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Pupillary Responses as a Biomarker of Early Risk for Alzheimer's Disease

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Abstract

Task-evoked pupillary responses may be a psychophysiological biomarker of early risk for mild cognitive impairment (MCI) and Alzheimer's disease (AD). Pupil dilation during cognitive tasks reflects cognitive effort until compensatory capacity is surpassed and performance declines are manifest, and reflects activation in the locus coeruleus, where degenerative changes have been found in the earliest stages of AD. We recorded pupillary responses during digit span recall in 918 participants ages 56–66. Despite normal performance, amnestic single-domain MCI (S-MCI) participants showed greater pupil dilation than non-amnestic S-MCI and cognitively normal (CN) participants at lower cognitive loads. Multi-domain MCI (M-MCI) participants failed to modulate effort across cognitive loads and showed poorer performance. Pupillary responses differentiated MCI and CN groups. Amnestic S-MCI participants required compensatory effort to maintain performance, consistent with increased risk for decline. Greater effort in CN individuals might indicate risk for MCI. Results are consistent with dysfunction in locus coeruleus-linked brain systems. This brief task shows promise as a biomarker for early MCI and AD risk prediction.

Keywords

Alzheimer's disease; compensatory cognitive effort; mild cognitive impairment; pupillometry; pupillary responses

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SUPPLEMENTARY MATERIAL

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Introduction

There is widespread agreement about the need for early identification of risk for Alzheimer's disease (AD) with minimally-invasive, inexpensive measures in community settings [1, 2]. Toward that end, we examined a novel psychophysiological biomarker—cognitive task-evoked pupil pupillary responses—in the early identification of mild cognitive impairment (MCI). Pupillary responses reflect activation in the locus coeruleus (LC) [3–11] where degenerative changes have been found in the earliest stages of AD [12, 13]. Pupillary responses provide a biomarker of cognitive effort required to perform tasks *before* overt performance declines are manifest [14–18]. Pupil size during cognitive tasks increases in response to increased demands, is inversely related to cognitive ability (individuals with lower ability show greater dilation/compensatory effort) and—pupil size decreases and performance declines when task demands exceed abilities and compensatory capacity [15–18]. Someone requiring more effort to achieve the same score as another person is likely to be closer to maximum compensatory capacity and, therefore, at higher risk for decline.

To examine whether greater pupil dilation (compensatory effort) is associated with greater risk for AD, we compared pupillary responses during digit span tasks in cognitively normal (CN), single- and multi-domain MCI (S-MCI; M-MCI) participants. We hypothesized that: 1) Less severely impaired MCI participants, likely to have near normal maximum spans, would show greater pupil dilation at lower loads and greater drop-off in dilation with capacity overload compared with CN participants, and 2) more impaired MCI participants, likely to have below normal maximum spans, would show less pupil dilation at all loads, suggesting greater overload of compensatory capacity even at moderate loads.

Based on prior research [15–18], we first carried out proof-of-concept analyses to demonstrate that pupil dilation reflects compensatory effort at lower loads and capacity limits at higher loads. At lower loads, individuals can maintain performance by increasing cognitive effort to compensate for lower ability, but at higher loads that exceed the compensatory capacity of most individuals, pupil dilation declines. We examined the relationship between maximum forward span from the Wechsler Memory Scale–III (WMS-III) Digit Span subtest and pupillary responses during 3-, 6-, and 9-digit span recall in a late-middle aged sample. We hypothesized that pupil dilation would increase with increasing processing load from 3 to 6 digits, then decrease with overload of capacity in the 9-digit condition, and that individuals with lower ability (shorter maximum spans) would show greater pupil dilation (reflecting compensatory effort to maintain performance) under low load (3 digits) and less pupil dilation (reflecting overloaded capacity limits) under high load (9 digits) relative to individuals with greater ability (longer maximum spans).

Methods

Participants

Participants were 918 individuals from wave 2 of the Vietnam Era Twin Study of Aging, [VETSA; 19] (Sample characteristics in Table 1). The VETSA is a longitudinal behavioral genetic study with a primary focus on cognitive and brain aging in men. It comprises a subset of twins from the Vietnam Era Twin Registry, a registry of middle-aged all male-male

twin pairs who both served in the military at some time during the Vietnam era (1965–1975), but nearly 80% reported no combat exposure. Returning participants from wave 2 of the VETSA were tested at one of the two VETSA sites: University of California, San Diego or Boston University. Two pupillome-try devices were used at each site and device was used as a covariate in all analyses. VETSA participants comprise a national, community-dwelling sample similar to American men in their age range with respect to health and lifestyle characteristics based on Center for Disease Control and Prevention data [19]. Exclusion criteria for these analyses were: self-reported history of glaucoma in either eye, penetrating eye wounds to both eyes, eye surgery to both eyes involving the muscle, or use of cholinesterase inhibitors or prescribed ocular medications; equipment failures or excessive blinking; self-reported history of seizure disorder, multiple sclerosis, stroke, HIV/AIDS, schizophrenia, serious alcohol dependence, brain cancer, or dementia; or insufficient cognitive data for determination of MCI status. One hundred participants were excluded based on these criteria. Depression and head injury were not exclusions because they are risk factors for dementia. The study was approved by institutional review boards at participating institutions.

