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ORIGINAL RESEARCH

Associations of an eye-tracking task and pupillary metrics with age and ASA physical status score in a preoperative cohort

Alexander Papangelou[1] · David W. Boorman[1] · Milad Sharifpour[2] · Haresh P. Patel[3] · Tuan Cassim[4] · Paul S. García[4]

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Abstract
Advanced age, American Society of Anesthesiologists physical status (ASA) classification and the presence of cognitive impairment are associated with an elevated risk of postoperative morbidity and mortality. The visual paired comparison (VPC) task, which relies on recognition of novel images, examines declarative memory. VPC scores have demonstrated the ability to detect mild cognitive impairment and track progression of neurodegenerative disease. Quantitative pupillometry may have similar value. We evaluate for associations between these variables of interest and the feasibility of performing these tests in the preoperative clinic. Prospective data from 199 patients seen in the preoperative clinic at a tertiary academic center were analyzed. A 5 min VPC task (Neurotrack Technologies, Inc, Redwood City, CA) was administered during their scheduled preoperative clinic visit. Pupillary light reflexes were measured at the same visit (PLR-3000™, Neuroptics Corp, Irvine, California).Thirty-four percent of patients were categorized as ASA 2 and 58% as ASA 3. Median age was 57 (IQR: 44–69). Associations were demonstrated between age and ASA physical status (Mann–Whitney U Test, $p < 0.0001$), maximum pupil size (Spearman Rank Correlation, $r = -0.40$, $p < 0.0001$), and maximum constriction velocity (Spearman Rank Correlation, $r = -0.39$, $p < 0.0001$). Our data also revealed an association between VPC score and age (Spearman Rank Correlation, $p = 0.0016$, $r = -0.21$) but not ASA score (Kruskal–Wallis Test, $p = 0.14$). When compared to a nonsurgical cohort with no history of memory impairment, our population scored worse on the VPC task (Mann–Whitney U Test, $p = 0.0002$). A preoperative 5 min VPC task and pupillometry are feasible tests in the preoperative setting and may provide a valuable window into an individual's cognition prior to elective surgery.

Keywords Visual paired comparison task · Pupillometer · Maximum constriction velocity · Maximum pupil size · Cognitive impairment · Preoperative

1 Introduction

In an aging population with increasing demand for surgical interventions, risk stratification has become a vital component of the preoperative evaluation. The American Society of Anesthesiologists physical status (ASA PS often referred to as "ASA score") classification system was developed 80 years ago as a simple categorization of a patient's operative risk [1]. Advanced age and ASA score have each been independently associated with an elevated risk of postoperative morbidity and mortality, including perioperative neurocognitive disorders [2–5]. The importance of cognition and the adverse impact of cognitive impairment on perioperative outcomes are topics of research interest [7, 8]. The selection of the ideal cognitive screening tool or battery to identify high-risk patients remains a matter of debate [9–11]. Several studies have relied on the Mini–Cog, a convenient screening test administered by non-specialists [6, 12–14]. However, the clock-drawing portion may challenge individuals lacking regular exposure to analog clocks, experience in drawing or writing, and those with very low levels of educational attainment. As such, an objective, quantitative measure of cognitive status would be an attractive addition to the preoperative

✉ Alexander Papangelou
apapang@emory.edu

1 Department of Anesthesiology, Emory University School of Medicine, Atlanta, GA, USA

2 Department of Anesthesiology, Cedars Sinai Medical Center, Los Angeles, CA, USA

3 Department of Internal Medicine, Wellstar Kennestone Regional Medical Center, Marietta, GA, USA

4 Department of Anesthesiology, Columbia University, New York, NY, USA

screening visit. The utility of the visual paired comparison (VPC) task and pupillometry as potential measures of cognition deserves consideration.

