). Given that our laboratory protocols included four cognitive tasks during our cognitive test battery sessions, we also performed the

mixed-model analyses of variance on the procedural learning outcomes with adjustment for multiple comparisons across all cognitive tasks (using false discovery rates). We observed significant “group” effects for type of trial and sequence-specific learning, whereas the interaction of “group” versus “light condition” was not significant following adjustment across cognitive tasks (Table 2). Patients with UV lens replacement remained significantly outperforming non-cataract controls for the type of trial, and both controls and patients with BB lens replacement sequence-specific learning. By contrast, these effects were not significantly associated with a specific light exposure.

4 | DISCUSSION

We show that intraocular lens replacement in patients with cataracts may be associated with the beneficial blue-light effects

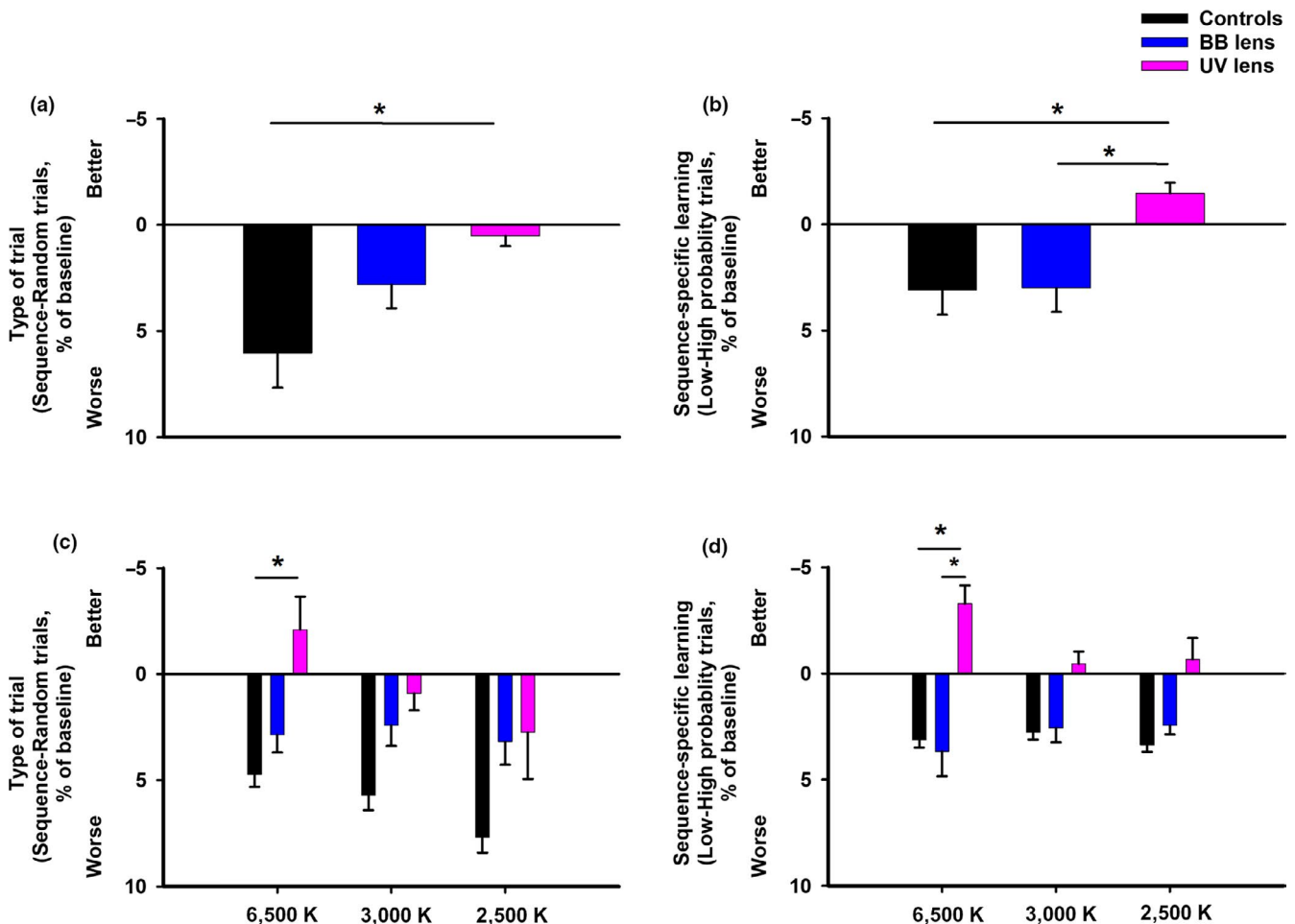


FIGURE 2 Lens replacement in patients with cataracts may potentially impact procedural learning. (a) Type of trial (difference between sequence and random trials, % of baseline) significantly improved in patients with UV lens replacement as compared to non-cataract controls. (b) Sequence-specific learning (difference between low and high probability trials, % of baseline) significantly improved in patients with UV lens replacement as compared to patients with BB lens replacement and non-cataract controls. (c) Type of trial significantly improved during acute evening light exposure at 6,500K in patients with UV lens replacement as compared to non-cataract controls. (d) Sequence-specific learning significantly improved only during acute evening light exposure at 6,500K in patients with UV lens replacement as compared to patients with BB lens replacement and non-cataract controls. Blue bar corresponds to data of patients with BB lens, violet bars to data of patients with UV lens, and black bars to non-cataract controls. $n = 16$ for controls and $n = 13$ for patients with cataract ($n = 8$ in BB group, $n = 5$ in UV group). Data are mean \pm SEM. * $p < .05$