Neuropsychological assessment

We administered 18 neuropsychological measures covering six cognitive domains (Table 2). Using the same approach, we showed that MCI could be identified in this sample during wave 1 when participants were only in their 50 s [20]. As in that previous work, all neuropsychological measures were adjusted for general cognitive ability (GCA) scores from when participants averaged 20 years old so that MCI would reflect change over time rather than just longstanding low cognitive performance. Age 20 GCA also provides a cognitive ability measure that is unaffected by later aging-related changes. GCA was assessed by the Armed Forces Qualification Test, which is highly correlated ($r = 0.84$) with standard IQ measures and has a 35-year test-retest reliability of 0.74 [21]. Our determination of whether someone was at that threshold for defining impairment on a given test was then based on the adjusted scores, i.e., after age 20 GCA scores were regressed out of the current individual neuropsychological scores.

We defined MCI according to the Jak/Bondi actuarial-neuropsychological approach [20, 22–24]. Within this approach, impairment was typically defined as 2 + measures within a domain, each greater than 1 SD below age- and education-adjusted normative means [22–24]. We defined impairment more conservatively (1.5 SD cut-off for 2 + measures) because it resulted in the most reasonable numbers and proportions with respect to individuals with MCI, and the balance between those converting to MCI and reverting to CN status between longitudinal VETSA assessments. We identified S-MCI (n=53 amnestic; n=47 non-amnestic), M-MCI (2 + domains impaired; $n = 25$) and CN ($n = 793$) individuals. Non-amnestic S-MCI comprised subgroups with impairment in the following domains: executive (40.4%); language (21.3%); attention/working memory; visual-spatial; processing speed (12.8% each). MCI comprised 13.6% of the full sample. A 1 SD cut-off would have resulted in 32.3%, which is comparable to previous studies using this approach [22–24], but the base rate should be substantially lower in VETSA because participants average 15–20 years younger than those prior studies.

Pupillometry

Handheld NeurOptics PLR-200 (Irvine, CA; accuracy ± 0.1 mm, NeurOptics, 2010) pupillometers were modified by the manufacturer to record pupil diameter from one eye at 30 Hz for up to 15 seconds, while participants viewed a gray dot on a constant white light background (~200 lux) inside in a viewing tube. The device is the size of a television remote with recording optics inside one end of a 1.5-inch viewing tube that surrounds the eye. Ambient light is blocked from reaching one eye by the viewing tube, and participants closed and held their hand over the other eye.

Pupillary responses were recorded during blocks of trials of 3 (low load), 6 (moderate/near capacity load), and 9 (high/overload) digits presented aurally on a laptop computer at the rate of one per second. Participants heard “Ready” one second before the first digit and “Repeat” one second after the last digit. Experimenters initiated pupillary response recording when the word “Ready” was presented. Each trial was inspected for artifacts in a graphic display on the device. Trials were administered until two clean trials were recorded or four trials were attempted per digit-span condition. Trials were discarded and re-administered if 50% of data during digit presentation contained artifacts or data during presentation of the last digit contained artifacts.

Trials were averaged within each digit-span condition. Pupil diameter samples were averaged for each second of recording (30 per second), which corresponds to the presentation of digits at one-second intervals. The primary dependent variable was change relative to baseline at the last digit presented. Baseline pupil size at the start of each trial was regressed from the pupil change score, to remove individual differences in tonic pupil size. To determine the maximum span, we administered the WMS-III Digit Span subtest without recording pupillary responses before the pupillometry session. The time of day of testing was counter-balanced such that half of the sample was administered these tests in the morning and half in the afternoon. Order of administration did not impact max span performance on the WMS-III ($t = –0.07$, $p = 0.944$).