The VPC task has shown promise in detecting memory impairment in rats, nonhuman primates and humans with hippocampal injury [15–17]. Damage to structures of the medial temporal lobe, including hippocampus, has led to impaired declarative memory, which gives rise to the memory complaints observed in Alzheimer's dementia (AD) [18]. Importantly, the 30 min VPC task has been shown to be sensitive enough to detect mild cognitive impairment (MCI), and it has demonstrated the ability to predict the progression of MCI to dementia over a 3 years' time span [18, 19].

An abbreviated 5 min version of the VPC task (Neurotrack Technologies, Inc, Redwood City, CA) has demonstrated moderate convergence with the 30 min VPC and other validated measures of cognition [20]. A test of this length would be potentially useful in a clinic setting, but little is known about the validity of a VPC task in the perioperative environment. The VPC task records eye movements to interrogate recognition memory. Individuals with intact memory spend on average two-thirds of their viewing time on the novel picture. A lack of novelty preference suggests impaired memory and serves as an early predictor of cognitive decline [19]. On the 5 min version of the VPC, a threshold score of 0.75 may distinguish between the cognitively normal and those with a mild cognitive impairment (MCI), as diagnosed by the Montreal Cognitive Assessment (MoCA) [20, 21].

Another ophthalmologic-based test, the pupillary light reflex (PLR), also deserves attention given its brevity and simplicity to administer. Data supports the possibility of the PLR as a biomarker of AD [22]. The physiologic basis lies in the dysfunction of the autonomic system, most significantly loss of cholinergic neurons in the Edinger-Westphal nucleus as well as sympathetic neurons in the locus coeruleus [22]. In considering all pupillary metrics, maximum constriction velocity (MCV) and maximum constriction acceleration are the most accurate parameters that differentiate between AD and controls, although the PLR may fall short in differentiating MCI from controls [22–26]. It is fairly well-established that maximum pupil size decreases with advancing age regardless of wavelength of light [27]. This leads to an interesting observation where the pupil may provide a window into both chronological age and cognition, given MCV and MCA's ability to detect deterioration of cognition irrespective of chronological age.

We conducted a prospective observational study, enrolling subjects in the preoperative evaluation clinic, who were to undergo general anesthesia for elective surgery. In addition to the standard preoperative evaluation, subjects underwent 5 min VPC testing and pupillometry. Our primary objective was to establish the feasibility of performing these tests in the preoperative setting. Secondly, we were interested in studying associations between age, ASA score, 5 min VPC testing results, maximum pupil size and MCV. Our investigation is explorative in nature, as we intend on examining associations between established predictive variables of surgical outcome and those from promising tests that are novel to the preoperative setting, rather than validating these tests with other cognitive tools that have been used in prior preoperative studies. In addition, to gain some appreciation of the cognitive baseline of our study population, we compared our VPC distribution to that of a non-surgical cohort from a prior research survey where participants had no history of memory loss or dementia.

2 Materials and methods

2.1 Design

This study was approved by the Emory University Institutional Board (IRB00103151). This prospective observational trial was performed at Emory University Hospital between March 2018 and March 2020. This manuscript reports on the preoperative component of the trial.

2.2 Inclusion/exclusion criteria

Adult patients greater than 18 years of age undergoing elective, non-cardiac, non-neurosurgical procedures under general anesthesia were deemed eligible if recovery was anticipated to occur in the Post-Anesthesia Care Unit. Subjects were ineligible if the planned procedure was ophthalmologic or facial, precluding pupillometry assessment. Patients were asked "how confident are you filling out medical forms by yourself," and if determined to have poor health literacy, were not considered for enrollment.

2.3 Staff training

Research staff were trained in the administration of the VPC task and pupillometry by authors AP and PG. Research personnel were familiar with pupillometry testing from prior research studies performed at Emory [28]. The research team self-administered the VPC task, so as to facilitate full understanding of the testing procedure. Neurotrack scored all tests and were available for troubleshooting and quality control.

