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Physiology of Higher Nervous (Cognitive) Activity in Humans

Pupillometry in the Assessment of Psychoemotional State and Cognitive Functions in Humans

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Pupillometry is an investigation method yielding quantitative assessment of pupil diameter. Pupil size is regulated by structures of the autonomic nervous system (the oculomotor nerve nuclei, the ciliospinal center) and is associated with the level of illumination. However, overlying brain structures, in particular the cortex, acting via the locus coeruleus, pretectal olivary nuclei, and superior colliculi, have modulating effects on pupil reactions which are not related to illumination. Initial pupil diameter and changes in diameter associated with the performance of certain tasks can be used for objective assessment of subjects' psychoemotional state and cognitive functions. There is evidence of changes in pupil reactions in autism spectrum disorders and depression, as well as in Alzheimer's disease, Parkinson's disease, and other organic brain diseases. Further research into pupillometry techniques is needed to identify new areas of application.

Keywords: pupil, pupillometry, eye-tracking, photoreaction, psychoemotional disorders, cognitive functions.

This review will examine the physiological basis of the regulation of pupil diameter, the role of brainstem and cortical structures in this process, and the potential of pupillometry in the objective assessment of subjects' psychoemotional state and cognitive functions, as well as the features of changes in pupil reactions in a number of brain diseases. This work represents an attempt to provide a comprehensive assessment of the question of the regulation of pupil reactions, from biological mechanisms to applications in clinical practice. The information provided will be useful to both physiologists and clinical specialists.

The pupil is a round aperture in the center of the iris through which light rays enter the eye. Pupil diameter changes depending on the level of illumination, during accommodation, as part of the orientation reflex, and during arousal and mental stress. In this regard, assessment of pupil diameter can be used to study the functional state of the brain [Joshi and Gold, 2020; Ferencová et al., 2021].

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Pupillometry is a method which provides quantitative assessment of pupil diameter. The first method of assessing pupil diameter was visual. A variety of pupilloscopes were used – these were templates or scales which were held up to the eye to allow pupil diameter to be compared with marks on the device. With the progress of science and technology, video cameras came into use for pupillometry, supporting assessment of pupil diameter over time. Near-infrared technology is now widely used in combination with high-resolution cameras [Barabanshchikov, 2011]. Pupillometry provides objective and noninvasive assessment of the state of the human central nervous system (CNS) [Mathôt, 2018; Oshorov et al., 2021] and is widely used in psychology, sociology, pedagogy, and medicine [Puchkova et al. 2017; Devyatko et al., 2021; Goryushko and Samochadin 2021; Sakhovskaya et al. 2022; Pokhodai et al. 2022].

Basic Mechanisms of Pupil Reactions. Pupil reactions are regulated as reflexes by the autonomic nervous system (ANS). Changes in pupil diameter are produced by contraction of muscles which dilate (dilator) and constrict (sphincter) the pupil. The sphincter of the pupil is innervated by parasympathetic, and the dilator by sympathetic nerves. Balanced activity of the sympathetic and parasympathetic divisions of the ANS supports the reaction of the pupil to light – the photoreaction [Mathôt, 2018].

The photoreaction of the pupil includes not only constriction of the pupil due to activation of the parasympathetic ANS (the direct pathway), but also its dilation. Light increases the level of wakefulness and activates the suprachiasmatic and dorsolateral nuclei of the hypothalamus, which in turn have an activating effect on the locus coeruleus and, as a result, the sympathetic nervous system (the indirect pathway) [Mathôt, 2018].

Pupillometry is used for dynamic assessment of pupil light reactions (dynamic pupillometry). Initial pupil diameter, constriction latency, constriction amplitude, constriction time, constriction speed, dilation latency, dilation time, dilation speed, and total reaction time are assessed. Pupillography results are displayed graphically as plots of pupil diameter vs. time from the moment of application of the pulse of light [Kutsal et al., 2018].

