

## REVIEW

*This paper is dedicated to the 70<sup>th</sup> anniversary of the founding  
of Physiologia Bohemoslovaca (currently Physiological Research)*

## Eye Pupil – A Window into Central Autonomic Regulation via Emotional/Cognitive Processing

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### Summary

If the eyes are windows into the soul, then the pupils represent at least the gateway to the brain and can provide a unique insight into the human mind from several aspects. The changes in the pupil size primarily mediated by different lighting conditions are controlled by the autonomic nervous system regulated predominantly at the subcortical level. Specifically, parasympathetically-linked pupillary constriction is under the Edinger-Westphal nucleus control and sympathetically-mediated pupillary dilation is regulated from the posterior hypothalamic nuclei. However, the changes in the pupil size can be observed at resting state even under constant lighting, these pupillary changes are mediated by global arousal level as well as by various cognitive factors. In this context, autonomic pathways modulating changes in the pupil size in response to the different light levels can be influenced by multiple central descending inputs driving pupillary changes under steady lighting conditions. Moreover, as the pupillary response is involved in emotional (task-evoked pupillary dilation as an index of emotional arousal) and cognitive (task-evoked pupillary dilation as an index of cognitive workload) stimulation, it can be used to detect the impact of mutual subcortical and cortical structures (i.e. overlapping brain structures included in autonomic, emotional and cognitive regulation) on the pupillary innervation system. Thus, complex understanding of the baseline pupil size' and pupillary dynamics' mechanisms may provide an important insight into the central nervous system functioning pointing to the pupillometry as a promising tool in the clinical application.

### Key words

Pupil size • Pupillary light reflex • Autonomic regulation • Emotional and cognitive processes • Clinical application

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### Introduction

Autonomic nervous system (ANS) activity under central control plays a crucial role in the maintaining of body's homeostasis. However, disturbances in the central-peripheral autonomic integrity as well as dynamic imbalance between the parasympathetic and the sympathetic nervous system activity may represent important pathomechanisms in the development of various disorders (e.g. Boyce *et al.* 2001, Thayer *et al.* 2010). In this context, pupillary changes (mediated by the parasympathetic and sympathetic nervous system) commonly categorized as tonic pupil size and phasic pupillary response in the pupillometric research (Mathôt 2018), may provide a "window" into the complex psychophysiological regulatory network mechanisms. More specifically, the evaluation of the pupil size and pupillary reactivity to the light stimulation (pupillary light reflex – PLR) by automated pupillometry (enabling the quantification of the parasympathetic and the sympathetic-linked pupillary control) may provide an unique insight into autonomic regulation (Hall and Chilcott 2018). Further, as emotional and cognitive influences are commonly indexed by various

physiological behaviors predominantly mediated by ANS, including pupillary response, the assessment of the pupillary reactivity to emotional and cognitive stimuli (i.e. task-evoked stimulation) is thus increasingly used to identify potential abnormalities in emotional/cognitive processing (Bradley *et al.* 2008, Einhäuser 2017). This review is aimed to summarize the significance of the changes in the pupil size/reactivity in the integrity of central autonomic, emotional, and cognitive regulation whose abnormalities are associated with various disorders, and to point out a significance of the pupillometric measurement in direct clinical application.