Statistical analysis

Here we conducted non-genetic analyses in which the individual rather than the twin pair was the unit of analysis using linear mixed effects models in SAS (Proc Mixed, version 9.3). Unique identifiers nested within the pairs were entered as random effects with a varying intercept to allow for inter-subject variability. In proof-of-concept analyses, we examined the effect of ability level by dividing participants into 6 subgroups (≤4 to 9 + maximum span). Subsequent analyses examined differences in pupil dilation as a function of MCI group. Both sets of analyses proceeded in two stages. In stage 1, we compared group differences in pupil dilation at each of the three cognitive loads. In stage 2, we compared pupil dilation change (slope) from 3- to 6-digits and from 6- to 9-digits by testing group × digit-span condition interactions. Because we were interested in pupil dilation as a biomarker for prediction of early MCI, we focused particularly on planned comparisons between the CN group and the less severely impaired S-MCI groups. All models adjusted for the potential effects of age, pupillometry device, and medications with anticholinergic properties

(Supplementary Table 1). Results were based on type III test of fixed effects, indicating the unique association of each element of the model independent of the others.

Results

Sample characteristics

As shown in Table 1, CN and MCI groups did not differ significantly in age, education, depression, *APOE-ε*4 status, or baseline pupil diameter. MCI participants had a trend toward slightly fewer years of education relative to CN participants ($p = 0.09$). Some MCI participants had significantly lower GCA at age 20 and more frequent history of head injury. Maximum digit span did not differ between the CN and amnestic S-MCI groups, or between the non-amnestic S-MCI and M-MCI groups, but the former two groups had significantly longer maximum spans than the latter two groups *(ps* < 0.008, 0.05).

Proof of concept: Pupillary responses and compensatory effort

The maximum span groups were as follows: ≤4 (n=15), 5 (n=122), 6 (n=187), 7 ($n = 296$), 8 ($n = 210$), and ≥9 ($n = 88$) digits. Pupil dilation at the 3-digit load followed a stepwise increase exactly in the order of maximum span ability, with the greatest dilation (compensatory effort) in the ≤ 4-digit group and smallest dilation in the ≥ 9-digit group ($F_{(5375)} = 4.17$, $p < 0.002$). At the 6-digit load, the stepwise increase in pupil dilation with decreasing maximum span ability was largely preserved ($F_{(5i367)} = 3.48$, $p < 0.005$). At the 9-digit load, the relationship between maximum span and pupil dilation was largely reversed; individuals with lower maximum-span scores showed less dilation, but group differences were not significant overall ($F_{(5,355)} = 0.76$, $p = 0.58$) (see Fig. 1).

The maximum-span group × cognitive load interaction was significant ($F_{(10,1806)} = 5.10$, $p < 0.001$). Follow-up tests indicated that there were significant or near-significant group differences in slope from the 3-to6-digit loads ($F_{(5,911)} = 2.21$, $p = 0.051$) and from the 6- to 9-digit loads ($F_{(5,893)} = 7.98$, $p < 0.001$).

Pupillary responses and MCI status

Pupillary responses for the CN and MCI groups are presented in Fig. 2. Comparisons within each digit span condition are shown in Table 3. There were significant overall group differences in the 3-, 6-, and 9-digit conditions ($F_{(3,907)} = 4.15$, $p < 0.007$; $F_{(3,896)} = 4.02$, $p = 0.008$; $F_{(3,878)} = 2.90$, $p = 0.04$). At low and moderate loads (3-, 6-digits), amnestic S-MCI participants showed significantly greater pupil dilation than the other groups. At the high processing load (9-digits), non-amnestic S-MCI participants showed less pupil dilation than amnestic S-MCI or CN participants.

Table 4 shows pupillary response change estimates from 3- to 6-digits and from 6-to 9-digits for each group, as well as tests of between-group slope differences. There were significant group × cognitive load interactions ($F_{(6,1803)} = 3.96$, $p < 0.001$). Follow-up tests indicated that group differences were significant in slope from both 3- to 6-digits ($F_{(3,908)} = 3.18$, $p < 0.03$) and from 6-to 9-digits ($F_{(3,898)} = 3.14$, $p < 0.03$). As shown in Fig. 2, M-MCI participants showed minimal change in pupil dilation with changing processing demands.

This group was too small to subdivide for statistical analysis, but subgroups of 15 (60%) amnestic and 10 (40%) non-amnestic M-MCI participants both had similarly flat profiles. In contrast, the CN and S-MCI participants increased pupil dilation with increasing load from the 3- to 6-digit conditions and showed decreases in pupil dilation from the 6- to the 9-digit condition. Rate of change (slope) from the 3- to 6-digit conditions did not differ between CN, amnestic S-MCI, or non-amnestic S-MCI participants (Table 4). The slopes from 6- to 9-digits did not differ for the amnestic and non-amnestic S-MCI groups, but the non-amnestic S-MCI group showed a steeper drop in pupil dilation compared with the CN group (Table 4).