2.4 Data collection

After informed consent, participants underwent a five-minute VPC assessment. Testing was performed on a study computer equipped with a webcam in a quiet room in the preoperative clinic. The VPC assessment procedure has

been described in detail elsewhere [29, 30]. In brief, testing started with a familiarization phase where subjects were instructed to view and memorize 20 images which were displayed in pairs for 5 s. During the testing phase, subjects were directed to view the novel picture, and were then shown 2 images, one novel and one from the familiarization phase. The amount of time viewing novel images would determine a novelty preference score, ranging from 0 to 1.0 with higher scores indicating better declarative memory. Pupillary metrics were recorded with a PLR-3000™ automated pupillometer (Neuroptics Corp, Irvine, California). A pre-formed silicone membrane on the device limited the impact of ambient light. The PLR was generated by a 0.8 s light stimulus with pulse intensity of 50 µW. This process has been described elsewhere [31]. A 3.01 s video of the PLR was recorded and variables were displayed on the device including maximum pupillary size, constriction latency, constriction velocity (average and maximal), minimum pupillary size, T75 (time to reach 75% recovery) and dilation velocity. Anisocoria was defined as an interpupil difference of greater than 1 mm, consistent with prior studies in critical care [32].Study data were collected and managed using Research Electronic Data Capture (REDCap) hosted at Emory University [33, 34]. Variables of interest included patient demographics, comorbidities, ASA score, VPC score and PLR variables.

2.5 Study outcomes

VPC distributions were compared between our surgical population and that of a non-surgical population. The raw data from the non-surgical population was donated by Neurotrack Technologies, Inc. The data are unpublished and part of an online market research platform, recruiting participants between the ages of 40–79 with no self-reported history of memory loss or dementia. Associations between the ASA score, VPC score, age, maximum pupillary size and MCV were evaluated in our study population. Pupillary metrics were chosen from the variables available on the PLR-3000™ automated pupillometer that were predictive of age and cognition. An average measure from both the left and right eye was utilized for statistical analyses.

2.6 Statistical analysis

Data presented are a subset of an ongoing study (ClinicalTrials.gov IRB00103151) with a targeted sample size of 250 subjects with complete datasets, which was powered at 80% using logistic regression analysis. All statistics were performed using SAS 9.4 (Cary, NC). Normality was assessed visually through histograms and more formally through the Kolmogorov–Smirnov Test. Nonparametric statistical tests were used to avoid assumptions of normality and equal variance. This includes the Spearman Rank Correlation (equivalent to linear regression and Pearson Correlation), Mann–Whitney U Test (equivalent to the t-test), Kruskal–Wallis Test (equivalent to ANOVA) and the Fisher Exact Test (for 2×2 tables).

3 Results

Two hundred fifty subjects were enrolled between March 2018 and March 2020 before the study was placed on hold as a result of the COVID-19 pandemic. Two hundred forty-eight subjects completed preoperative testing (99.2%). Of those, 31 had unscorable VPC tasks (87.5% task success rate). The reasons for unscorable VPC tasks with frequency in parenthesis included: corrupted or missing video and inability to process (13); glare from glasses (5); shadows cast on eyes (4); too far of a distance from the camera (5); poor angle between eyes and camera (1); eyes closed for long periods during assessment (2); and too much participant movement (1). Eighteen pupillometry data sets were excluded due to erroneous or missing readings and anisocoria (Fig. 1).

Demographic data are demonstrated in Table 1. Of note, 64.5% of patients were women and only 22.6% of patients were 70 years of age and older. The vast majority of patients were ASA 2 and ASA 3, with only 5% graded as ASA 1 and 3% as ASA 4. Most of the patients were presenting for general surgery, followed by urologic and gynecologic surgery. Pre-existing neuropsychiatric diagnoses were infrequent in our population. The overall incidence of subjects with a neuropsychiatric comorbidity was low with 72% of subjects having no documented diagnosis. Notably, only 2 subjects, representing less than 1% of those enrolled, reported a diagnosis of dementia when questioned during the preoperative visit. With regards to data distributions, age and anisocoria