## **Pupil as a window into the complex autonomic integrity**

### *Pupil size regulation under ambient lighting conditions*

In everyday life, the pupil size is strongly influenced by the ambient lighting. Thus, the fundamental function of the autonomic pathways regulating the pupil size is to regulate the amount of light illuminating the retina. In other words, the pupil size under the global ambient lighting conditions is regulated by the balanced activity of the sympathetic and parasympathetic nervous systems. Specifically, higher levels of ambient lighting conditions predominantly lead to greater activation of the parasympathetic nervous system regulated from Edinger-Westphal (E-W) nucleus resulting in the pupillary constriction. More specifically, higher lighting levels stimulate retinal photoreceptors, bipolar cells, and retinal ganglion cells. Retinal signals are transmitted to the pretectum of the mesencephalon and subsequently to the E-W nuclei in the midbrain. Preganglionic parasympathetic axons of the cholinergic neurons of E-W nuclei synapse with the ciliary ganglion neurons that send postganglionic axons innervating the iris sphincter muscle resulting in parasympathetic-mediated pupillary constriction (McDougal and Gamlin 2015). Contrary, lower levels of ambient lighting conditions lead to greater activation of the sympathetic nervous system regulated from posterior hypothalamic nuclei synapsing at the intermediolateral (IML) cell column of the cervical/thoracic spinal cord and subsequently superior cervical ganglion (SCG) that sends postganglionic axons to innervate *via* the ciliary nerves the contraction of the iris dilator muscle resulting in the pupillary dilation (Cherng *et al.* 2020). Besides relatively straightforward parasympathetic and sympathetic pathways there exist other autonomic pathways controlling pupil size that are

less understood. From this aspect, pupillary constriction may also involve high levels of ambient lighting conditions-related inhibition of the sympathetic tone resulting in the iris dilator muscle relaxation. Similarly, pupillary dilation may involve low levels of ambient lighting conditions-linked parasympathetic withdrawal resulting in the iris sphincter muscle relaxation (Lowenstein and Loewenfeld 1950, McDougal and Gamlin 2015, Joshi and Gold 2020).

### *Pupil size regulation to standardized light stimulus - pupillary light reflex*

Pupillary light reflex (PLR), i.e. pupillary constriction (mediated by the contraction of the parasympathetically-innervated iris sphincter muscle) and subsequent pupillary dilation (mediated by the contraction of sympathetically-innervated iris dilator muscle) of the pupil in response to the standardized intensity and length of the light stimulation by using automated pupillometers that offer an opportunity for quantifying the parasympathetic as well as the sympathetic regulation of the pupil indexed by different PLR parameters, may provide an important metric of autonomic nervous system integrity (Girkin 2003, Hall and Chilcott 2018). Firstly, the initial pupil diameter (reflecting baseline pupil size) is assessed before measuring the dynamics of PLR consisting of pupillary response latency (time delay between the light onset and start of the constriction) followed by pupillary constriction (until the minimal pupil size is reached) and consequent pupillary redilation to the baseline pupil size (initial pupil diameter) (Hall and Chilcott 2018). Constriction phase-linked PLR parameters (i.e. parameters under direct parasympathetic control) such as absolute and relative constriction amplitude (ACA, RCA), and maximum constriction velocity (MCV) represent the most commonly used indices for detecting the parasympathetic (dys)function (Hall and Chilcott 2018, Wang *et al.* 2016). As sympathetic activity-linked PLR parameter we can consider the time required for the pupil diameter to return to 75 % of the baseline pupil diameter from the peak of the pupillary constriction (T75) (Lowenstein and Loewenfeld 1950). In addition, Muppidi *et al.* (2013) proposed other indices associated with the pupillary redilation phase such as dilation velocity at T75 (DV75), and a ratio of T75 and ACA as other potential markers of the sympathetic (dys)function.

Interestingly, while the light stimulation has a robust effect on the parasympathetic activity, it has

a dual (inhibitory and stimulatory) effect on the sympathetic activity. Thus, the sympathetic outflow is controlled by separate light-inhibited and light-stimulated pathways during the PLR. The light-inhibited sympathetic pathways originating in the retina-receptive neurons of the pretectum and the suprachiasmatic nucleus are coupled with the parasympathetic pathway mediating the PLR (Szabadi 2018). In other words, parasympathetic-linked pupillary constriction is facilitated by concurrent inhibition of the sympathetic-mediated pupillary dilation (McDougal and Gamlin 2015). Further, the light-stimulated sympathetic pathways involve the noradrenergic and serotonergic ones (Szabadi 2018). The hub of the noradrenergic pathway is the locus coeruleus (LC) – primary source of the noradrenaline in the central nervous system regulating thus global arousal (Aston-Jones and Waterhouse 2016) – functioning as sympathetic as well as parasympathetic nucleus. More specifically, LC contains both excitatory sympathetic neurons projecting to the sympathetic preganglionic neurons in the spinal cord and inhibitory parasympathetic neurons projecting to the E-W nucleus. The excitatory sympathetic LC neurons stimulated by the light *via* the retina – suprachiasmatic nucleus – dorsomedial hypothalamus – LC pathway can lead to the increased output to the pupil *via* LC – IML – SCG – dilator muscle pathway mediating the pupillary dilation (González and Aston-Jones 2006, Szabadi 2018). The hub of serotonergic pathway is the dorsal raphe nucleus containing serotonergic neurons, some of which function as sympathetic neurons projecting to the IML where by 5-HT<sub>2A</sub> receptors' stimulation mediate the sympathetic-linked dilation effect on the pupil (Hornung 2003, Szabadi 2018).

