PupilMetrics Neuro

Clinical Pupillometry Platform for Neurological Assessment and TBI Recovery Monitoring

Vision

The human pupil is one of the most underutilized diagnostic tools in medicine. It is the only part of the central nervous system visible to the naked eye — a direct, real-time readout of brainstem function that requires no blood draw, no radiation, no sedation, and no patient cooperation beyond simply opening their eyes.

PupilMetrics Neuro was built on a single clinical premise: if the brain is healing, the pupil will show it.

This application is designed for neurologists, concussion clinics, sports medicine physicians, and clinical researchers who need a quantitative, repeatable, and scientifically grounded tool to:

- Establish a pupillary baseline at initial presentation
- Track pupillary light reflex (PLR) metrics across serial visits
- Detect subtle autonomic changes that may precede or accompany clinical recovery
- Monitor the effects of CNS-active medications on pupillary tone
- Identify bilateral asymmetry (anisocoria) that may signal lateralized neurological compromise

This is not a screening tool for impairment, substance use, or employment fitness. It is a clinical monitoring instrument — built to measure healing, not to make accusations.

The Science: Why the Pupil Reflects Brain Health

The Pupillary Light Reflex Pathway

When light strikes the retina, it triggers one of the most anatomically rich reflexes in neurology. Understanding that pathway explains why PLR metrics are so sensitive to brain injury.

Afferent limb (incoming signal):
Light → Retinal ganglion cells → Optic nerve (CN II) → Optic chiasm → Pretectal nucleus (dorsal midbrain)

Efferent parasympathetic limb (constriction):
Pretectal nucleus → Edinger-Westphal nucleus (midbrain) → Oculomotor nerve (CN III) → Ciliary ganglion → Pupillary sphincter → **Constriction**

Efferent sympathetic limb (dilation):
Hypothalamus → Ciliospinal center (C8–T2) → Superior cervical ganglion → Long ciliary nerve → Pupillary dilator → **Dilation**

This reflex arc passes through the midbrain, upper brainstem, and involves both parasympathetic and sympathetic tone. Traumatic brain injury disrupts these pathways in measurable, graded ways.

How TBI Alters the Pupil

Traumatic brain injury produces pupillary changes through several distinct mechanisms:

1. Direct brainstem injury
The pretectal nucleus, Edinger-Westphal nucleus, and oculomotor fascicles lie in the midbrain — a region particularly vulnerable to rotational acceleration-deceleration forces (the hallmark of concussion). Even mild diffuse axonal injury (DAI) at these structures produces measurable slowing of PLR latency and constriction velocity before any clinical signs appear.

2. Elevated intracranial pressure (ICP)
As ICP rises, the uncus of the temporal lobe herniates through the tentorium and compresses CN III. The earliest sign is a sluggish, asymmetric PLR — detectable by pupillometry before the pupil becomes visibly abnormal on exam. In severe cases, this produces the classic "blown pupil" of transtentorial herniation.

3. Autonomic dysregulation
TBI consistently disrupts the hypothalamic-brainstem autonomic network. This manifests as abnormal resting pupil size (too small or too large for ambient conditions), delayed sympathetic redilatation after the flash, and increased pupil unrest (hippus amplitude). These are not dramatic signs — they are subtle shifts in autonomic tone that accumulate into a measurable clinical picture.

4. Cortical modulation loss
The cortex, particularly the frontal lobe, normally modulates PLR habituation — the progressive reduction in response amplitude across repeated stimuli. A healthy brain habituates by 0–15% across three trials. Loss of cortical inhibitory input after TBI can produce either excessive habituation (>25%) or paradoxical sensitization (negative habituation index), both of which indicate disrupted cortico-midbrain feedback loops.

Key PLR Metrics and Their Neurological Significance

Metric	Normal Range	What It Reflects
Baseline pupil diameter	3–7 mm (photopic)	Sympathetic/parasympathetic resting tone; affected early in autonomic dysregulation
PLR latency	200–300 ms	Signal propagation through pretectal nucleus; slows with midbrain injury or elevated ICP
Constriction amplitude	20–40%	Integrity of parasympathetic efferent limb (CN III, Edinger-Westphal); primary TBI marker
Constriction velocity	3–8 mm/sec	Brainstem processing speed; sensitive to diffuse axonal injury

Redilatation velocity	2–5 mm/sec	Sympathetic recovery; disrupted in autonomic dysfunction
Anisocoria	<1 mm	Bilateral symmetry of neurological function; >1 mm is clinically significant
Habituation index	0–15%	Cortical modulation of the PLR; reflects frontal-midbrain circuit integrity

The Dark-Adapted Baseline: Why 3 Seconds Matters

A fundamental design decision in PupilMetrics Neuro is the **3-second dark baseline before the PLR flash**. This is not arbitrary — it is grounded in the photoreceptor adaptation physiology.

