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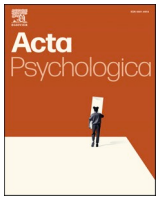

Pupil size as a biomarker of cognitive (dys)functions: Toward a physiologically informed screening of mental states

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ABSTRACT

The objective assessment of cognitive processes is of critical importance to understanding the mechanisms underlying various mental functions and dysfunctions. In recent years, the technological innovations related to the eye-tracking industry made the time right to organically integrate pupillometry in the assessment of cognitive profiles. Here, we review evidence showing that pupillometry offers a uniquely sensitive biomarker of the functioning of several distinct networks, cognitive functions, emotional states, and individual differences in their instantiation. We outline why and how pupillometry can be effectively exploited to enrich current research and behavioral paradigms, including those designed for clinical testing. By making the cases of anxiety disorders (both generalized and specific - e.g., generalized anxiety vs. math anxiety) and substance use disorders, we then exemplify how pupillometry can be leveraged to obtain clinically meaningful variables. We finally conclude by arguing that measuring pupil size has the potential to complement more traditional, but coarse assessment methods, to return a more graded, objective, and physiologically informed picture of cognitive functioning.

1. Introduction

One fundamental challenge of cognitive psychology has always been that of accessing one's mental states in an objective and quantifiable way. The key early method to test cognitive models consisted of measuring accuracy and reaction times in completing a task (Friston et al., 1996; Meyer et al., 1988). However, these behavioral measures are influenced by factors such as age, gender, education, and prior experience, thus complicating comparisons across different groups (Dykiert et al., 2012b, 2012a; Era et al., 2011). Experimental psychology has also massively exploited self-report measures to quantify individuals' perceptions and assess cognitive and affective functions (e.g., perception, attention, emotions, memory). Questionnaires have also been widely used to detect symptoms related to specific disorders or to evaluate the effectiveness of interventions. While these tools have obvious advantages, such as being low-cost, easy, and quick to administer on a large scale, they may be imprecise for various reasons (e.g., response biases, social desirability) and limited by the individual's verbal and self-insight abilities (Demetriou et al., 2015). Due to these limitations, overt responses are often insufficient for studying cognitive processes or formulating clinical diagnoses.

The development of cognitive neuroscience introduced advanced methods like EEG, fMRI, and measures of peripheral nervous system activation (e.g., heart rate, skin conductance, pupil size), that largely escape voluntary control, thereby avoiding subjective response biases. These physiological responses enable a detailed temporal analysis of neural processes, providing comprehensive, more reliable measurements of individuals' mental functioning along with its putative neural underpinning (Cohen et al., 1996; Kosslyn, 2005). Importantly, these techniques enhance our ability to differentiate cognitive processes and identify their dysfunctions by relying on neural and physiological signatures, i.e., biomarkers. Biomarkers not only offer objective and accurate measures of specific mental states but might also provide clinically relevant information useful for differential diagnosis and treatment monitoring. One of the main advantages of these covert measures is that they do not require the individual to have developed advanced metacognition and critical reflection on their own functioning. Biomarkers can thus reveal abilities and difficulties early, potentially anticipating future diagnoses and allowing for more effective and timely interventions. It is therefore paramount to enhance our grasp of these methods for optimizing their ecological validity and the significance of the ensuing results.

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Here, we aim to deepen our understanding of the pupillometry technique – including strengths, limits, and pitfalls - to achieve a cost-effective balance in its use and explore its relevance in psycho-clinical settings. This objective is grounded in vast experimental evidence showing that a range of cognitive and emotional processes can be read out from changes in pupil size. This understanding has been made possible by leveraging recent advancements in the eye-tracking industry, which has produced precise and relatively affordable devices tailored for research purposes. We argue that exploiting this physiological signal can provide a very reliable and informative proxy of mental activity, which can be leveraged to build more refined cognitive models. Providing a direct window to the mind, pupillometry may then help differentiate health from clinical conditions. At the very least, pupil size is an indicator that stems directly from the physiological mechanisms underlying the respective mental states, thus avoiding the multiple biases that affect behavioral performances (e.g., expertise), response times (e.g., motor confounds), or questionnaire answers (e.g., social desirability, degree of self-insight, etc.).