#### *Pupil as an insight into central autonomic network*

Notably, the noradrenergic sympathetic pathway can be through the multiple inputs modulated by variety of physiological and psychological influences, and consequently through its outputs transmit these modulations to the pupillary response (Szabadi 2018). Further, this pathway is *via* LC-linked sympathetic and parasympathetic widespread connections integrated into wider central autonomic network (Samuels and Szabadi 2008, Szabadi 2013). Central autonomic network (CAN) described by Benarroch (1993) represents an integrated system of brainstem, subcortical, and cortical structures that play a key role in ANS functioning. Structurally, CAN consists of the anterior cingulate, the insular, and

the ventromedial prefrontal cortices, the central nucleus of the amygdala, the paraventricular and related nuclei of the hypothalamus, the periaqueductal gray matter, the parabrachial nucleus, the nucleus of the solitary tract, the nucleus ambiguus, the ventrolateral and the ventromedial medulla, and the medullary tegmental field (Benarroch 1993). Importantly, while in the sympathetic regulation are involved the prefrontal, the anterior, and the mid cingulate, the right ventral anterior insular, and the left posterior insular cortices; the parasympathetic regulation is controlled by the cingulate cortex, the lateral temporal cortices, the bilateral dorsal insular cortices, and the hippocampus. Some regions such as the left amygdala, the right inferior parietal lobule, and a small area in the right anterior insular cortices have shown a dual role in both sympathetic and parasympathetic regulation (Beissner *et al.* 2013). Notably, many of the structures within the CAN overlap with important brain regions involved in other central networks such as emotional and cognitive circuits (Sklerov *et al.* 2019). From this perspective, autonomic pathways mediating changes of the pupil size and PLR are influenced by central emotionally/cognitively-driven descending inputs from multiple brain regions. To sum, the evaluation of the baseline pupil size and pupillary dynamics to the standardized light stimulus (by automated pupillometers) may help unravel the complexity of autonomic regulation and provide a simple, non-invasive method for broader application in the neuroscience research (Hall and Chilcott 2018), as discussed below.

### **Pupil as a window into the cognitive and emotional processes**

#### *Baseline pupil size*

Baseline pupil diameter refers to spontaneous fluctuations in the pupil size (Peysakhovich *et al.* 2017). During visual experiments, the baseline pupil size indicating spontaneous fluctuations under resting-state is measured when an individual is not performing any task, often while viewing a screen with a uniform or neutral background with no meaningful stimuli to attend (except a fixation point) (Aminihajibashi *et al.* 2019). From psychophysiological point of view, the baseline pupil size is associated with individual cognitive-related differences in higher-order cognitive abilities such as fluid intelligence, working memory capacity, and attention control (Tsukahara *et al.* 2016, Tsukahara and Engle 2021, Unsworth and Robinson 2017, Unsworth *et al.*

2019). Tsukahara *et al.* 2016 proposed that it is predominantly fluid intelligence that is linked to the baseline pupil size and that individual differences in fluid intelligence are related to the functional organisation of the resting-state brain arising from neuromodulatory role of the LC-noradrenaline system. More specifically, larger baseline pupil size may reflect stronger functional brain connectivity originating from optimal baseline activity of the LC (Tsukahara *et al.* 2016).