An additional mechanism for regulating illumination-dependent pupil diameter includes decreases in sympathetic nervous system activity as illumination increases, leading to relaxation of the muscle that dilates the pupil and constriction of the latter. A decrease in the degree of illumination leads to a decrease in the activity of the parasympathetic nervous system and relaxation of the sphincter of the pupil and, thus, dilation of the pupil [Joshi and Gold, 2020].

Changes in pupil diameter are not only influenced by light [Gusso et al., 2021]. Pupil dilation is also seen as part of the orienting reflex and in responses to various types of stimulation (tactile, visual, sound), as well as emotional stimuli or cognitive load. The latter variants are sometimes referred to as psychosensory responses [Gusso et al., 2021; Ferencová et al., 2021].

Neurons in the intermediate layer of the superior colliculus, which receives various types of information (motor, somatosensory, cognitive, but not visual) from the cerebral cortex, also have a modulating effect on activity in the Edinger–Westphal nucleus [Wang and Munoz, 2015]. The superior colliculus is closely connected with the frontal and frontoparietal areas of the cortex [Peinkhofer et al., 2019]. Connections between the superior colliculus and ANS structures probably operate via a number of pathways. Single spikes in the area of the superior colliculus have been shown to correlate with pupil dilation, while longer-lasting bioelectrical activity in this area is associated with pupil constriction [Joshi and Li, 2016]. Activation of the superior colliculus in various conditions leads to either dilation (as in the orienting reflex) or constriction of the pupil [Wang et al., 2014].

Changes in pupil diameter during emotional arousal and cognitive load are associated with the influences of overlying brain structures on the autonomic nuclei [Mäki-Marttunen, 2021]. This mechanism is mediated by changes in the activity of the locus coeruleus and underlies the psychosensory reaction [Szabadi, 2013]. The main brain structures involved in the regulation of pupil diameter are presented in Fig. 1.

Thus, pupil diameter is regulated by the ANS and changes depending on illumination. It can also change under the influence of emotional stimuli and cognitive stress. In the latter case, important roles are played by the superior colliculus and the locus coeruleus, which modulate the activity of ANS nuclei.

The Role of the Locus Coeruleus and Cortical Structures in the Regulation of Pupil Diameter. The locus coeruleus is a group of noradrenergic neurons in the pontine region, closely connected to other areas of the brain and responsible for regulating situation-specific behavior in humans [Benarroch, 2023]. The functions of the locus coeruleus in regulating behavior are explained by adaptive gain theory. This theory holds that human and animal behavior can be divided into exploitation and exploration. In the former, a person is focused on one activity, from which some particular reinforcement is received (for example, eats and becomes satiated). The locus coeruleus functions in phasic mode, while norepinephrine is released in pulses and pupil diameter pupil remains relatively small. In exploration, a person investigates the environment in search of a source of better reinforcement and is easily distracted, switching to other activities. In this case, the locus coeruleus operates in tonic mode, with constant norepinephrine release, maintaining the pupil in a dilated state [Aston-Jones and Cohen, 2005]. These two types of behavior alternate; as one need is satisfied, the person is distracted by seeking another type of activity with a more attractive result (reinforcement). This theory provides a convincing explanation of differences in pupil diameter in people in different conditions in terms of locus coeruleus activity [Joshi et al., 2015].

Along with the brainstem structures, the cerebral cortex plays an important role in regulating pupil diameter. In particular, the locus coeruleus has tight connections with the insular cortex, the anterior and posterior cingulate cortex, and the prefrontal cortex [Peinkhofer et al., 2019]. All these structures, together with the central nuclei of the amygdala, paraventricular nuclei of the hypothalamus, periaqueductal gray matter, as well as the ventromedial and ventrolateral nuclei of the medulla oblongata, constitute the central autonomous (autonomic) network, which plays a key role in regulating ANS activity [Quadt et al., 2022]. While some structures are involved in the regulation of exclusively sympathetic (prefrontal cortex, left posterior part of the insular cortex, anterior and middle parts of the cingulate gyrus, etc.) or parasympathetic (certain areas of the cingulate gyrus, hippocampus, dorsal part of the insula, etc.) components of the ANS, some structures affect both (left amygdala, right inferior parietal lobule) [Beissner et al., 2013]. The central autonomic network is tightly connected with cerebral structures responsible for such phenomena as vigilance, maintenance of attention, and the formation of emotional arousal [Sklerov et al., 2019]. Activation of these structures leads