In the last few years, several authoritative reviews have covered in great detail the physiological and cognitive underpinnings of pupil dynamics (Binda & Murray, 2015a; Einhäuser, 2017; Laeng et al., 2012; Mathôt, 2018; Mathôt & Van der Stigchel, 2015; Sirois & Brisson, 2014; Strauch et al., 2022). Reiterating these contributions or offering a systematic overview of current knowledge on human pupillary responses is beyond the scope of this work, which aims to provide essential information and then discuss more applied perspectives. In particular, the present review does not aim to cover all potential clinical applications of pupillometry. For example, pupillometry has clear implications for neurological conditions such as disorders of consciousness (e.g., coma, vegetative states; Hsu & Kuo, 2023; Lieberman et al., 2003; Peluso et al., 2022; Romagnosi et al., 2022; Sangare et al., 2023) and neurodegenerative diseases (e.g., Alzheimer's, Parkinson's; Chougule et al., 2019; Romagnoli et al., 2023; Steiner & de Zeeuw, 2024). This review primarily focuses on pupil size potential as a sensitive biomarker of cognitive functions and dysfunctions, and to this aim, we will bring two exemplary cases, that is anxiety disorders (generalized and specific) and substance use disorders.

2. Neurophysiology of pupil responses

The pupil is the opening located in the center of the eye, whose diameter varies between 2 and 8 mm to regulate light entry (Loewenfeld & Lowenstein, 1993). The pupil has indeed evolved primarily as a tool for vision, whose core and fundamental purposes are to manage the amount of light reaching the retina to optimize visual acuity (Campbell & Gregory, 1960), as well as to block peripheral light rays as to improve image quality on the retina (Banks et al., 2015; Loewenfeld & Lowenstein, 1993). For cognitive neuroscientists, the most interesting piece of information is thus to be found in the residual pupillary dynamics, i.e., the far smaller but meaningful variations that do not respond directly to these necessities. Dilation and constriction of the pupils are controlled by two muscles in the iris: the sphincter muscle, which causes the pupil to constrict (miosis), and the dilator muscle, which causes the pupil to dilate (mydriasis). Pupil diameter is therefore determined by the synergic action of these two muscles, each of them classically associated with distinct parts of the autonomic nervous system (ANS) which regulates bodily functions, mostly outside of voluntary control.

The parasympathetic branch of the ANS is involved in homeostatic processes and, at rest, keeps vital functions in check and promotes relaxation. This is mostly accomplished via the release of acetylcholine (Larsen & Waters, 2018), which slows down the heart rate and allows the pupils to constrict and adjust properly as a function of environmental light levels – i.e., the Pupillary Light Reflex (PLR). The PLR is triggered once the light hits the retina, stimulating its photoreceptors; information then reaches the Edinger-Westphal nucleus (EWn) through the optic nerve (II) and then the Olivary Pretectal Nucleus (OPN) (afferent pathway). The efferent pathway inducing miosis begins at the EWn which, through the oculomotor nerve (III), innervates the ciliary ganglion and from there the sphincter muscle.

The sympathetic branch of the ANS regulates bodily functions in conditions of stress and is involved in arousal, wakefulness, and fight-or-flight responses. This is achieved both by actively suppressing parasympathetic activity and by increasing the levels of noradrenaline (NA). Increased sympathetic activity speeds up heart rate, increases sweating, and enlarges pupil size. The so-called psychosensory pupil response is the dilation of the pupil occurring in response to increased arousal, mental effort—or more generally, anything that 'activates the mind' (Beatty & Lucero-Wagoner, 2000; Mathôt, 2018). This dilation can occur via direct connections with the dilator muscle as well as indirect connections with the sphincter muscle, through inhibition of the EWn.

The parasympathetic and sympathetic pathways thus interact abundantly; delineating clear boundaries is therefore neither easy nor warranted (Blini et al., 2024). However, for the sake of simplicity and in line with previous authors (Mathôt, 2018), in the following sections, we will describe the neural circuits and known modulators separately for the parasympathetic pupil light responses and the psychosensory pupil responses associated with sympathetic activation.