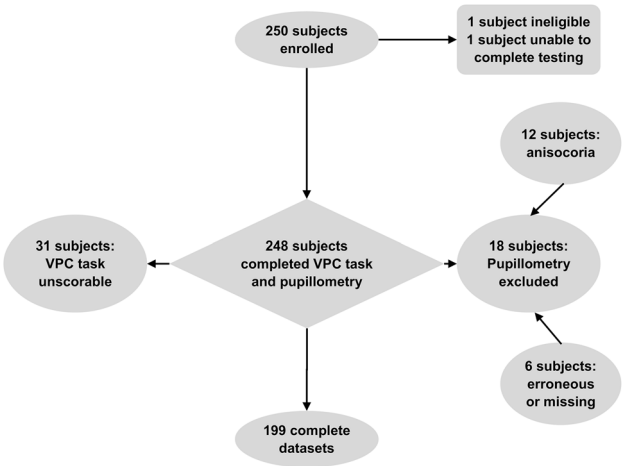

Fig. 1 Flow Chart of Patient Enrollment

Table 1 Descriptive statistics of demographics, surgeries and comorbidities

Category/variable	Variable/subset	Value
Demographics, N = 248	N	248
	Age, yrs, median (IQR)	57 (44–69)
	Gender, female, N (%)	160 (64.5%)
Surgery type, n = 243 (%)	General	122 (50%)
	Urology	43 (18%)
	Gynecology	35 (14%)
	Plastic/breast	20 (8%)
	Oral & maxillofacial surgery (OMFS)	2 (0.8%)
	vascular	1 (0.4%)
	Other	20 (8%)
ASA level, n = 240 (%)	1	12 (5%)
	2	81 (34%)
	3	139 (58%)
	4	8 (3%)
Neurologic and psychiatric comorbid conditions, n = 248 (%)	Sleep disorder	25 (10%)
	Anxiety	17 (7%)
	Depression	17 (7%)
	Chronic pain	13 (5.2%)
	Cerebrovascular accident (CVA)	8 (3%)
	Drug abuse	5 (2%)
	Seizure	3 (1.2%)
	Dementia	2 (0.8%)
	Post-traumatic stress disorder (PTSD)	2 (0.8%)
	Postoperative cognitive dysfunction (POCD)	2 (0.8%)
	Parkinson's disease	1 (0.4%)
	Stimulants	0 (0%)
	None[a]	179 (72%)

[a]Does not sum to 248 since some patients (n = 19, 7.6%) have multiple comorbidities

IQR Interquartile range, *ASA* American Society of Anesthesiologists physical status level

were platykurtic (too flat). VPC was negatively skewed, while MCV and procedure length were positively skewed. Only max pupil size was normally distributed. Because of low sample sizes in ASA 1 (n = 9) and ASA 4 (n = 8), they were combined with ASA 2 and 3, respectively, for analyses. ASA 1–2 was significantly younger than ASA 3–4 (Mann–Whitney U Test, Z = − 6.1, p < 0.0001, Supplemental Information Fig. 1). The distribution of age within ASA 1–2 was positively skewed with median 48 years old (IQR 38–59) while within ASA 3–4, it was negatively skewed with median 62 years old (IQR 40–71).

Maximum pupillary size demonstrated a negative correlation with age (Spearman Rank Correlation, r = − 0.40, p < 0.0001, Fig. 2a). In the case of MCV and age, a correlation was also demonstrated (Spearman Rank Correlation, r = − 0.39, p < 0.0001, Fig. 2b). After stratifying to ASA 1–2 or ASA 3–4 groupings, the correlations were similar with the exception of age versus MCV within ASA 1–2, where there was no longer significance (Spearman Rank Correlation, p = 0.13).