Results were similar in additional models that further adjusted for depression, head injury, *APOE* status, and maximum span. Comparisons with these covariates within each digit span condition are shown in Table 5. There were significant overall group differences in the 3-, and 6-digit conditions ($F_{(3,887)} = 3.79$, $p = 0.010$; $F_{(3,876)} = 4.39$, $p = 0.005$, while the 9-digit condition was reduced to a tend level effect ($F_{(3,858)} = 2.01$, $p = 0.11$). At low and moderate loads (3-, 6-digits), amnestic S-MCI participants showed significantly greater pupil dilation than the other groups. At the high processing load (9-digits), non-amnestic S-MCI participants showed less pupil dilation than amnestic S-MCI or CN participants.

Discussion

In proof-of-concept analyses, individuals with lower WMS-III maximum digit-span scores allocated greater cognitive effort to achieve the same performance as individuals with longer span capacity, suggesting pupillary responses reflected compensatory effort. This finding is consistent with research that found greater pupil dilation in healthy individuals with lower relative to higher cognitive abilities [17, 18]. As expected, pupil dilation dropped off at high processing loads (9-digits) for all groups except those who were not well beyond their capacity (i.e., those with maximum spans ≥ 8 digits).

In the MCI comparisons, individuals with more severe M-MCI did not show compensatory effort at any cognitive load and did not modulate cognitive resource allocation in accordance with changing task demands. In more advanced MCI, there appears to be a disconnect between cognitive effort and cognitive load, with little ability to appropriately adapt cognitive effort, suggesting that modulatory and compensatory functions have become exhausted with advancing disease.

Individuals with amnestic S-MCI showed significantly greater pupil dilation at low and moderate loads relative to both CN and non-amnestic S-MCI participants. These results suggest that pupil dilation in mild amnestic MCI reflects a need for greater compensatory effort in neural systems that are functioning less efficiently, but still efficiently enough to be able to exert and benefit from increased cognitive effort to maintain normal performance. The lack of a performance difference is consistent with amnestic MCI being defined by episodic memory impairment, rather than attention (digits forward). The trend toward greater drop-off from moderate to high loads in the amnestic S-MCI group relative to CN participants may also indicate neural systems becoming more easily overloaded at high loads. These results are consistent with functional MRI studies indicating greater

compensatory prefrontal activation in at-risk individuals with normal verbal learning performance, but not in individuals with abnormal performance [25, 26]. These results also suggest that pupil dilation at lower loads (e.g., 3- to 6-digit span conditions) may provide the best marker of risk for cognitive decline; perhaps in combination with other variables (e.g., performance, demographics, other risk biomarkers). Future research is needed to identify the optimal combination of predictors of risk for AD.

As noted, our results showed negligible changes after adjusting for digit span performance, indicating that the pupil dilation differences were not simply a reflection of differences in performance or capacity. On the other hand, the findings do suggest that task performance, pupil dilation at lower cognitive loads, and change in dilation with increased cognitive load must all be taken into account when drawing inferences about pupillary responses as a risk predictor. The non-amnestic S-MCI group did not show greater pupil dilation than CN participants and had significantly lower maximum spans than CN or amnestic S-MCI participants. Thus, they did not (perhaps could not) sufficiently increase effort to improve performance at low or moderate loads. They also showed significantly greater drop-off in pupil dilation at high processing loads compared to CN participants suggesting resource overload. Findings for the more severe M-MCI participants, who had lower maximum spans and did not modulate resource allocation according to processing load, were consistent with the notion that they were beyond their capacity to compensate. The M-MCI and non-amnestic S-MCI groups also had significantly lower GCA at age 20 compared with amnestic S-MCI or CN participants (see Table 1), consistent with reduced compensatory capacity due, in part, to lower cognitive reserve.

These impairments in compensatory capacity likely reflect dysfunction in the LC and related brain systems that modulate cognitive effort allocation. Increases in cognitive effort to improve performance appear to stem from interactions between the anterior attention system and the LC noradrenergic system [3, 6, 27–29]. This LC-attention network is associated with mental resource recruitment to manage cognitive load, and pupil dilation is a marker of activation in this network [4, 5, 7–11]. A link between LC activity and pupillary dilation is supported by single-cell recordings, pharmacological, and fMRI studies [4, 5, 7–11]. Pupillary responses are increasingly being used as a biomarker of the integrity of this LC neuromodulatory system [3–5]. Although controversial [30], degenerative changes in this LC-attention system have been found in the earliest stages of AD [12, 13, 31]. Postmortem data show that the LC is where tau protein misfolding may initially occur, and the formation of pre-tangle pathology first appears in its long projections before spreading to the cortex [2, 31]. Neurofibrillary tangles have been found in the LC [32, 33], and abnormal LC cell loss is well documented and becomes more prominent throughout the course of AD [34, 35]. The magnitude of LC degeneration and associated cortical noradrenergic depletion are also correlated with severity of dementia and cognitive impairment [36, 37]. Therefore, given the links between pupil dilation and functioning of the LC neuromodulatory system, as well as perhaps between the LC and AD, pupillary responses may provide a biomarker of functioning in a brain system that is affected in the earliest phases of AD.