#### *Task-evoked pupillary response to the emotional/cognitive stimuli*

*Task-evoked*, also called event-related pupillary response usually measured as a change relative to the baseline pupil diameter, refers to the pupillary changes during the task performing and therefore is directly associated with task-related processes (Aminihajbashi *et al.* 2020). The most commonly observed pupillary response following emotional and cognitive stimulation is pupillary dilation that can be driven by sympathetic activation or parasympathetic inhibition (or reduced parasympathetic activation). However, the relative contributions of the sympathetic and parasympathetic nervous systems on the pupillary response induced by emotion and cognition may be different (Cherng *et al.* 2020). Changes of the ANS activity during the emotional processes may provide important information related to the main emotional dimensions – arousal (reflecting psychophysiological levels of activation) and valence (reflecting the appetitive and/or aversive value - pleasant vs. unpleasant - of the emotional stimuli) (Lang *et al.* 1993, De Zorzi *et al.* 2021). From this aspect, healthy individuals showed larger pupillary dilation during viewing emotionally arousing stimuli regardless of valence (positive/negative) indicating thus a pupillary dilation as an important index of emotional arousal (Bradley *et al.* 2008, 2017, Henderson *et al.* 2018, Wang *et al.* 2018). Moreover, Bradley *et al.* (2017) proposed an enhanced pupillary dilation as a single sympathetically-mediated process beginning shortly after picture onset and continuing throughout whole emotional visual stimulation interval. Greater pupillary dilation during affective pictures viewing correlated with the changes in the skin conductance response (SCR) as a peripheral index of the sympathetic activity, further supporting the hypothesis that the modulation of the pupil size during emotional processing is mediated by the sympathetic nervous system with the pupil size reported as a more reliable indicator of emotional arousal compared to SCR

(Bradley *et al.* 2008, 2017). More specifically, pupillary modulation during affective visual perception – pupillary dilation – begins after approximately 500 ms after picture onset and continues throughout the viewing interval with greater dilation for emotionally arousing pictures (scenes of erotica, mutilation, attack) compared to neutral ones in healthy individuals reflecting an effect of emotional arousal on the sympathetically-driven action of the dilator muscle (Bradley *et al.* 2017). SCR occurs about 1000-5000 ms after stimuli onset indicating thus the pupil response as a time-sensitive measure of autonomic arousal compared to SCR considered as a more delayed index of the sympathetic reactivity (Bradley *et al.* 2017, Burley and van Goozen 2020).

Similarly, task-evoked pupillary dilation was reported in association with cognitive processing. For instance, pupillary dilation was observed during memory tasks (e.g. Boyer *et al.* 2018), attention (e.g. Sulutvedt *et al.* 2018), mental arithmetic (e.g. Szulewski *et al.* 2017), or decision making (e.g. Van Slooten *et al.* 2018). Pupillary dilation during tasks requiring a high attention such as memory retrieval or mental arithmetic is predominantly suggested to be associated with the sympathetic activation (Peinkhofer *et al.* 2019). However, Steinhauer *et al.* (2004) revealed the enhanced cognitive task-related pupillary dilation in the light compared to dark lighting condition pointing to the cortical (frontal cortex) inhibitory effect on the parasympathetic-linked E-W nucleus. Moreover, this parasympathetic inhibition-linked pupillary dilation was clearly elucidated using pharmacological blockade of the sympathetic iris dilator muscle by dapiprazole, and was eliminated by pharmacological blockade of the parasympathetically-mediated iris sphincter muscle activity by tropicamide (Steinhauer *et al.* 2004). As the pupillary dilation has long been considered as an index of the cognitive load that is associated with the amount of attentional or working memory needed to perform a given task (Just *et al.* 2003), it can reflect the use of processing resources – larger pupillary dilation is considered to correspond with greater cognitive load (Vogels *et al.* 2018). Interestingly, the pupillary dilation increases until the available processing capacity is filled up with the tendency to decrease when the capacity is “overloaded” (Einhäuser 2017). However, overall changes of the pupil size during cognitive stimulation seem to be too slow to accurately capture the cognitive response to stimuli that rapidly succeed each other or overlap (Vogels *et al.* 2018). Thus, the Index of Cognitive Activity (ICA) – number of rapid