Our surgical study population demonstrated a significantly lower median VPC score when compared to a non-surgical population, as detailed in the methods section (Mann–Whitney U Test, Z = − 3.7, p = 0.0002, Fig. 3a). Although differences were not statistically significant at the evidence-based cutoff for MCI at 0.75 (Fisher Exact Test, p = 0.19), when dichotomized at 0.80, there were significantly more surgical patients below that threshold (Fisher Exact Test, p = 0.0039, Supplemental Information Fig. 2). Despite a similar median age between the groups, the nonsurgical cohort was constrained to subjects between 40 and 79 years old. Twenty-one percent of our sample were outside this age range (< 40 y.o. n = 45, 18.2%; > 79 y.o. n = 7, 2.8%). When limiting the surgical population to the same age range of 40–79, our population once again had a lower median VPC compared to the non-surgical population (Mann–Whitney U Test, Z = − 3.7, p = 0.0003, Supplemental Information Fig. 3).

Interestingly, VPC scores negatively correlated with age in our sample (Spearman Rank Correlation, r = − 0.21,

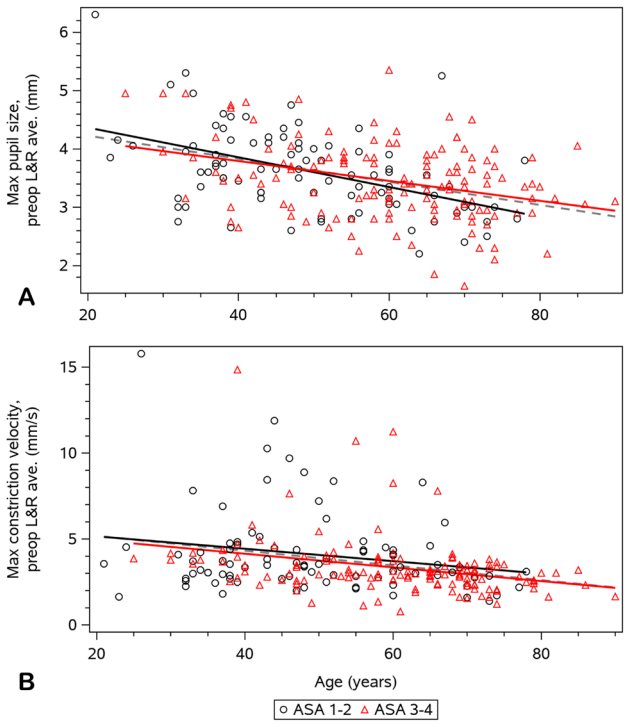

Fig. 2 Scatterplots of the preoperative maximum pupil size (**a**) and maximum constriction velocity (MCV) (**b**) as a function of age grouped by ASA physical status level. Values represent the average of left and right pupils. A significant negative correlation of both maximum pupil size and MCV with age exists (Spearman Rank Correlation, r = − 0.40 and r = − 0.39 respectively, p < 0.0001). Trend lines are added to both, with the gray dashed trend line reflecting all data points; however, linear regression cannot be performed on MCV vs age because of violations of the assumption of equal variance

p = 0.0016, Fig. 3b), but did not demonstrate an association with ASA score (Kruskal–Wallis Test, $\chi^2 = 5.5$, p = 0.14, Fig. 3c). The lack of correlation remained after combining ASA 1 and 2 and ASA 3 and 4 (Mann–Whitney U Test, Z = 1.5, p = 0.13). There was no significant difference found between VPC score and maximum pupil size (Spearman Rank Correlation, p = 0.96, Fig. 3d). Similarly, there was no significant correlation between VPC score and MCV (Spearman Rank Correlation, p = 0.081, Fig. 3d). However, all patients with VPC scores less than 0.75 had velocities of 5 or less, and 24% of patients with velocities 5 or less had VPC of less than 0.75 (Fisher Exact Test, p = 0.015).