2.1. Modulations of pupillary light responses

The circuit linking increased light levels and pupillary constriction is largely reflexive in nature. It is, however, no stranger to more cognitive-driven modulators via subcortical and cortical structures implicated in high-level processes. For example, the EWn receives direct projections from the intermediate layers of the Superior Colliculus (SC), which may then directly or indirectly inhibit the pupillary constriction pathway inducing pupil dilation (Wang et al., 2012). As for cortical areas, electrophysiological evidence in macaques demonstrated that the PLR circuit receives inputs from the Frontal Eye Field (FEF; Becket Ebitz & Moore, 2019) either directly or indirectly through the occipital cortex and SC (Binda & Murray, 2015a, 2015b).

The SC is a firmly multisensory area that is involved in the instantiation of low-level saliency maps (White et al., 2017), and therefore automatic orienting responses (e.g., eye movements, covert attention) to relevant stimuli or events (Ignashchenkova et al., 2004). The effects of (spatial) orienting and covert attention on pupil size have now been described by several studies (Binda & Murray, 2015b; Strauch et al., 2022; Ten Brink et al., 2023), although these effects are short-lasting and very subtle (up to one order of magnitude smaller than those due to changing light levels, which often co-occur). These effects appear to result in either constriction or dilation depending on the type of stimulus being used: changes in visual input typically evoke a transient pupil constriction (Barbur et al., 1992), whereas non-visual stimuli are expected to elicit a fast transient dilation (Mathôt, 2018). Furthermore, the amplitude of pupil-orienting responses depends on the specific context, such as attentional biases or degree of awareness toward the external stimuli (Binda & Gamlin, 2017; Mathôt & Van der Stigchel, 2015). This is a fascinating feature and object of active research, as it has been suggested that this mechanism may contribute to actively tuning vision so that the optimal amount of light enters the eyes in the current situation or even in the immediate future, depending on the specific needs (Mathôt, 2020; Mathôt & Van der Stigchel, 2015). For example, having dilated pupils and more light entering the eyes can enhance visual sensitivity for dim and faint stimuli (e.g., detection), whereas smaller pupils may yield a benefit in central acuity whenever vision would benefit from more sharpness (e.g., recognition and discrimination). Furthermore, the intention to attend, or the expectation to be soon attending to stimuli of different luminance (e.g., brighter or darker; Laeng et al., 2022; Purves et al., 2014) may trigger preemptive adjustments in pupil size so that no abrupt transitions occur in the amount of light entering the eyes. Beyond the role of expectations and predictive coding, the PLR appears to reflect not only the objective physical

stimulation from the environment (e.g., light levels), but also the content of perception, and the overall context. For example, even when the luminance of the stimuli is kept constant, the pupil response can be modulated by feature and spatial attention (Binda et al., 2014; Binda & Murray, 2015b; Mathôt et al., 2013; Naber et al., 2013), perceptual illusions (Caponi et al., 2024; Castaldi et al., 2021; Suzuki et al., 2019; Tortelli et al., 2021; Zavagno et al., 2017), visual imagery (Laeng & Sulutvedt, 2014; Mathôt et al., 2017), and the semantic content of images (Binda et al., 2013; Castellotti et al., 2020; Castellotti, Francisci, & Del Viva, 2021; Castellotti, Scipioni, et al., 2021; Sperandio et al., 2018).

In short, while traditionally the PLR has been linked to low-level pupillary reflexes, a more careful assessment shows that the picture is more nuanced and that several modulations by cognitive processes are at play.

2.2. Modulations of psychosensory pupil responses

Increased NA levels and sympathetic activation lead to increased pupil size. One major noradrenergic hub in the brain is the Locus Coeruleus (LC), which has been implicated in a broad array of cognitive functions, the most studied of which are perhaps wakefulness and arousal, although several authors have offered more nuanced views (Aston-Jones & Cohen, 2005). In particular, the LC may contribute to adopting a flexible reconfiguration of brain networks (Dahl et al., 2022; Guedj et al., 2017), as ideally suited for the task at hand (Reynaud et al., 2019, 2021). The activity of the LC in humans, measured non-invasively through fMRI and the BOLD signal, covaries with pupil diameter (Murphy et al., 2014). A causal link between LC activity and pupil dilation comes from microstimulation studies, which also highlight a complex and non-selective interaction (Joshi et al., 2016). The modulation can occur via direct connections with the dilator muscle as well as indirect connections with the sphincter muscle, through inhibition of the EWn. In doing so, the LC acts in concert with the SC, the cingulate cortex (both anterior and posterior), and the hypothalamus, with whom the LC entrains excitatory connections and forms evolutionarily ancient, yet flexible, pathways for defensive responses (Li & Wang, 2018). The hypothalamus, in particular, is a limbic structure that connects the nervous and endocrine systems, therefore mediating responses to stress with the regulation of hormones such as cortisol. As part of the limbic system, it is densely connected with the amygdala and areas more tightly associated with the processing of emotions (Dureux et al., 2021). In short, networks and cognitive processes mediating pupil dilation are much more diverse and complex than those mediating pupil constriction to light (DiNuzzo et al., 2019), which adds several layers of uncertainty to modern research. That said, among the many cognitive processes whose signature effect on pupil size has been described, the common denominator is most likely arousal.