Adjusted for multiple comparisons (using false-discovery rates)	Mixed-model analyses (fixed effects and interaction)		
	"Group"	"Light condition"	"Group" versus "light condition"
Baseline (dim-dark adaptation)			
Type of trial performance	$F_{2,25} = 0.6; p = .71$	$F_{2,222} = 0.76; p = .63$	$F_{4,222} = 0.31; p = .98$
Sequence-specific performance	$F_{2,25} = 0.62; p = .7$	$F_{2,220} = 1.25; p = .61$	$F_{4,220} = 0.79; p = .72$
Acute light exposure (6,500K, 2,500K and 3,000K)			
Type of trial performance	$F_{2,25} = 17.5; p = .01$	$F_{2,222} = 5.9; p = .02$	$F_{4,222} = 2.5; p = .16$
Sequence-specific performance	$F_{2,25} = 13.1; p = .01$	$F_{2,220} = 1.25; p = .14$	$F_{4,220} = 2.4; p = .15$
Morning after sleep (dim light)			
Type of trial performance	$F_{2,26} = 0.15; p = .97$	$F_{2,221} = 2.61; p = .16$	$F_{4,220} = 1.6; p = .29$
Sequence-specific performance	$F_{2,26} = 2.22; p = .31$	$F_{2,220} = 1.07; p = .49$	$F_{4,220} = 0.63; p = .75$

TABLE 2 Mixed-model analyses of variance results for procedural learning performance following adjustment for multiple comparisons across all cognitive tests (see Section 2)

on procedural learning performance. The data suggest that the naturally occurring yellowing of the lens with advancing age (Pescosolido, Barbato, Giannotti, Komaiha, & Lenarduzzi, 2016), which reduces the transmission of the short blue-light wavelength range to the retina, may be a potential contributor to the earlier observed age-dependent declines in implicit learning (Nemeth & Janacek, 2011). Studies in healthy adults have shown that evening blue-enriched light induces acute beneficial effects on some aspects of cognitive performance, such as sustained attention (Chellappa et al., 2011), working memory and declarative memory (Cajochen et al., 2011). Increasing ambient light levels for 1 week have been shown to minimize cognitive impairment in patients with dementia (Riemersma-van der Lek et al., 2008). With respect to cataract, patients with cataract who had UV lens replacement had better attentional performance (Chellappa et al., 2019). Although the ASRT performance does not tease apart whether domain-independent sequence learning or sequence-learning-specific reaction times are impacted by light exposure in patients with previous cataract, the beneficial effects of blue light exposure may have potentially impacted both aspects of procedural learning. Collectively, our current and previous findings (Chellappa et al., 2019) speak to potential IOLs replacement effects on cognitive function, when patients are postoperatively assessed within 2 months. Long-term effects of cataract surgery indicate a physiological adaptation for cognition and brain function (Daneault et al., 2018; Hall et al., 2005; Lin et al., 2018). Preoperatively, older patients with cataract exhibited attenuated fMRI-assessed brain function together with structural changes in visual areas, whereas 6 months after surgery, brain function and structure (particularly in the visual cortex) improved and was comparable to that of healthy age-matched controls (Lin et al., 2018). Plasticity to light sensitivity with ageing also seems to occur, such that 4 years following cataract surgery, IOLs replacement did not affect the daytime light effect on cognitive

brain function (Daneault et al., 2018). These results indicate that cognitive function and brain function/structure may display long-term physiological adaptations following cataract surgery.

Blue light-blocking IOLs mimicking the natural colouring of the human crystalline lens were introduced to counteract macular degeneration (Brondsted et al., 2015). The underlying assumption is that the retina might be protected from phototoxic blue light, purported to be involved in age-related macular degeneration (Cruickshanks, Klein, Klein, & Nondahl, 2001). Although visual function between BB and UV-only IOLs might be comparable (Mester, Holz, Kohlen, Lohmann, & Tetz, 2008; but see also Steinemann et al., 2019) for differences between these IOLs, the reduced transmittance of blue light, which is pivotal to circadian photoentrainment, has led to concern that BB IOLs may adversely impact circadian rhythmicity (Brondsted et al., 2017; Chellappa et al., 2019). Taken together, the benefits of specific IOLs for circadian rhythmicity and cognitive function still remain to be fully established.

Despite our stringent inclusion/exclusion criteria and study design, our study is essentially a carefully controlled laboratory study with a limited sample size. Our findings highlight the importance of (field-based) studies with larger sample sizes to establish the interrelationship of light exposure and type of IOLs on cognitive function. Therefore, caution should be taken in extrapolating our findings to larger populations with cataract. Collectively, our stringent within-subject randomized laboratory study suggests that lens replacement in older patients with cataract, particularly UV lens, has a potential association with the beneficial effects of light on procedural learning.

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CONFLICT OF INTEREST

The authors declare no conflicts of interests.

AUTHOR CONTRIBUTIONS

SLC designed the experiment, analysed the data and wrote the manuscript; VB and SF performed the experiment; TS and DB provided ophthalmological expertise; CC designed the experiment and wrote the manuscript; CFR assisted with data analyses and data interpretation and wrote the manuscript.

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