Pupillary responses are associated with activation in multiple brain regions in addition to the LC, especially the anterior attention system. Increases in task performance with increasing

effort may stem from modulation of cortical resource allocation through interactions between the anterior attention system and LC noradrenergic system [3, 27–29, 38, 39]. For example, Raizada and Poldrack [6] showed that LC activation on fMRI correlated with task demands and that areas in the frontal, parietal, visual, and auditory cortex showed strong correlations with LC activation. This finding is consistent with the hypothesis that the LC system may facilitate the modulation and functional integration of brain areas involved in task performance. In another fMRI study [4], pupil diameter increased with the number of objects to be tracked (load) during a multiple object visual tracking task. Pupil dilation was correlated with activity in the LC, superior colliculus, right thalamus, and anterior attention network that manages competing demands for working memory resources [38]. Importantly, these studies showed that load-dependent activity in the anterior attention system and LC could be indexed in the autonomic periphery by pupillary dilation. Additional research is needed to link pupil dilation more specifically to pathology associated with MCI in LC and/or cortical regions with strong connections with LC.

In early MCI, when most cognitive performance is intact, performance does not always inform risk. Compensatory effort helps maintain performance until compensatory capacity is overloaded. With disease progression, dysfunction in the LC-attention system leads to failure to compensate and to modulate resource allocation in accordance with task demands. This LC-driven compensatory effort and resource modulation can be detected in the pupil and, when combined with behavioral performance, may inform risk and staging of LC pathology in the dementia pro-drome. Consistent with an inverted-U function, our results suggested increased compensatory effort to maintain performance in mild amnestic S-MCI, but reduced cognitive effort and failure to modulate effort in accordance with changing task demands in more severe M-MCI participants. In this latter group, we infer the LC-attention system was likely more dysfunctional. Despite early LC damage, compensation is still possible in preclinical individuals and early damage to the LC may actually result in a paradoxical increase in both LC firing rate and noradrenergic metabolism [40, 41].

This study has some limitations. Because our sample included only men and was primarily Caucasian, we cannot know how generalizable the results are to women or racial/ethnic minorities. Given the younger age range, we infer that AD is the predominant underlying pathophysiology of our MCI groups and that other pathologies (e.g., cerebrovascular disease, hippocampal sclerosis, TDP-43, Lewy bodies) are far less likely in this age cohort [42], although we did not measure for specific AD biomarkers. Only a longitudinal design with AD biomarkers (e.g., cerebrospinal fluid amyloid and p-tau) can confirm whether pupillary responses can provide a predictive biomarker of risk specific to AD-related declines. We hypothesize that those who show greater dilation at lower loads will be more likely to convert to MCI at VETSA follow-up.

In sum, when individuals achieve the same score, test performance is uninformative. A practical measure of the amount of cognitive effort needed to achieve that score, however, could serve as a predictor before cognitive performance declines. This simple, brief pupil dilation task, therefore, may provide a novel biomarker of AD risk linked to early impaired functionality of the LC years prior to diagnosis.

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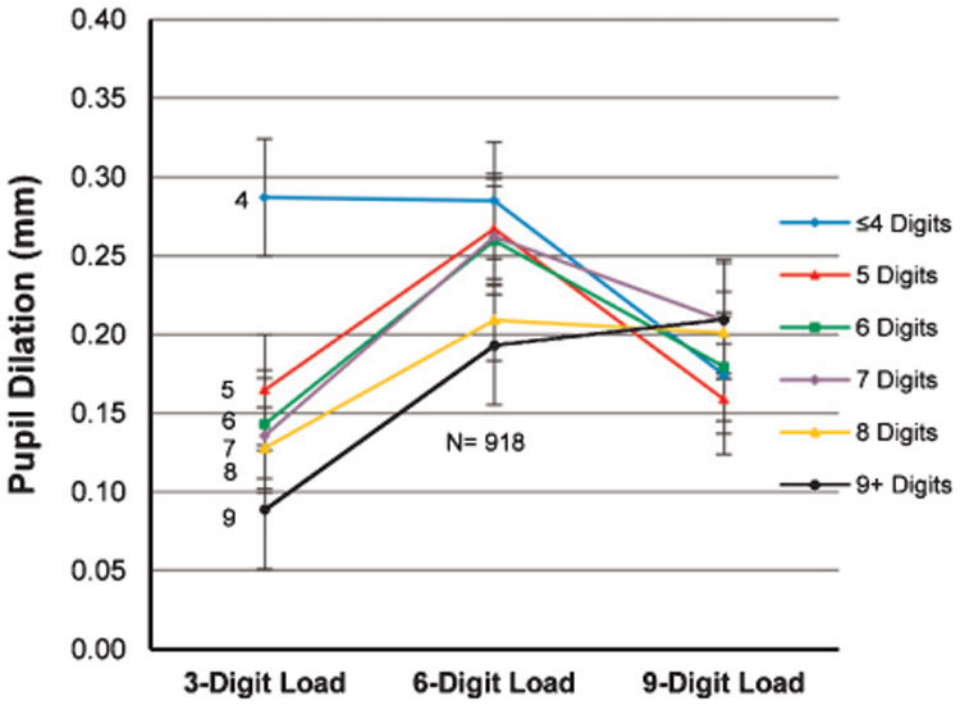