increases in the pupil size during a certain time period calculated from the overall pupil size - has been developed as another reliable pupillometric measure of cognitive load (Marshall 2000, 2002) which received attention only recently. It is important to note that overall pupil size changes (larger pupillary dilation) differs from ICA (that not increase, but even decrease) during increased situational demand (more difficult dual-tasking) - attentional resources distributed over multiple tasks result in decrease of rapid pupillary dilations, the ICA is thus suggested to serve as a more sensitive index of cognitive load during tasks with rapid events series or overlapping stimuli compared to overall pupil size changes (Vogels *et al.* 2018).

#### *Pupillary light reflex (PLR) in emotional/cognitive stimulation*

It is important to note that the emotional content (pleasant/unpleasant) of stimuli may also modulate the initial PLR primarily occurring in response to the changes in the brightness. Specifically, Henderson *et al.* (2014) revealed emotional-linked attenuation of the initial pupillary constriction when viewing brightness-matched erotica (pleasant) or violent (unpleasant) scenes compared to neutral ones in healthy probands. Similarly, an initial constriction of the pupil was attenuated during anticipation of aversive event such as possible presentation of an electric shock (i.e. "fear-inhibited light reflex") (Bitsios *et al.* 1996, 2004).

Despite the fact that previous studies revealed reduced parasympathetically-mediated PLR responses during demanding cognitive processing (Steinhauer *et al.* 2000), the knowledge in this area is still rare. However, PLR can be modulated by the visual awareness and visual attention (Naber *et al.* 2011, Mathôt and van der Stigchel 2015). More specifically, attention associated with eye-movement preparation towards a bright object is associated with pupillary constriction, probably to facilitate a rapid pupillary light response (Mathôt *et al.* 2015). Moreover, PLR can be modulated by a subjective perception (i.e. interpretation) of brightness overriding the effects of real light intensity (Laeng and Endestad 2012, Laeng and Sulutvedt 2014).

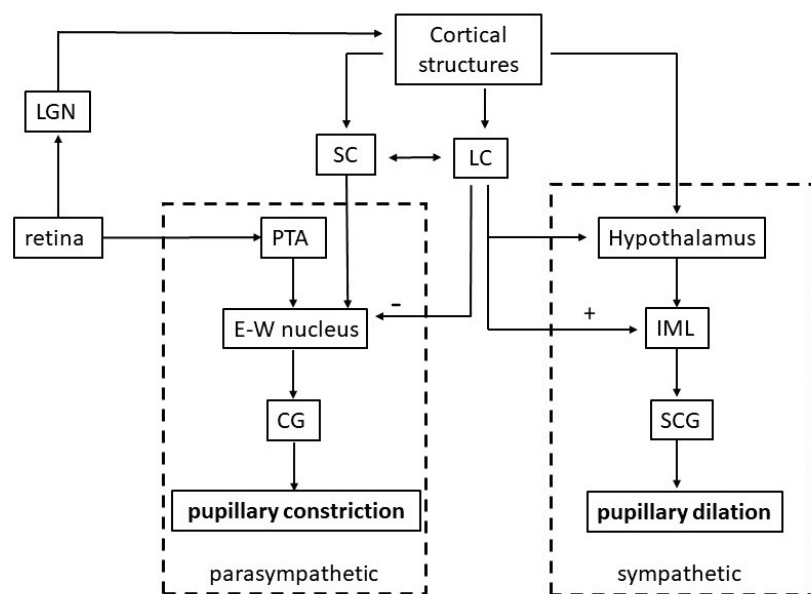
#### *Neuro-psycho-physiological regulatory mechanisms*