Under constant dim illumination, the pupillary sphincter maintains partial constriction through ongoing parasympathetic drive. The dynamic range available for a subsequent light-evoked constriction is therefore reduced. By extinguishing all light for 3 full seconds before the flash:

- Rod photoreceptors begin scotopic adaptation, increasing retinal sensitivity
- The pupillary dilator maximizes dilation under sympathetic drive
- Baseline pupil diameter reaches its true dark-adapted maximum
- The subsequent PLR amplitude is measured from a consistent, maximally dilated starting point

In our testing, this change alone increased measured constriction amplitude from approximately 6 percentage points (with a dim LED baseline) to 17+ percentage points — a nearly threefold improvement in the measurable signal. This matters clinically: a patient with a true 15% amplitude recorded with a contaminated baseline might appear to have only 5%, pushing them below detection threshold and producing a false-negative result.

Real Timestamps: The Frame Rate Problem

Dino-Lite iriscope recording through the Windows COM bridge presents a subtle but clinically significant challenge: the USB frame capture call (`GrabFrame()`) blocks the UI thread for approximately 90 milliseconds per call, producing an actual frame rate of ~11 fps — not the nominal 30 fps. If timestamps are assigned as `frame_index × 33 ms`, the PLR analysis pipeline places the stimulus onset at the wrong time, misclassifies baseline frames as post-stimulus frames, and produces artifactual or undetected PLR results.

PupilMetrics Neuro solves this by **embedding actual wall-clock timestamps in every frame filename** at the moment of capture — `frame_000031_0003038.jpg` indicates the 31st frame was captured at exactly 3038 ms after recording start. The analysis pipeline reads these timestamps directly, ensuring that the baseline window (0–3000 ms) and post-stimulus window (3100–5600 ms) are correctly assigned regardless of actual frame rate variability.

This is the difference between a research-grade measurement and a consumer-grade approximation.

What PupilMetrics Neuro Delivers

PLR Recording and Analysis

The core of PupilMetrics Neuro is a structured, protocol-driven PLR capture using the Dino-Lite digital iriscope on Windows desktop. Each recording follows a precise sequence:

1. **3-second dark baseline** — LED off, pupil dilates to maximum dark-adapted diameter
2. **Single bright flash at 3000 ms** — 200 ms duration, capturing the full constriction response
3. **2.6-second recovery recording** — capturing redilatation kinetics
4. **Automated frame analysis** — pupil detection and tracking across all captured frames
5. **5-point median smoothing** — eliminates single-frame noise artifacts before metric extraction
6. **Grade assignment** — A through F based on signal-to-noise ratio and constriction amplitude

Each analysis report includes baseline diameter, constriction amplitude, percent constriction, latency estimate, and overall PLR grade with clinical interpretation.

3-Trial Habituation Protocol

The drug monitoring and habituation assessment module runs three consecutive PLR trials with standardized rest intervals, producing:

- **Per-trial metrics** — baseline diameter, constriction amplitude, and percent constriction
- **Habituation index** — `(Trial 1 - Trial 3) / Trial 1 × 100%`
  - 0–15%: Normal cortical modulation
  - 15–30%: Moderate habituation, may indicate cortical involvement
  - >30%: Excessive habituation — disrupted cortico-midbrain feedback
  - Negative: Sensitization — paradoxical increase across trials
- **Waveform overlay** — three PLR curves displayed on a single timeline for direct visual comparison

CNS Pharmacological Monitoring

The Drug Effect Monitor applies the same 3-trial PLR protocol to assess the pharmacological state of the autonomic nervous system. The scientific basis is well-established:

CNS Depressants (opioids, benzodiazepines, barbiturates, alcohol, general anesthetics) act at GABA-A receptors and opioid receptors in the brainstem and cortex, producing miosis and reduced PLR amplitude through suppression of Edinger-Westphal nucleus activity and increased parasympathetic tone.

CNS Stimulants (amphetamines, cocaine, MDMA, norepinephrine reuptake inhibitors) act at monoaminergic synapses, producing mydriasis through peripheral sympathomimetic effects on the pupillary dilator and central suppression of parasympathetic tone.

A critical ethical constraint is built into every pattern interpretation: the system displays a comprehensive list of prescribed medications that produce identical pupillary findings. A miotic, hypo-reactive pupil pattern is equally consistent with morphine for post-operative pain, methadone for addiction treatment, clonidine for ADHD, or simply profound exhaustion. PupilMetrics Neuro presents the physiological finding — the clinical context is the physician's domain.