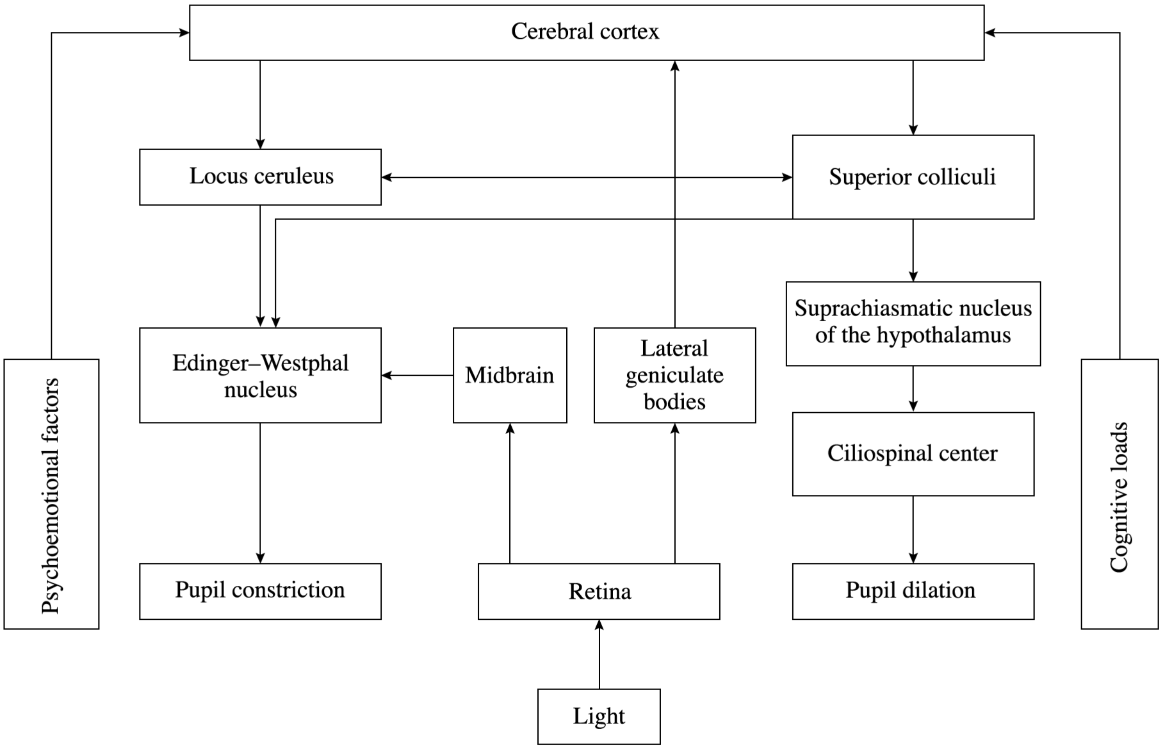

Fig. 1. Neural regulation of pupil diameter.

to stimulation of the locus coeruleus with resultant increases in sympathetic nervous system activity and decreases in parasympathetic nervous system activity – and the pupil dilates. In other words, pupil dilation occurs due to activation of the sympathetic nervous system during emotional arousal and cognitive load and is a reflection of the level of activity of the overlying parts of the brain [DiNuzzo et al., 2019]. A study using resting functional MRI showed that pupil dilation is associated with increased activity in the thalamus and frontoparietal cortex, which are parts of the salience network [Schneider et al., 2016].