2.2.1. Arousal and its pervasive role in cognitive processes

Studies have shown that pupil size decreases with time awake, though this trend is influenced by circadian rhythms (Daguet et al., 2019). Also, both general anesthesia and sedation have been shown to significantly reduce baseline pupil size and the variability of pupillary responses, including spontaneous oscillations like pupillary hippus (Behrends et al., 2019). Factors such as mindfulness meditation have been reported to modulate these oscillations, possibly affecting the autonomic nervous system's balance (Pomè et al., 2020). Additionally, prolonged engagement in mentally demanding tasks can reduce pupil size, linked to mental fatigue and decreased sustained attention (Benitez & Robison, 2022; Hopstaken et al., 2015). Overall, thus, pupil size can be exploited as a relatively good proxy measure of vigilance and arousal, which are themselves – other than basic physiological states – hallmark features or byproducts of several cognitive processes and experimental manipulations. This is true to the point that many cognitive components, traditionally studied in isolation, can actually be reframed in very similar terms when considering their effects on arousal, and thus be effectively measured by pupillometry.

For example, motivation can be conceptualized as the increased willingness to endure costs and undertake some level of physical or cognitive effort to achieve one or more desirable outcomes (Chong et al., 2016). Thus, motivation can be reframed as the amount of arousal elicited by selected reinforcers. To optimally assess and cope with costs and benefits, and their tradeoff, mechanisms that evaluate them must be in place, but an activating system that ultimately provides such energy must also be invoked. While the first task is chiefly ascribed to dopaminergic neurons in the basal ganglia or anterior cingulate cortex, the latter is ideally subserved by noradrenergic neurons in the LC (Varazzani et al., 2015). As a result, motivational aspects are fully captured by changes in pupil size, which has been found to dilate consistently with rewards of different kinds (e.g., monetary; Bijleveld et al., 2009;Manohar & Husain, 2015; Muhammed et al., 2016). In particular, Bijleveld et al. (2009) found that the presentation of monetary rewards of different amounts was associated with a corresponding degree of pupil dilation, even when rewards were presented subliminally, but only when the task required considerable mental effort. These results suggested that pupil dilation responses to different rewards are automatic, but also reflect the involvement of strategic processes (i.e., the evaluation of cost-benefit tradeoffs) that occur outside of awareness. The invigorating effects of rewards on performance were then exploited as biomarkers of blunted sensitivity to rewards in Parkinson's disease or clinical apathy (Manohar & Husain, 2015; Muhammed et al., 2016), in that autonomic reactions to these reinforcers were, in these clinical groups, largely diminished with respect to controls. Apathy occurs frequently in a broad range of neurological and psychiatric conditions (Le Heron et al., 2019); the most common tools for its assessment are structured interviews or questionnaires (e.g., Sockeel et al., 2006). Having shown that pupil size can capture one hallmark feature of clinical apathy (i.e., sensitivity to rewards) is thus important for at least two reasons: first, it provides evidence that pupil size may offer a more precise, objective biomarker stemming directly from the neurocognitive processes involved in the clinical syndrome; second, it suggests that it can be leveraged upon to study the neurocognitive architecture, thus potentially disentangling the contribution of different brain networks or cognitive constructs. With this example, we thus start putting forward the notion that the assessment of pupil size offers a sensible way to enrich the diagnosis and the follow-up of the treatment of clinical conditions, with both impact on society and the quality of life of patients.