Fig. 1.

Model-derived estimates of pupillary responses (change relative to baseline) as a function of maximum digit span forward group.

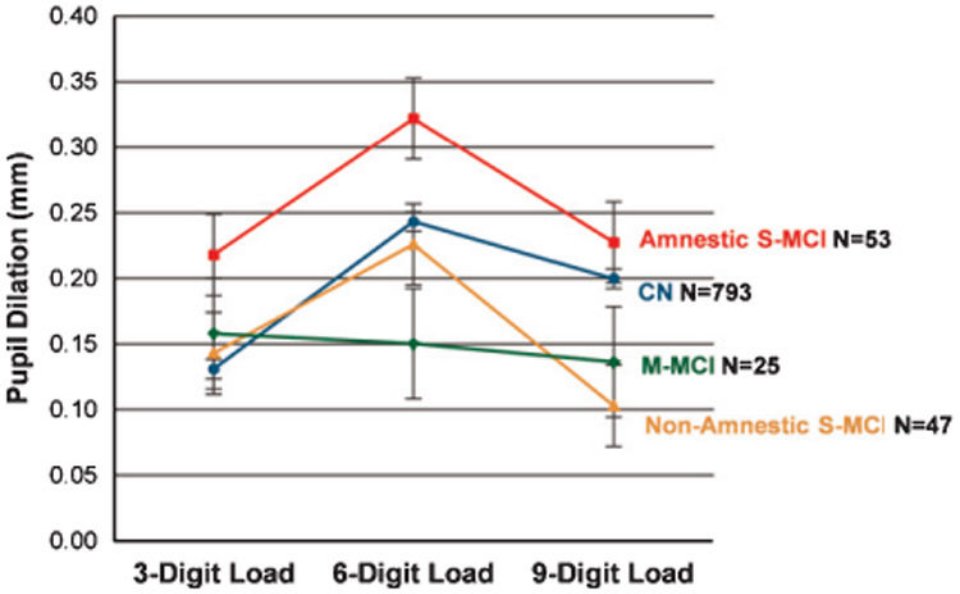

Fig. 2.

Model-derived estimates of pupillary responses (change relative to baseline) as a function of MCI status. CN, cognitively normal; S-MCI, single-domain; M-MCI, multiple-domain.

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Table 1

Sample characteristics

	Cognitively Normal (*n* = 793)	Single-Domain Non-Amnestic (*n* = 47)	Single-Domain Amnestic MCI (*n* = 53)	Multi-Domain MCI (*n* = 25)	*p*
Age (years)	61.5 (2.4) Range: 56–66	61.76 (2.5)	62.17 (2.3)	61.6 (2.6)	0.34
Education (years)	13.9 (2.1)	13.4 (2.0)	13.8 (1.8)	13.2 (2.0)	0.10
Age 20 AFQT (percentile)	62.2 (21.1)	52.9 (24.9)	65.0 (24.8)	53.4 (26.6)	0.05[a]
Max Digit Span Forward	7.0 (1.3)	6.4 (1.4)	6.8 (1.0)	6.1 (1.4)	0.002[b]
CES-D ≥ 16 (*n*, %)	92 (11.7%)	7 (15.2%)	9 (17.0%)	5 (20.8%)	0.35
History of Head Injury (*n*, %)	218 (27.5%)	11 (23.4%)	4 (7.6%)	7 (28.0%)	0.02[c]
APOE-ε4 Status (*n*, %)	241 (30.8%)	17 (36.2%)	16 (30.8%)	5 (20.8%)	0.63
Average baseline pupil diameter (mm)	3.3 (0.5)	3.2 (0.6)	3.3 (0.5)	3.2 (0.4)	0.29

Results are presented as mean and standard deviation unless otherwise specified. AFQT, Armed Forces Qualification Test; CES-D, Center for Epidemiological Studies Depression Scale.