Experimental work has shown that the frontal oculomotor field and the lateral intraparietal area, which are associated with spatial attention and saccadic eye movements in response to visual stimuli, can modulate the pupil photoresponse by influencing ANS structures, in particular the Edinger–Westphal nucleus, acting via the pretectal olivary nuclei [Henderson, 2014]. For example, looking at a picture of the sun causes the pupil to constrict relative to its original diameter, which does not occur when looking at a picture without a clear image of the sun under similar lighting. Furthermore, pupil constriction is observed when a person imagines something bright (a sunny sky) or even on reading the word "lamp" [Sperandio et al., 2018]. Microstimulation of the prefrontal cortex (the oculomotor field) leads to changes in pupil photoreaction parameters [Ebitz and Moore, 2017].

Thus, existing data indicate that various parts of the cerebral cortex and its connections have important roles in the regulation of pupil reactions. These exert their effects on pupil size through the central autonomic network and the locus coeruleus. Changes in pupil diameter can be used to judge not only ANS tone, but also the state of the overlying parts of the brain.

Pupillometric Assessment of Psychoemotional State in Humans. A person's psychoemotional state can be assessed using initial pupil diameter, the magnitude of its spontaneous fluctuations, and task-induced pupil reactions. Initial pupil diameter is a measure of pupil size when the patient is looking at a blank screen without performing any tasks. Initial pupil diameter is associated with the functional activity of the noradrenergic system of the brain and the functional organization of brain activity at rest. A larger initial pupil diameter indicates more efficient functional connections in the brain and optimal functioning of the locus coeruleus [Ferencová et al., 2021].

In practice, pupil diameter at rest reflects the state of regulatory functions: fluid intelligence, working memory, and selective attention [Aminihajibashi et al., 2019]. However, some large studies have been unable to confirm these findings [Robinson et al., 2022]. This may be due to the experimental designs. In particular, the color of the screen that the subject looks at during the experiment, along with room lighting and a number of other factors all influence pupil diameter. Thus, people of different ages should be included in pupillometric studies and multiple tests should be used for assessment of cognitive functions. Sample size must be sufficient to achieve intersubject variation in pupil diameter and other indicators; the lighting conditions of the room in general and the monitor in particular, and the method for assessing illumination must be described in detail. When planning pupillometric studies, account must be taken of subjects' consumption of coffee and psychoactive drugs, the degree of emotional arousal at the time of the experiment, the duration of sleep the night before, age, and other factors that may affect ANS tone [Tsukahara and Engle, 2021].

Pupil diameter undergoes spontaneous changes at rest; this is termed pupil restlessness or hippus (pupillary athetosis). These changes are associated with fluctuations in the activity of the locus coeruleus and reflect a person's level of wakefulness. Spontaneous fluctuations in pupil diameter are most marked in the state of fatigue, without any ongoing activity [Mathôt, 2018; Marzouki et al., 2017]. Hippus is associated with the activity of the parasympathetic division of the ANS – experimental data indicate that instillation of the anticholinergic (blocking activity of the parasympathetic branch) drug tropicamide into the conjunctival sac reduced hippus frequency, while instillation of phenylephrine, which increases activity of the sympathetic branch of the ANS, did not affect hippus frequency [Turnbull et al., 2017].

Comparative analysis of pupillometric measures at rest in adults and children showed that children had a significantly greater median pupil diameter and a significantly greater frequency of fluctuations in its diameter (hippus). These data, along with indicators of skin electrodermal activity and heart rate variability, indicated higher ANS tone in children, associated with the active process of body development [Bufo et al., 2022].

The extent of spontaneous fluctuations in pupil diameter increases as a person feels tired and is probably associated with fluctuations in the level of brain activity. Hippus is most marked in the absence of any activity, while performance of a task (for example, mental arithmetic) leads to the disappearance of oscillations [Bouma and Baghuis, 1971].