Another example of how pervasive arousing effects are is the domain of emotional and affective processing. The observation of angry faces, for example, is thought to evoke arousing, fight-or-flight responses in light of their tapping onto evolutionary ancient mechanisms for self-defense. The result is an activation of the sympathetic, autonomic system that is fully captured by pupil dilation (Bogdanova et al., 2022; Dureux et al., 2021; Kret et al., 2013; Wang et al., 2018). Consequently, arousing effects of angry or fearful faces have been exploited in the quest for biomarkers of anxiety disorders (Kleberg et al., 2019; Price et al., 2013), where pupillary responses often indicate either heightened vigilance or active avoidance in anxious individuals, and autism, where blunted pupillary responses have been discussed in relation to impaired social communication skills (Anderson et al., 2006). More generally, naturalistic images linked to danger (like snakes) induce a heightened arousal state, that can be detected through pupil dilation and helps distinguish extreme reactions, such as in people with specific phobias (Hoehl et al., 2017; Rosa et al., 2015). Overall, the fact that the pupils similarly dilate to both negative (e.g., threatening) and positive (e.g., rewards) stimuli suggests that, beyond valence, what driving this effect is a more general arousing property of the stimuli or the task at hand (Finke et al., 2021).

Beyond specific examples and domains, pupil size generally correlates with the real or expected difficulty of a motor task (Koevoet et al., 2023; Moresi et al., 2008; Wang et al., 2016). This is probably related to the preparation of a quicker and more intense motor response (Akdoğan

et al., 2016; Blini & Zorzi, 2023) reflecting yet again the core function of arousal. Disorders of voluntary movement and movement preparation lead to dysfunctions of this anticipatory circuit, so that, for example, pupillary responses of this kind are blunted in Parkinson's disease (Wang et al., 2016). This finding parallels well that of a decreased sensitivity to rewards in these patients, again exemplifying how pupil dilation, in conjunction with a suitable behavioral paradigm, can offer rich and complementary information, capable of sensibly enhancing diagnosis and providing a fine-grained resolution for one's individual cognitive profile.

2.2.2. *Mental preparation, effort, and cognitive load*

Anticipatory and in-task pupil dilation is also seen for tasks without a motor component but differing in their degree of difficulty. The fact that pupil size appears to be modulated by the amount of (cognitive) resources allocated to the task at hand closely aligns with the definition of alertness as the overall state of the brain that allows optimal processing of information (Petersen & Posner, 2012; Posner, 2008). Pupil size thus covaries with the mental effort deployed across tasks of varying difficulty, i.e., cognitive load.

Pupillometry has long been recognized as a powerful tool for investigating high-level mental processes, with its prominence solidified by landmark studies from the mid-20th century (Beatty & Kahneman, 1966; Hess & Polt, 1964; Kahneman & Beatty, 1966; for a review see Beatty & Lucero-Wagoner, 2000). Interestingly, a closer examination of historical literature reveals that much of what we know today about pupil size changes was already observed as early as the 1920s (for reviews see Loewenfeld & Lowenstein, 1993; Strauch, 2024). Nevertheless, the work of Hess and Polt, along with Kahneman and Beatty, remains particularly influential for showcasing the sensitivity of pupil size as an index of task difficulty and cognitive effort (Beatty & Kahneman, 1966; Hess & Polt, 1964; Kahneman & Beatty, 1966). For instance, Hess and Polt (1964) found that pupil dilation increased significantly when participants solved more challenging arithmetic problems that involved complex computations, compared to simpler tasks requiring only fact retrieval. Later, Kahneman and Beatty (1966) explained this effect by linking it to variations in working memory load, demonstrating that pupil dilation consistently dilates with the number of digits retained in memory. Thus, these seminal studies paved the way for the adoption of pupillometry by showing that it could be used to complement response times in behavioral paradigms. Furthermore, this early interest led to the first attempts to use task-evoked pupillary dilation as a biomarker of cognitive processes and related constructs. For instance, Ahren and Beatty showed that the amount of pupil dilation to mental arithmetic problems was higher in individuals with low scores in scholastic aptitude tests with respect to their peers with higher scores, which was interpreted in terms of this group needing to invest more effort in order to accomplish the tasks (Ahren & Beatty, 1979). Decades later, these results have been confirmed and expanded upon: task-related pupil dilation to varying levels of the cognitive load has been proposed as a sensitive biomarker of the early stages of dementia such as Alzheimer's (Granholm et al., 2017). The underlying assumption, once again, is that the increased dilation seen in this group reflects the increased mental effort, which, once the capacity of compensatory mechanisms is surpassed, may result in cognitive impairments. As these changes in cognitive capacity can be precisely indexed by changes in pupil responses, evidence has been gathered that pupil size may provide a very sensitive proxy of brain cognitive dysfunctions (i.e., degeneration of the LC has been often reported in the early stages of dementia; Jacobs et al., 2023). Obviously, the possibility to achieve early detection of the degeneration of brain functions has tremendous potential for the patients and their caregivers, in that it allows a prompt response to the disease and sets realistic expectations for the future.