Cerebral structures involved in the modulation of the pupillary responses during cognitive and emotional processes include LC, superior colliculus, and multiple cortical regions (Peinkhofer *et al.* 2019), where LC seems

to be the most influential mediator of the pupil size/reactivity. LC presumably function at least in two firing (tonic and phasic) modes (Aston-Jones and Cohen 2005). Tonic mode is characterized by the elevated baseline LC firing rate without phasic bursts of activity. High levels of baseline LC activity firing is linked to diffuse attention focus and increased ability to detect new stimuli. The phasic mode represents brief, rapid increases in firing rate and is associated with focused attention and behavioral responses to salient stimuli (Aston-Jones and Cohen 2005, Vazey *et al.* 2018). According to the Adaptive Gain Theory (Aston-Jones and Cohen 2005), LC activity can adaptively shift to a different mode (from tonic to phasic or *vice versa*) due to current task requirements - if attentional focus is needed on a specific task, the LC will respond with a higher frequency of phasic activity; if the task is resolved and the brain needs to be open for exploring new inputs, LC will switch to the tonic activity. In this context, as the pupil size is considered as an indirect index of LC activity, it has been proposed that tonic pupil size can reflect the tonic LC activity, while phasic pupillary response may indicate its phasic activity (Peysakhovich *et al.* 2017). LC-linked pupillary changes are mediated through LC-linked excitatory projections to the sympathetic IML neurons and LC-related inhibitory connections to the E-W nucleus resulting in the sympathetically-driven pupillary dilation and attenuation of the parasympathetically-mediated constriction of the PLR (Szabadi 2012). Besides the LC, the superior colliculus (SC) - a subcortical motor nucleus for saccadic eye movements and for the control of spatial selective attention (Gandhi and Katnani 2011, Krauzlis *et al.* 2013) - may also play an important role in the regulation of the pupil size and PLR (Wang and Munoz 2015). Specifically, SC may modulate the parasympathetic-linked pupillary size changes through direct and/or indirect (*via* mesencephalic cuneiform nucleus - MCN) connections with E-W nucleus. SC is also (in)directly connected to LC and is influenced by descending cortical inputs from brain structures such as the frontal and the frontoparietal cortex (Joshi *et al.* 2016, Peinkhofer *et al.* 2019) potentially contributing to the modulation of the pupillary responses. Additionally, multiple cortical brain areas are involved in the modulation of the pupil size/reactivity such as frontal/prefrontal, orbitofrontal, cingulate, insular cortex (Peinkhofer *et al.* 2019, Joshi and Gold 2020, Fig. 1). More precisely, recent study revealed BOLD-fMRI activations correlated with changes in the pupil diameter

within the brain regions implicated in arousal, selective attention, salience, error-detection, and decision-making such as LC, thalamus, posterior cingulate cortex, dorsal

anterior cingulate and paracingulate cortex, orbitofrontal cortex, and right anterior insular cortex (DiNuzzo *et al.* 2019).



**Fig. 1.** Simplified schematic diagram of the cortical modulation on the pupillary innervation system. Neural pathways connecting cortical areas *via* subcortical structures such as locus coeruleus (LC) and superior colliculus (SC) to the pupillary innervation system are inhibitory (-) and activating (+), where inputs from the locus LC inhibit parasympathetic nervous system through direct projections to the Edinger-Westphal (E-W) nucleus and activate sympathetic nervous system *via* direct connections and indirect projections through the hypothalamus to the intermediolateral cell column of the spinal cord (IML) resulting in pupillary dilation. SC neurons *via* direct and indirect projections to the E-W nucleus influence the parasympathetic pupillary control. LC and SC are mutually interconnected and both structures receive multiple descending cortical inputs. LC receives descending inputs from dorsolateral and dorsomedial prefrontal cortex, anterior cingulate cortex, somatosensory, parietal and temporal cortex. SC receives inputs from ventrolateral prefrontal cortex. CG – ciliary

ganglion, LGN – lateral geniculate nucleus, PTA – pretectal area, SCG – superior cervical ganglion.

## Pupillometry – a promising diagnostic tool? (from research to clinical application)

Pupillometry, i.e. evaluation of the baseline pupil size/phasic pupillary reactivity by eye-tracking systems, and the assessment of the PLR by using automated pupillometers, is increasingly used in the psychophysiological research (Kret and Sjak-Shie 2019, Sekaninova *et al.* 2019a).