In general, a small pupil corresponds to a low level of brain activity and correlates with low oculomotor activity. In such situations, a person usually involuntarily looks at objects that attract attention (bright light, for example). Pupil dilation, conversely, is associated with increased cerebral activity, when a person exhibits voluntary visual activity, looking at objects associated with some task, for example, searching for something specific [Marzouki et al., 2017].

Task-induced pupil responses are assessed in terms of changes in pupil diameter on task performance relative to initial pupil diameter. Emotional stimuli typically induce pupil dilation via activation of the sympathetic or inhibition of the parasympathetic divisions of the ANS [De Zorzi et al., 2021]. The degree of pupil dilation correlates with other measures of sympathetic nervous system activity, such as the extent of electrodermal activity [Bradley et al., 2017]. On the other hand, pupil dilation during cognitive loading may be associated with decreased activity in the parasympathetic Edinger–Westphal nucleus as a result of the inhibitory influence of the cortex [Steinhauser et al., 2016]. This is confirmed by the fact that greater pupil dilation in response to cognitive load occurs in light than in darkness, while pre-administration of atropine-like compounds prevents the development of such a reaction [Steinhauser et al., 2016]. Emotional factors can alter the extent of the pupil photoreaction. For example, looking at a screen with emotionally arousing pictures caused less marked pupil constriction than looking at emotionally neutral pictures, despite the absence of any difference in screen illumination [Henderson et al., 2014]. Assessment of pupil responses to emotional stimuli can be used to judge the extent of activation of the nervous system in response to a stimulus, as well as its valence (subjective attractiveness or unattractiveness) [Strauch et al., 2022].

Pupillometry, along with other indicators of ANS activity, can be used to detect lies. Psychoemotional stress accompanying the utterance of false information leads to an increase in the tone of the sympathetic nervous system and an increase in pupil diameter, as well as a decrease in the amplitude of fluctuations in its diameter [Romanova et al., 2008].

Thus, a patient's psychoemotional state can be judged from initial pupil diameter, its fluctuations at rest, and changes in response to various stimuli. Emotional factors lead to pupil dilation. The extent of this reaction can be used to judge the characteristics of the brain's reaction to a specific stimulus.

Pupillometry in Cognitive Research. In cognitive studies, videooculography is used in combination with traditional techniques to capture data on the nature of cognitive processes during performance of a variety of tasks. Pupil reactions are investigated during performance of tasks involving working memory [Miller et al., 2019], various types of attention [Strauch et al., 2022], and mental arithmetic [Sulutvedt et al., 2018], as well as in the analysis of difficulties in speech recognition [Engen and McLaughlin, 2018].

Pupillometry is used in research in the field of cognitive control – one of the attention systems responsible for the selection of information and the coordination and execution of relevant processes with suppression of irrelevant processes [Posner et al., 2004]. Tests for cognitive control functions, in particular, Stroop techniques and flanker (suppression), n-back (update), and switching tasks are used [Velichkovskii, 2009]. For the Stroop task, in which subjects are asked to name the color of a stimulus that may be congruent or incongruent with a written word, an increase in pupil diameter was demonstrated for incongruent trials, which may indicate greater recruitment of cognitive control resources as compared with trials where the word and color matched [Rondeel et al., 2015; Laeng et al., 2011]. Similar data have been obtained in the n-back test (a continuous performance task in which the subject is continuously shown various images and must determine whether he saw them n positions ago): pupil size increased with increases in the quantity of cognitive control resources involved in the task [Yeung et al., 2021]. Pupillometric studies of cognitive processes during behavioral tasks are particularly valuable because standard methods for assessing cognitive functions cannot be applied when subjects cannot provide verbal responses (for example, in childhood and in partially or completely immobilized patients) [Richardson et al., 2007].