A good share of the success of pupillometry in providing biomarkers for cognitive states and dysfunctions can be ascribed to the increased resolution of eye-trackers in capturing even subtle, short-lived changes in pupil dilation. Another determinant, however, has been an increased understanding of the manifold variables that impact pupil dynamics, encompassing both low-level (e.g., reflexes to light or depth) and high-level (e.g., executive functions) aspects of cognition (Lisi et al., 2015; Strauch et al., 2022; Wahn et al., 2016). For example, Lisi et al. (2015) found that concurrent task demands – i.e., single- or multi-tasking under identical conditions of sensory and perceptual stimulation – yield robust pupil dilation regardless of the sensory modality in which the secondary task is presented. Thus, pupillometry can capture signatures of divided attention – a purely top-down and high-level construct that is, however, much more specific than the general umbrella term of “cognitive load”. In the last years, thus, after a surge in pupillometry research, it has been increasingly clear that pupil dilation may indeed reflect the state of several distinct attentional networks and provide an integrated readout of their combined activation and functioning (Strauch et al., 2022), extending far beyond arousal. This property ultimately provides flexibility, sensitivity, and a sharp discriminatory power, especially when used in conjunction with suitable behavioral paradigms. In the following sections, we offer perspectives on how this could be the case in exemplary applied domains.

3. Future avenues and opportunities

In the previous paragraphs, we have outlined how and why pupillometry can be effectively exploited to enhance current research and behavioral paradigms, briefly mentioning those designed for clinical testing. In this section, we further tackle this general core message by focusing on two test cases, anxiety disorders (both generalized and specific - e.g., generalized anxiety vs. math anxiety) and substance use disorders, areas where pupillometry might play a key role in improving the sensitivity of disease assessment and therapeutic rehabilitative procedure efficiency.

3.1. *A perspective for anxiety disorders*

In this paragraph, we attempt to provide a perspective of how pupillometry could be leveraged, combined with a suitable behavioral task, to study multiple facets of cognitive processes as they often coexist in ecological situations, such as in clinical disorders. We focus specifically on anxiety, which tends to occur with a high degree of comorbidity, even though the underlying neurocognitive processes may differ in some distinctive features. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (APA, 2013) encompasses 11 separate disorders of anxiety, each associated with distinctive features apt for differential diagnosis. The common feature of these disorders is the presence of excessive and enduring fear, concern and/or the avoidance of perceived threats (Craske et al., 2017). Threats can refer to the external (e.g., social situations) or internal (e.g., bodily sensations) environment. The avoidance behaviors can range from a refusal to enter certain situations to more subtle strategies aimed at relying on others or procrastinating. Panic attacks can occasionally characterize anxiety disorders as a type of abrupt fear response (Grupe & Nitschke, 2013), and are defined by a range of autonomic reactions (e.g., increased heart rate and blood pressure, respiratory frequency, pupil dilation, pallor and/or sweating). At any rate, anxiety disorders constitute the largest group of mental disorders in most Western societies and are a leading cause of disability (Craske et al., 2017).

In neurocognitive terms, anxiety can unfold, be assessed, and be characterized at least in three different stages. The first part concerns the anticipation of future threats; this stage is thus future-oriented and may involve some degree of preparation and/or avoidance of the eliciting situations. Then, a second stage entails coping with environmental threats; this stage is instead present-oriented and involves some degree of excessive fear and the accompanying autonomic reactions. Last, anxiety may be related to others' judgment in general or with reference to one's own performance; this is particularly pertinent in the most

performative domains of anxiety (e.g., test anxiety). Thus, this part follows the specific threats or performances (being somehow "past-oriented") but nevertheless is potentially capable of shaping future instances of the same situations and feed a vicious loop consisting of increasing anxiety. Here we show that pupillometry can characterize and provide useful information for all these three stages, provided that the experimental design allows for such distinction.