### Pupillometry in Psychiatry

Emotional dysregulation represents a hallmark in psychiatry. In this context, physiological changes in response to emotional stimuli are fundamental to the emotional experience, and adaptive regulation of the physiological arousal is vital for healthy functioning (Scarpa 2015). Physiological arousal increases as a result of the activation of the neural pathways in response to potentially life-threatening aversive and life-sustaining appetitive stimuli triggering a cascade of psychophysiological regulatory changes (e.g. affective, cognitive) involved in approach or avoid behavioral tendencies (Lang and Bradley 2010). Thus, abnormal physiological arousal (hypo-/hyper-arousal) in response to emotional stimuli has been associated with the onset of

psychopathology (Hajcak and Patrick 2015). From this perspective, abnormal baseline pupil size as well as pupillary responses to visual (e.g. emotional) stimulation were found in individuals suffering from mental disorders such as depression, anxiety, and autism spectrum disorder (Sekaninova *et al.* 2019b, Kleberg *et al.* 2019, de Vries *et al.* 2021).

### Pupillometric findings in autism spectrum disorder (ASD)

Studies regarding evaluation of the baseline pupil size in ASD reported different patterns. While Anderson and Colombo (2009) found greater baseline pupil size in ASD children compared to aged-matched controls, Martineau *et al.* (2011) reported smaller baseline pupil size in ASD children. Fan *et al.* (2009) and Nuske *et al.* (2014) revealed no differences in the resting pupil size in children with and without autism. Similarly, no differences in the baseline pupil size were found between ASD adults and healthy individuals (Lawson *et al.* 2017). Task-evoked pupillary dilation in ASD research has been investigated as a marker of *social cognition* by the presentation of social cues and as a marker of *sensory-perceptual processing* by the presentation of basic sensory stimuli and ambiguous figures (Bast *et al.* 2019). Regarding social cognition,

children with ASD showed attenuated pupillary dilation in a joint attention task, when gaze cues were incongruent to the target location (Erstenyuk *et al.* 2014) and to static emotional faces (Anderson *et al.* 2006). In addition, Aguillon-Hernandez *et al.* (2020) reported atypical pupillary reactivity to social stimuli in ASD with a good discriminating performance (around 75-80 %) between ASD and typically developing children. ASD adults showed attenuated pupillary dilation to static emotional faces compared to controls (Gotham *et al.* 2018) and attenuated pupillary dilation to observed social pain (Krach *et al.* 2015). Concerning sensory-perceptual processing, ASD toddlers showed increased pupillary dilation during a visual search paradigm (Blaser *et al.* 2014). Decreased pupillary dilation amplitudes in reaction to dark screens has been reported in ASD children compared to healthy children (DiCriscio and Troiani 2017). Study on brightness illusion in ASD adults revealed no differences in pupillary dilation compared to controls (Laeng *et al.* 2018). Further, Fan *et al.* (2009) referred to altered PLR (longer latency, smaller constriction amplitude, slower constriction velocity) in ASD children that can be used to discriminate ASD from controls with high accuracy.

#### *Pupillometric findings in major depressive disorder (MDD)*

Studies regarding child and adolescent depression are predominantly focused on task-evoked pupillary response. For instance, Silk *et al.* (2007) found that depressive adolescents exhibited less pupillary dilation in response to negative words compared to never depressed youth. Contrary, Burkhouse *et al.* (2017) revealed greater pupillary dilation in response not only to sad/fearful faces but also to happy faces in depressive adolescents. In addition, children of depressed mothers showed increased pupillary responses to sad faces (Burkhouse *et al.* 2014). With respect to PLR, abnormal PLR parameters (smaller percentual change of the pupil size during constriction and slower constriction velocity) was found in adolescent depression (Mestanikova *et al.* 2017). Interestingly, Cohen *et al.* (2019) found convincing evidence that individual differences in pupillary dilation uniquely predicted depression onset. Specifically, youth with subthreshold depressive symptoms and elevated pupillary dilation were over twice as likely to develop a first episode of depression (Cohen *et al.* 2019). Studies regarding MDD in adults reported greater baseline pupil diameter (Schumann *et al.* 2017)

and greater pupillary dilation to negative emotional stimuli (Siegle *et al.* 2003) in depressive compared to never depressive adults. Further, smaller PLR-linked constriction amplitude was reported in adult depression (Bär *et al.* 2004).