4 Discussion

These results suggest that VPC testing and pupillometry are feasible in a preoperative setting. We believe many of the reasons accounting for the VPC failure rate would be correctable during subsequent studies. The results also demonstrate associations between our variables of interest in the preoperative setting. Lower VPC scores were associated with advanced age, but somewhat unexpectedly VPC scores were not associated with ASA physical status. Even though those with ASA 3 and 4 scored lower in the VPC task than the ASA 1 and 2 group, this did not reach statistical significance. This finding is particularly interesting as it may indicate some discordance between the burden of medical disease, as categorized by the ASA score, and the presence of cognitive impairment, although conclusions must be tempered given the small sample sizes in the ASA 1 and 4 groups.

In our study population, cognitive status, evaluated broadly by the presence or absence of dementia, is established during a quick review of systems in clinic, while those in the nonsurgical cohort broadly denied a history of dementia and memory loss. Other than two subjects with dementia and two with POCD, our population lacked subjective memory complaints and diagnoses. Based on these findings, one may have expected similar cognitive results between cohorts if controlled for age. It is noteworthy, however, that these self-reports may lack accuracy, as the presence of MCI and dementia is underrecognized and underdiagnosed [35–37]. In fact, in a large systematic review and meta-analysis, a 37% pooled prevalence of unrecognized cognitive impairment was discovered in 27,845 patients undergoing non-cardiac surgeries, while 18% of subjects had diagnosed cognitive impairment amongst 11,676 patients [38]. Screening methods varied widely, as did scoring cutoffs. The mean age for the unrecognized cognitive impairment patients was 75.1 ± 7.1 years, while diagnosed cognitive impairment patients also had a mean age over 70 (72.2 ± 8.2 years). This underscores the need for objective testing in the preoperative clinic setting.

Our surgical population scored lower on the VPC task when compared to the nonsurgical cohort, and although there was no difference when VPC score was dichotomized at 0.75, we suspect our finding may indicate a disparity in cognitive baselines between the two cohorts. Our secondary analysis, which restricted the surgical population to 40–79 years of age, did not change the statistical conclusions comparing the two populations. Given that the removal of 45 patients under 40 years of age (18.2% of our database) and only 7 patients over 79 years of age did not impact our VPC statistics, this may imply a greater impact