This module was conceived following the pioneering work of clinical researchers in the late 1990s and early 2000s who recognized that objective pupillometry could provide a pharmacodynamic endpoint for CNS drug effects without requiring invasive biomarker collection. This application brings that concept into a modern, integrated, clinical workflow.

Bilateral Comparison and Anisocoria Detection

Every bilateral scan computes the absolute difference in pupil-iris ratio between right (OD) and left (OS) eyes. Anisocoria exceeding physiological norms is flagged with severity grading:

- **Physiological** (<5%): Common in healthy individuals, no neurological significance
- **Mild** (5–10%): Warrants monitoring, particularly in serial scans showing progression
- **Significant** (>10%): Requires clinical evaluation for CN III palsy, Horner syndrome, or asymmetric intracranial pathology

Tracking anisocoria across serial visits transforms a single ambiguous finding into a trend — and trends are what drive clinical decisions in TBI recovery.

Serial Trend Monitoring

Recovery from TBI is not a single event — it is a trajectory that unfolds over days, weeks, and months. The PLR Sessions screen in PupilMetrics Neuro allows clinicians to load past scans and compare PLR metrics across time, building an objective longitudinal record of:

- Pupillary diameter normalization (autonomic tone recovery)
- PLR amplitude improvement (parasympathetic efferent recovery)
- Anisocoria resolution (bilateral symmetry restoration)
- Habituation normalization (cortical-midbrain circuit recovery)

A patient who presents with a Grade D PLR at day 3 post-concussion and a Grade A PLR at week 6 has demonstrated measurable neurological improvement — documented, timestamped, and exportable to PDF for the clinical record.

Target Clinical Applications

Concussion Clinics and Sports Medicine

Sports-related concussion (SRC) produces a characteristic constellation of neurological impairments, many of which resolve over days to weeks. PLR metrics are sensitive to the acute phase (within 72 hours) when standard neurological examination is often normal. PupilMetrics Neuro enables:

- Sideline baseline capture (pre-season reference data)
- Post-injury quantitative assessment within hours of the event
- Serial monitoring to establish return-to-play readiness
- Documentation for regulatory bodies (athletic commissions, school sports programs)
- Research data collection for outcome studies

The objective, timestamped PLR record provides evidence that a return-to-play decision was based on measurable neurological recovery — not athlete self-report alone.

Neurology and Neurotrauma

For neurologists managing TBI patients from mild concussion through severe traumatic injury, PupilMetrics Neuro provides a bedside-capable, quantitative pupillometry platform that complements existing tools:

- Serial PLR monitoring in the ICU or clinic setting
- Early detection of neurological deterioration before clinical signs
- Autonomic function assessment in patients with brainstem pathology
- Pharmacodynamic monitoring of CNS-active medications
- Longitudinal documentation for medicolegal and disability proceedings

Clinical Research

For researchers investigating neurological recovery, autonomic function, or CNS pharmacology, PupilMetrics Neuro provides:

- Structured, protocol-driven data collection
- Machine-readable JSON export of all PLR metrics
- Consistent, reproducible measurement conditions (dark-adapted baseline, calibrated flash)
- Multi-trial habituation protocols
- Bilateral comparative data
- PDF reports suitable for case documentation and publication figures

The Technology Stack

PupilMetrics Neuro is built on a modern, cross-platform foundation:

- **Flutter** (Dart) — cross-platform UI targeting Windows desktop (primary), iOS, and Android
- **Dino-Lite Digital Iriscope** — USB-connected clinical-grade eye imaging device with built-in LED

- **32-bit C# COM bridge** — interfaces with the DNVideoX SDK for frame capture and LED control, communicating with the Flutter application via file-based IPC
- **ONNX Runtime** — on-device machine learning inference for hybrid pupil detection (classical CV + ML ensemble)
- **SQLite** — local scan history with full anonymization support
- **PDF export** — structured clinical reports via the `printing` package

All processing is performed locally — no cloud connectivity is required for clinical operation. Patient data never leaves the device.

A Note on Scientific Validation

PupilMetrics Neuro is a clinical monitoring tool intended to support, not replace, physician judgment. The PLR metrics it measures are grounded in decades of established neurophysiology and are consistent with the quantitative pupillometry literature. However, this specific software has not been submitted for FDA 510(k) clearance or CE marking, and its outputs should be interpreted by qualified clinicians in the context of the full clinical picture.

The goal is to put a research-grade measurement in the hands of every clinician who works with neurologically vulnerable patients — and to make objective, longitudinal pupillary data as routine as a blood pressure cuff.

PupilMetrics Neuro — developed at CNRI. Built to measure healing.