[a] AFQT: Approximation of Cohen's d* effect sizes are 0.44–0.49 for all pairwise comparisons except the cognitively normal (CN) versus the amnestic single-domain MCI (S-MCI) group (d = 0.13).

[b] Max Digit Span: CN versus non-amnestic S-MCI (d = 0.46); CN versus multiple-domain MCI (M-MCI) (d = 0.69); amnestic S-MCI versus M-MCI (d = 0.62); non-amnestic S-MCI versus amnestic S-MCI (d = 0.34); non-amnestic S-MCI versus M-MCI (d = 0.21); CN versus amnestic S-MCI (d = 0.16).

[c] Head injury: All groups have significantly greater frequency of head injury compared to the amnestic single-domain MCI group.

[*] Effect sizes based on Cohen's d are approximate because there is no accepted way to determine exact effect sizes from mixed models.

Table 2
Neuropsychological tests and scores used to define MCI

Cognitive Domain	Tests and Measures	No. of Measures
Episodic Memory	CVLT-II: Sum of trials 1–5; delayed free recall (composite) *	3
	WMS-III: Logical memories immediate, delayed free recall (composite) *†	
	WMS-III: Visual reproduction immediate and delayed free recall (composite) *	
Executive Function	DKEFS Trails: Switching (condition 4)	4
	DKEFS Fluency: Category switching	
	Stroop: Color-word, interference	
	WASI: Matrix reasoning	
Attention/Working Memory	WMS-III: Digit span	4
	WMS-III: Spatial span	
	WMS-III: Letter-number sequencing	
	DKEFS Trails: Cancellations (condition 1)	
Verbal/Language	DKEFS: Letter fluency	2
	DKEFS: Category fluency	
Visual-Spatial	Gottschaldt Hidden Figures	3
	Card rotation	
	WMS-III: Visual reproduction copy	
Processing Speed	DKEFS Trails: Number sequencing, letter sequencing (conditions 2 and 3 composite) *	2
	Stroop: Word condition, color condition (composite) *	

CVLT-II, California Verbal Learning Test–Version II; WMS-III, Wechsler Memory Scale–Version III; DKEFS, Delis-Kaplan Executive Function System; WASI, Wechsler Abbreviated Scale of Intelligence.

*Composite refers to the mean of two measures.

†Standard WMS-III instructions call for reading the second Logical Memories story a second time, but it was read only once in our administration.

Table 3

Within condition differences in pupillary responses as a function of MCI status

	Estimate	SE	95% CI	DF	*t*	*p*	*d*
3 Digit Load							
Normal versus Single Non-Amnestic	−0.006	0.024	(−0.053; 0.042)	887	−0.24	0.813	0.032
Normal versus Single Amnestic	−0.082	0.023	(−0.128; −0.036)	909	−3.52	<0.001	0.464
Normal versus Multi-Domain	−0.013	0.033	(−0.077; 0.052)	914	−0.38	0.704	0.070
Single Non-Amnestic versus Single Amnestic	−0.076	0.032	(−0.140; −0.013)	898	−2.35	0.019	0.469
Single Non-Amnestic versus Multi-Domain	−0.007	0.040	(−0.085; 0.072)	902	−0.17	0.866	0.042
Single Amnestic versus Multi-Domain	0.069	0.039	(−0.008; 0.146)	913	1.77	0.077	0.430
6 Digit Load							
Normal versus Single Non-Amnestic	0.016	0.032	(−0.046; 0.079)	878	0.51	0.607	0.072
Normal versus Single Amnestic	−0.069	0.031	(−0.129; −0.008)	898	−2.23	0.026	0.302
Normal versus Multi-Domain	0.105	0.042	(0.022; 0.189)	903	2.48	0.013	0.464
Single Non-Amnestic versus Single Amnestic	−0.085	0.043	(−0.168; −0.001)	889	−1.99	0.047	0.399
Single Non-Amnestic versus Multi-Domain	0.089	0.052	(−0.013; 0.191)	889	1.72	0.086	0.426
Single Amnestic versus Multi-Domain	0.174	0.051	(0.074;0.274)	902	3.41	0.001	0.821
9 Digit Load							
Normal versus Single Non-Amnestic	0.086	0.038	(0.012; 0.159)	865	2.28	0.023	0.328
Normal versus Single Amnestic	−0.024	0.035	(−0.094; 0.045)	879	−0.69	0.491	0.093
Normal versus Multi-Domain	0.089	0.052	(−0.012; 0.190)	886	1.73	0.084	0.341
Single Non-Amnestic versus Single Amnestic	−0.110	0.050	(−0.207; −0.013)	872	−2.21	0.027	0.443
Single Non-Amnestic versus Multi-Domain	0.004	0.062	(−0.119; 0.126)	873	0.06	0.955	0.018
Single Amnestic versus Multi-Domain	0.113	0.061	(−0.006; 0.233)	885	1.86	0.063	0.457