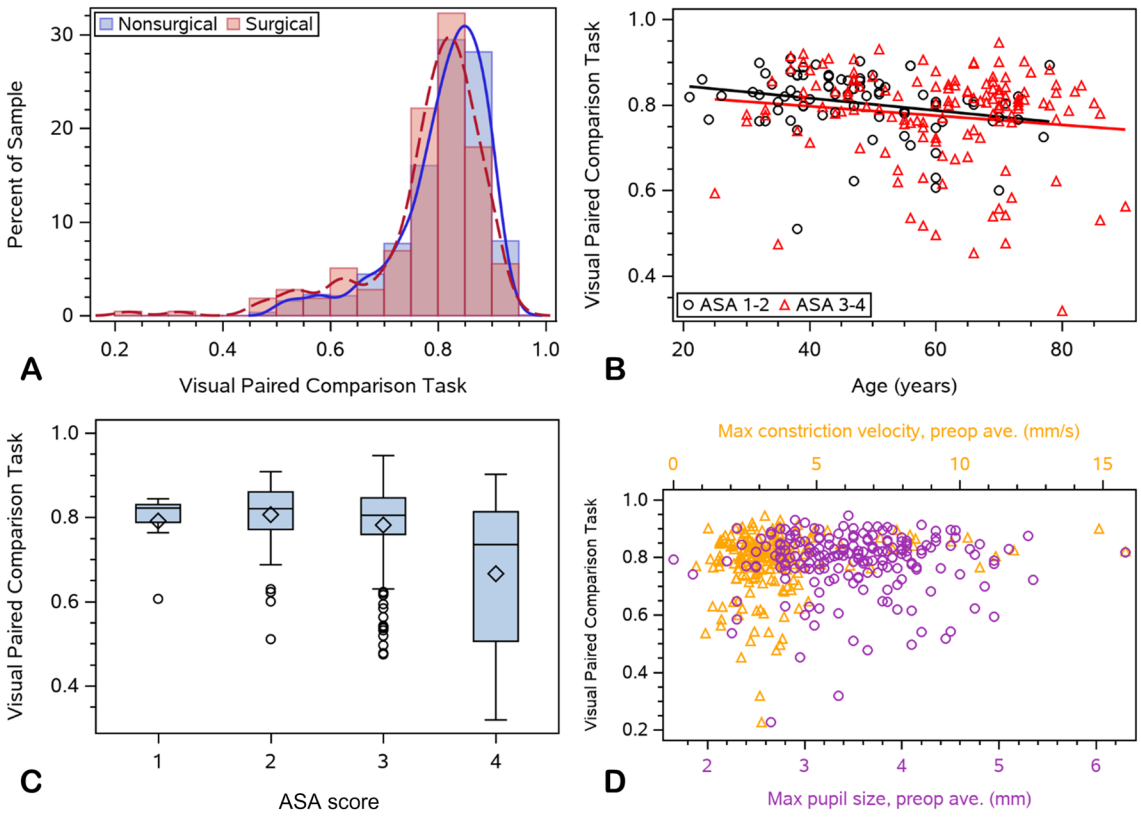

Fig. 3 Visual paired comparison task (VPC) associations. (**a**): Histogram of VPC by nonsurgical and surgical groups with kernel (nonparametric) density curves. VPC for the surgical group (our cohort) is significantly lower than for the nonsurgical group (Mann–Whitney U Test, Z = − 3.7, p = 0.0002). Note the higher proportion in the surgical group at 0.75–0.80 and the lower proportion at 0.85–0.90. (**b**): VPC (surgical) versus age by ASA Level in 2 groups. There is a negative correlation of VPC and age (Spearman Rank Correlation, r = − 0.12, p = 0.0016). (**c**): Boxplot of VPC (surgical) by ASA score. The rectangle reflects the Q1, median and Q3. The diamond demonstrates the mean, while circles beyond the whiskers represent outliers. No significant difference was found (Kruskal–Wallis Test, $\chi^2 = 5.5$, p = 0.14), although sample sizes for ASA 1 (n = 9 with an additional 3 missing VPC scores) and ASA 4 (n = 8) may be too small to establish a trend between these groups. (**d**): Scatterplot of the VPC (surgical) by maximum pupil size (purple circles, bottom axis) and MCV (orange triangles, top axis). All pupil measures are preoperative and reflect the average of left and right eyes. There was no significant correlation between VPC and either max pupil size (Spearman Rank Correlation, p = 0.96) or MCV (Spearman Rank Correlation, p = 0.081). However, all patients with VPC < 0.75 had velocities less than 5, and 24% of patients with velocities less than 5 had VPC < 0.75 (Fisher Exact Test, p = 0.015)

of cognitive age over chronological age in our surgical population, as one would expect younger patients to have intact cognition. Our finding may suggest an increased likelihood of advanced cognitive age in complex surgical populations at academic centers.

We also found a strong association between age and maximum pupillary size, which supports prior data that pupil diameter decreases with biologic age [27]. Various intervals within the PLR, including MCV, have shown promise as biomarkers of dementia in prior studies, although the testing parameters may have significant impact on the results [22]. In one study, the testing parameter seemed to be vital to the findings differentiating those subjects with normal cognition, MCI and dementia [39]. In our dataset, we identified a potential signal of interest. Along with a trend toward significance between VPC score and MCV, it is noteworthy that all patients with VPC scores < 0.75 (indicating cognitive pathology) also had MCV less than 5, indicating a potential association. Further critical evaluation of pupillometry in the preoperative setting would be of interest and verification of its value as a biomarker could also have impact on preoperative care.