Dynamic assessment of pupil diameter is also used in studies of cognitive load, which is understood as a measure of the effort a person puts into solving one or more tasks that require mental effort [McKendrick and Harwood, 2019]. Three types of cognitive load are currently recognized: internal load (intrinsic load); external load (extraneous load) and corresponding load (germane load) [Sweller, 2010]. Intrinsic load reflects the difficulty of the task itself and is related to a person's cognitive abilities. External load is related to the form of presentation of material, i.e., its audiovisual characteristics, and germane load is related to the person's ability to understand material [Sweller, 1988].

Cognitive load is a subjective characteristic of the effort that a person expends to solve any cognitive task; it can be made objective by using measures such as *productivity*, which reflects a person's ability to solve the task assigned, as well as *subjective indicators* reflecting a person's impression of the load experienced by a patient while performing the task, and *physiological measures*, which are associated with assessment of the person's reactions recorded during the task [Wierwille and Eggemeier, 1993]. At the same time, the dynamics of physiological and behavioral indicators under cognitive load may differ: for example, pupil diameter increased in a study of the effect of load on verbal working memory in a visual search task, while reproduction accuracy increased on loading [Velichkovskii and Izmalkova, 2015]. Cognitive loads, like emotional factors, cause pupil dilation, due either to activation of the sympathetic or inhibition of the parasympathetic division of the ANS. The degree of pupil dilation reflects the degree of involvement of cerebral resources for information processing. It has been suggested that the degree of pupil dilation increases until resources are depleted, at which point it then begins to decrease [Mathôt, 2018]. The extent of pupil dilation is not a reliable marker of cognitive load, as it depends on the illumination of the room in which the experiment is being conducted and develops relatively slowly. This latter point is particularly relevant when performing rapidly changing or overlapping tasks. In this regard, a more sensitive pupillometric marker, the cognitive activity index (CAI), was proposed. This is calculated in terms of the number of rapid pupil dilations over a given period of time relative to the average pupil diameter and allows pupil dilation resulting from light to be discriminated from pupil dilation resulting from cognitive load. CAI is calculated using Daubechies wavelets [Vogel et al., 2018]. A meta-analysis of 14 studies (n = 751 participants) found that CAI reliably reflects cognitive load but is also influenced by light, and its diagnostic value requires further study [Czerniak et al., 2021]. Pupillometry can also be used to assess a person's state during motor learning, as well as to quantify this process [White and French, 2021; Yokoi and Weiler, 2022].

The accuracy of assessing cognitive load on the basis of pupil diameter ranged from 57% to 98% in different studies. Studies which divided people into two groups based on pupillometric data – those experiencing high and low cognitive load when performing tasks – yielded high accuracy levels. Accuracy in studies that sought to identify three groups of people – those experiencing high, medium, and low cognitive load – dropped to 43.8% [Skaramagkas et al., 2021]. However, inclusion of electrocardiography data in the analysis increased accuracy to 92% [Wanyan et al., 2014].

Among the challenges of cognitive pupillometry is that pupil responses can also vary due to non-experimental factors. For example, pupil response amplitudes will gradually decrease over the course of a 30-min experiment even if the demands of the task remain constant [Brown et al., 2020]. This effect is thought to be related to habituation to the task or stimuli, though some studies have linked it to fatigue [Morad et al., 2000]. It is also of note that pupillometry data from older and middle-aged adults indicate significantly smaller differences in pupil diameter under higher and lower cognitive load in older than younger adults [Van Gerven et al., 2004].

Thus, analysis of pupil reactions yields obtain information on cognitive processes when performing a number of different tasks. The degree of pupil dilation corresponds to the degree of effort that the patient applies to perform the task. One of the most accurate pupillometric markers of cognitive processes is the cognitive activity index; the accuracy of pupillometry in assessing cognitive function can be increased by using supplementary methods for assessing ANS activity.

Pupillometry in Clinical Investigations. Assessment of pupil diameter at rest and pupil reactions on presentation of different stimuli produces objective indications of the state of the patient's nervous system as a whole, as well as the strengths of emotional reactions and the degree of cognitive load experienced when performing various tasks. In this regard, pupillometry finds application in clinical neurology and psychiatry [Ferencová et al., 2021].