Table 4

Between condition change (slope) in pupillary responses as a function of MCI status

	Estimate	SE	95% CI	DF	*t*	*p*	*D*
3 to 6 Digit Load							
Normal versus Single Non-Amnestic	−0.029	0.032	(−0.092; 0.033)	1796	−0.92	0.359	0.140
Normal versus Single Amnestic	−0.008	0.030	(−0.066; 0.052)	1799	−0.26	0.795	0.037
Normal versus Multi-Domain	−0.120	0.042	(−0.203; −0.037)	1784	−2.84	0.005	0.575
Single Non-Amnestic versus Single Amnestic	0.021	0.042	(−0.062; 0.104)	1798	0.51	0.613	0.102
Single Non-Amnestic versus Multi-Domain	−0.091	0.052	(−0.192; 0.012)	1788	−1.75	0.080	0.436
Single Amnestic versus Multi-Domain	−0.112	0.051	(−0.211; −0.013)	1789	−2.21	0.027	0.541
6 to 9 Digit Load							
Normal versus Single Non-Amnestic	0.080	0.033	(0.016; 0.143)	1801	2.44	0.015	0.376
Normal versus Single Amnestic	0.051	0.030	(−0.008; 0.112)	1799	1.70	0.090	0.244
Normal versus Multi-Domain	−0.030	0.044	(−0.116; 0.057)	1816	−0.67	0.503	0.140
Single Non-Amnestic versus Single Amnestic	−0.028	0.043	(−0.113; 0.057)	1801	−0.65	0.517	0.132
Single Non-Amnestic versus Multi-Domain	−0.109	0.054	(−0.214; −0.004)	1812	−2.03	0.043	0.509
Single Amnestic versus Multi-Domain	−0.081	0.052	(−0.184; 0.022)	1812	−1.55	0.123	0.381

Table 5

Within condition differences in pupillary response as a function of MCI status, controlling for maximum digit span.

	Estimate	SE	95% CI	DF	*t*	*p*	*d*
3 Digit Load							
Normal versus Single Non-Amnestic	0.002	0.024	(−0.045; 0.050)	889	0.09	0.928	0.014
Normal versus Single Amnestic	−0.080	0.023	(−0.125; −0.034)	908	−3.45	0.001	0.449
Normal versus Multi-Domain	−0.001	0.033	(−0.065; 0.063)	914	−0.03	0.978	0.006
Single Non-Amnestic versus Single Amnestic	−0.082	0.032	(−0.145; −0.020)	901	−2.54	0.011	0.517
Single Non-Amnestic versus Multi-Domain	−0.003	0.040	(−0.081; 0.075)	904	−0.08	0.937	0.020
Single Amnestic versus Multi-Domain	0.079	0.039	(0.002; 0.155)	913	2.02	0.044	0.497
6 Digit Load							
Normal versus Single Non-Amnestic	0.028	0.032	(−0.035; 0.090)	874	0.87	0.383	0.131
Normal versus Single Amnestic	−0.066	0.030	(−0.125; −0.006)	899	−2.16	0.031	0.306
Normal versus Multi-Domain	0.123	0.042	(0.039; 0.206)	902	2.91	0.004	0.591
Single Non-Amnestic versus Single Amnestic	−0.093	0.042	(−0.176; −0.010)	887	−2.21	0.028	0.448
Single Non-Amnestic versus Multi-Domain	0.095	0.051	(−0.006; 0.196)	887	1.86	0.064	0.446
Single Amnestic versus Multi-Domain	0.188	0.051	(0.089; 0.288)	902	3.71	<0.001	0.948
9 Digit Load							
Normal versus Single Non-Amnestic	0.082	0.038	(0.008; 0.156)	865	2.19	0.029	0.328
Normal versus Single Amnestic	−0.025	0.035	(−0.094; 0.044)	878	−0.71	0.477	0.101
Normal versus Multi-Domain	0.085	0.052	(−0.016; 0.186)	885	1.65	0.100	0.335
Single Non-Amnestic versus Single Amnestic	−0.107	0.050	(−0.205; −0.010)	873	−2.16	0.031	0.438
Single Non-Amnestic versus Multi-Domain	0.003	0.062	(−0.119; 0.125)	873	0.04	0.965	0.011
Single Amnestic versus Multi-Domain	0.110	0.061	(−0.010; 0.230)	885	1.80	0.072	0.443