#### *Pupillometric findings in anxiety disorders*

Pupillary responses in anxiety disorders are less studied. While Keil *et al.* (2018) reported blunted pupillary dilation to emotional faces in social anxiety disorder in children, another study showed greater pupillary dilation when viewing angry faces and reduced pupillary dilation to neutral faces in children with mixed anxiety disorder (Price *et al.* 2016). Larger pupillary dilation amplitude to happy faces in adolescent social anxiety disorder was associated with worse treatment response (Kleberg *et al.* 2019). In addition, children of anxious mothers exhibited increased pupillary dilation to angry faces compared to youth of non-anxious mothers (Burkhouse *et al.* 2014). Adults with moderate or severe anxiety showed greater pupillary dilation compared to adults with mild or no anxiety (Santos *et al.* 2013). Bakes *et al.* (1990) observed a decrease in the PLR in anxious adult patients.

#### **Pupillometry in Neurology**

From the neurological perspective, a majority of neurodegenerative diseases are characterized by abnormal accumulation of misfolded protein leading to progressive dysfunction and damage of neuron populations associated with the loss of their physiological function resulting in a wide spectrum of clinical features (Csizmok and Tompa 2008, Kovacs 2018). Specifically, the progressive loss of brain matter leads to impairments in autonomic, motor, and cognitive functions (Huang *et al.* 2020). From this point of view, the pupillometry may represent a suitable insight into the autonomic as well as cognitive (dys)functions.

#### *Pupillometric findings in Alzheimer's disease (AD)*

Pupil size and reactivity to the light seems to be altered in Alzheimer's disease, where AD-related neurodegeneration in LC and E-W nucleus (Bondareff *et al.* 1987, Scinto *et al.* 2001) affecting parasympathetic and sympathetic control of the pupil may play an important role. More precisely, AD patients showed reduced baseline pupil size compared to healthy individuals (Prettyman *et al.* 1997). Further, studies revealed increased latency of pupillary constriction,

decreased constriction amplitude and decreased constriction velocity to the light stimulation, and faster redilation pointed to the parasympathetic dysfunction in AD patients compared to healthy individuals (as reviewed in Chougule *et al.* 2019).

#### *Pupillometric findings in Parkinson disease (PD)*

Studies regarding pupillary evaluation in Parkinson disease reported predominantly impaired pupillary reactivity to the light stimulation. More specifically, PD patients showed reduced constriction amplitude and prolonged constriction time of the PLR (Micieli *et al.* 1991). Similarly, Giza *et al.* (2011) reported increased latency and decreased constriction amplitude, constriction velocity, and constriction acceleration in PD patients compared to controls. Contrary, Ulep *et al.* (2017) found no significant differences in the PLR variables in PD patients compared to healthy probands. Studies focusing on the evaluation of the pupil size under stable lighting conditions are rare, where Tsitsi *et al.* (2021) reported smaller pupil size in PD patients compared to the control group.

Taken together, these pupillometric findings indicate alterations in the pupil size/reactivity in the above-mentioned disorders pointing to the pupillometry as a potentially helpful “diagnostic” tool in the clinical practice especially in the psychiatry where searching for

objective biomarkers is still under intensive research.

## Conclusion

In recent years, eye pupil as an easily accessible way to obtain important information regarding the human mind is gaining more attention. However, despite the intensive pupillometric research in cognitive and affective neuroscience, the exact “brain-pupil” relationships are still not well understood. Future research directions based on the complex approach of concurrent studying of the pupillometric (pupil size/reactivity), oculometric behavior (e.g. saccadic eye movements, fixations, eye blinks) in association with eye movement-related potentials by EEG recording (Jagla 2016, Jagla *et al.* 2007), and functional neuroimaging may elucidate this question and also bring novel detailed insight into what happens in the brain afflicted by the disease.

## Conflict of Interest

There is no conflict of interest.

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