Pupillometry is widely used in the study of autism spectrum disorders (ASD) [de Vries et al., 2021; Shic et al., 2022; Kumano et al., 2022]. Studies of the pupil at rest in this condition have yielded ambiguous results: some data indicate that ASD patients had a wider pupil diameter than healthy people [Andersen et al., 2009], while other results showed that they had narrower pupils [Martineau et al., 2011] or that pupil diameter was not significantly different from that in controls [Lawson et al., 2017]. Altered pupil photoresponses have been observed in ASD patients and were characterized by a longer latency period, smaller contraction amplitude, and slower pupillary sphincter contraction velocity [Fan et al., 2009].

Investigation of task-evoked pupil responses provides objective assessment of the state of social cognitive functions and sensory-perceptual functions in ASD [Shic et al., 2022]. In particular, patients showed atypical pupil responses (less marked dilation) to social stimuli (emotional faces, pain) [Aguillon-Hernandez et al., 2020]. Changes in sensory-perceptual functions have been demonstrated in visual search experiments, where ASD patients showed greater pupil dilation than healthy controls [DiCriscio and Troiani, 2017].

Pupillometry in affective disorders has revealed a range of pathological changes [De Zorzi et al., 2021]. Adolescents with major depressive episode showed less pupil constriction in response to words with negative connotations than healthy individuals without a history of depression [Siegle et al., 2003]. On the other hand, adolescents with depression showed greater pupil dilation in response to faces with emotional expressions (sad or happy) [Burkhouse et al., 2014]. Individual variability in pupil width, i.e., greater pupil width, was a predictor of the development of a first depressive episode in patients with subclinical depressive symptoms [Cohen et al., 2019]. Pupil photoreaction parameters in adolescents with depressive episode were also altered; they were characterized by a lower degree of pupil constriction [Mestanikova, 2019]. Adult patients with depression showed larger initial pupil diameter, greater pupil dilation in response to negative emotional stimuli, and less marked photoresponses [Marzouki et al., 2017]. Assessment of pupil responses during reinforcement tasks is a promising method for identifying patients with impairments to the process of evaluating reinforcement and as a biomarker for elevated risk of developing relapse of major depressive episode in patients in remission [Gauth et al., 2022].

More sluggish photoreactions and more marked pupil dilation are noted in anxiety disorders in adults. The pattern of changes in the pupil in children with anxiety disorder depends on the valence of the emotional stimulus: in one study, children shown faces with a neutral expression displayed less marked dilation [Keil et al., 2018], while in another, presentation of faces with an angry expression led to greater pupil dilation than in healthy people and faces with a neutral expression produced smaller decreases in diameter [Price et al., 2018]. Pupil response patterns have also been used as a biomarker of the potential effectiveness of treatments for mood disorders [Kleberg et al., 2019].

Initial pupil diameter and the characteristics of its photoreaction in infancy are genetically determined traits and may be predictors of the development of schizophrenia in older age [Portugal et al., 2022]. Decreased pupil photoresponses have been observed in people with schizophrenia. Photoresponse parameters correlated with the extent of cognitive decline and the severity of negative symptoms [Fattal et al., 2022].

ANS structures undergo degenerative changes in many degenerative diseases of the central nervous system, this occurring in the early stages of disease, and provide biomarkers for preclinical diagnosis and monitoring the dynamics of the pathological process [Chougule et al., 2019; Douglas et al., 2021]. In particular, studies of pupil photoresponses in Alzheimer's disease (AD) have demonstrated a number of changes: increased latency of pupil constriction to light, decreased amplitude of pupil constriction, more rapid redilation after removal of the light source, decreased maximum constriction velocity, and acceleration of maximum pupil constriction. All these changes were consistent with dysfunction of the parasympathetic nervous system [Chougule et al., 2019].