There is extensive literature that demonstrates that patients of advanced age and/or significant medical comorbidities, commonly categorized by ASA scores in anesthesia preoperative clinics, have elevated risks of morbidity and mortality [5]. Both age and ASA scores are included in the NSQIP surgical risk calculator, which was developed as a universal tool to more precisely estimate risk of surgical mortality and various morbidities [40]. Although not included in frailty scales, it has been well-established that pre-existing cognitive dysfunction is

a risk factor for the development of postoperative delirium [41–43]. The evaluation and prevention of postoperative delirium and postoperative cognitive dysfunction have been topics of intense research in anesthesiology for decades [7, 44–49]. For these reasons, the ability to reliably identify cognitive impairment preoperatively would be valuable, especially considering the aforementioned difficulty in the recognition of cognitive disorders by families and primary care physicians [35–37]. Investigations on methods to detect preoperative cognitive dysfunction, including our study, have been born out of these concepts.

Although the process of identifying patients with physiologic frailty is well-established, an optimal method for identifying cognitive vulnerability does not yet exist. An ideal cognitive screening test would need to be time-efficient and require limited expertise for its administration. The mini-Cog has shown promise in detecting at-risk individuals. Two prospective studies demonstrated abnormal mini-Cog scores in 24% and 35.1% of their study populations and showed an elevated risk of postoperative delirium and mortality in those patients [12, 13]. However, results employing the mini-Cog have not been universally positive, with one retrospective cohort revealing an increased observed-to-expected length of stay, while other endpoints were insignificant. Notably, delirium rates were not reported in this trial [6].

As discussed earlier, the abbreviated VPC task is an attractive cognitive assessment as it is rapid and requires minimal instruction to initiate the online program. Findings from a prior study suggests that a cutoff of less than 0.75 may detect MCI as diagnosed on the MoCA [20, 21]. Data on 55 subjects demonstrated an area under the receiver operating characteristic curve of 0.80 with sensitivity of 90% and specificity of 65% [21]. Of course, the value of the VPC in the perioperative period needs to be translated to postoperative endpoints of interest, including delirium and POCD. The objective nature of the VPC task, as well as the lack of learning effect, makes it an ideal marker to track cognition longitudinally.

The limitations of our study include the low enrollment rates of ASA 1 and ASA 4 patients. The ASA score distribution made it difficult to make granular conclusions about associations with other variables. These limitations may be inherent to the populations that present for elective surgery at an academic center. Secondly, although easy to administer, the VPC task still requires working hardware, a reliable internet connection, a quiet environment and proper patient orientation (distance from camera). Additionally, we did not perform cognitive evaluations such as the mini-Cog or MoCA, as our study was purely explorative and not intended on establishing correlations with these scales. We do not believe a gold standard brief cognitive test has been established in the preoperative setting and this steered us to our study design. Future studies could include establishing correlations with other preoperative cognitive tests and serial assessments of the VPC task prior to and after surgery.

Our explorative investigation demonstrated fascinating associations between our variables of interest and the 5 min VPC task as a possible surrogate of preoperative cognitive vulnerability. The potential for components of the PLR to serve as a biomarker for Alzheimer's dementia should also be appreciated. We will report on the performance of these variables as predictors of postoperative delirium in a future manuscript.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10877-023-00974-x.

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Author contributions Alex Papangelou, Milad Sharifpour and Paul Garcia contributed to study conception and design. Material preparation, data collection and analysis were performed by Tuam Cassim, Haresh Patel and David Boorman. The first draft of the manuscript was written by Alex Papangelou. All authors contributed to editing and approved the final manuscript.

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Declarations

Competing interests Alex Papangelou serves as a consultant to Vistendo, Inc on grants awarded by the Defense Health Agency (DHA).

Conflict of interests Alex Papangelou serves as a consultant to Vistendo, Inc on grants awarded by the Defense Health Agency (DHA). The authors otherwise have no relevant financial or non-financial interests to disclose.

Ethical approval The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Emory University Institutional Board (IRB00103151).

Consent to participate Informed consent was obtained from all individual participants included in the study.

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