The more contemporary method of chromatic pupillometry provides for separate assessment of the roles of rods, cones, and melanopsin-containing retinal ganglion cells (mRGC) in mediating pupil photoreactions by presentation of light stimuli with different wavelengths [Romagnoli et al., 2020]. mRGC death is seen at even the early stages of AD, so chromatic pupillometry is a promising method for early (preclinical) diagnosis of AD [Lustig-Barzelay et al., 2022], though further research is needed to evaluate the value of this technique [Romagnoli et al., 2020; Oh et al., 2019]. Assessment of pupil diameter at rest and during cognitive load can serve as a biomarker of the degree of cognitive impairment in AD and the effectiveness of treatment [El Haj et al., 2022].

Pupillometry is used to assess the state of cognitive functions in multiple sclerosis [de Rodez Benavent et al., 2022] and the state of the ANS in infection with the novel coronavirus COVID-19 [Daniel et al., 2022]. In the latter case, smaller initial pupil diameter was an unfavorable prognostic sign [Daniel et al., 2022].

Autonomic disorders also develop in the early stages of Parkinson's disease (PD). Studies of pupil photoreactions in PD have revealed a significant decrease in constriction amplitude, an increase in the duration of the latent period, and a number of other indicators [Alhassan et al., 2022]. Pupillometry can be used for early detection of PD, and it has been shown that at rest the pupil is narrower in PD patients than in healthy controls [Tsitsi et al., 2021]. Pupillometry data can be used to assess the state of the cholinergic system of the brain in PD. In particular, PD patients with freezing on walking, the development of which is associated with deficiency of the cholinergic system, were found to have larger pupil diameter in the light and greater prolongation of pupil constriction latency [Alhassan et al., 2022]. The rate of pupil contraction as part of the photoresponse decreases as PD progresses [You et al., 2021]. Marked changes in pupil responses are seen in multiple system atrophy [Park et al., 2019].

Portable pupillometry devices can be used to assess the functional state of the brain on the basis of the state of the oculomotor system in patients in intensive care. Pupillometric characteristics have been shown to predict the outcome of anoxic brain injury and to identify the early signs of increased intracranial pressure and transtentorial herniation

[Bower et al., 2021]. Given the important role of noradrenaline, which is mainly synthesized in the locus coeruleus, as a mediator of neuroplasticity, pupillometry could potentially be used to assess the plasticity of the visual cortex [Viglione et al., 2023].

Thus, pupillometry can be used in clinical neurology and psychiatry. Analysis of pupil reactions can be used in the early diagnosis of ASD, in particular to assess the characteristics of perception and social-cognitive functions in children. Pupillometry indicators can serve as markers for the diagnosis of schizophrenia for predicting the course and assessing treatment efficacy in affective disorders. Pupil reactions change in Alzheimer's disease and Parkinson's disease and can be used for early diagnosis of the latter.

Conclusions. Thus, the regulation of pupil diameter is a complex physiological process which reflects the state not only of the ANS, but also that of overlying structures. Changes in pupil diameter are associated with ANS activity in response to changes in lighting. However, emotional stimuli and cognitive loads can influence pupil size, via changes in ANS tone, regardless of lighting. This mechanism for regulating pupil reactions is realized through the locus coeruleus, superior colliculus and other brain structures.

Dynamic assessment of pupil diameter at rest and during performance of various tasks provides assessment of the functional state of the brain. Pupillometry is a promising method for objective assessment of psychoemotional and cognitive disorders in affective disorders, schizophrenia, depression, and degenerative brain diseases.

Further research is needed to address the mechanisms of regulation of pupil reactions. In particular, investigation of pupillometric parameters in combination with recording of eye movements and the use of other electrophysiological techniques, as well as the parallel use of pupillometry and functional imaging methods, is of particular interest. From the clinical point of view, there is a need to develop standardized tasks to assess specific aspects of brain activity using pupillometry for early diagnosis and monitoring of the course of nervous and mental diseases.

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