For many years, the predominant focus of research in clinical anxiety has been the heightened response to emotional and aversive stimuli or events. This formulation is more closely related to today's definition of "fear" as an appropriate, present-oriented, and short-lived response to a specific threat. Since it is defined in terms of an increased state of autonomic activation, this aspect can be easily picked up by pupil dilation (De Zorzi et al., 2021). The most natural way to measure this aspect is the simple exposure to anxiogenic stimuli, to which the pupils are expected to respond with a robust dilation reflecting arousal. One example is the observation of angry faces, or an aggressive context, which activates the sympathetic autonomic system, fully captured by pupil dilation (Bogdanova et al., 2022; Dureux et al., 2021; Kret et al., 2013; Wang et al., 2018). For this reason, the modulation of pupil size following the observation of emotional faces has been proposed as a biomarker for anxiety disorders. For example, Kleberg et al. (2019) found that individuals with Social Anxiety Disorders (SAD) show an atypical time course of the pupil dilation response to both angry and happy faces compared to control participants. They also found that increased pupil dilation amplitude to happy faces before the onset of a cognitive-behavioral treatment program predicted a less favorable outcome (Kleberg et al., 2019). Also, Price et al. (2013) found a sustained pupil dilation in anxious preadolescents in response to fearful faces compared to neutral faces, along with marked differences with respect to controls. These findings chiefly suggest a heightened vigilance state or active avoidance in anxious people (Price et al., 2013). Also, pupillary responses to naturalistic images directly bound to the threat and danger (e.g., images of spiders or snakes) can then be exploited to differentiate the extreme ends of humans' response to these cues as in the case of people affected by specific phobias (Hoehl et al., 2017; Rosa et al., 2015), allowing an objective evaluation of the stimuli induced reactions during treatment protocols (e.g., behavioral desensitization; Sturgeon et al., 1989).

More recently, the theoretical focus in anxiety research has shifted toward considering excessive anticipatory responses, especially under broad uncertainty (Grupe & Nitschke, 2013). Anticipatory reactions and mental representations of possible future events are also well detectable and can be objectively quantified by changes in pupil size, given the appropriate paradigm, in that they similarly invoke changes of a variable degree of alertness (Nassar et al., 2012). For instance, we have discussed that the pupils dilate steeply in anticipation of a motor response or with the temporal expectation of a stimulus to appear, and this correlates with the amount of anticipated mental effort and preparation (Moresi et al., 2008; Wang et al., 2016). Thus, a behavioral paradigm designed to highlight this aspect would rather focus on the pre-stimulus phase, appropriately cued in order to ingenerate expectations, in which larger pupil dilations may suggest a heightened alertness state. This aspect is very well illustrated by classic conditioning studies. Classic conditioning is the process by which a conditioned stimulus, previously neutral, gradually acquires behavioral salience due to its probabilistic pairing with an unconditioned stimulus associated with large autonomic reactions (e.g., a mild electric shock, a reward such as food). The process, therefore, involves learning processes, as well as the formation of memory associations that guide the predictions of future co-occurrences between the two classes of stimuli. Pupil dilation has been suggested to be a reliable index of learning and memory consolidation since Pavlov's seminal first reports, but it is only in the last two decades that improved eye-tracking technology has given a strong impulse to this line of research. As a result, a recent meta-analysis concluded that pupil dilation is a valid and sensitive biomarker of both appetitive and aversive conditioning (Finke et al., 2021), although the specific determinants and underlying mechanisms (beyond increased alertness) are still to be fully understood.

That said, it is interesting to note the similarity between the performance curve of anticipation anxiety and pupil dilation. Anticipation anxiety is not inherently detrimental to behavioral performance; to some extent, a variable degree of anticipation offers an adaptive fashion to better prepare and allocate mental resources and thus is often preferable to no preparation at all. On the other hand, excessive anxiety leads to performance decrements and distractibility, e.g., due to intrusive thoughts (Rosen & Schulkin, 1998). Likewise, the link between pupil dilation and behavioral performance seems to follow a similar, reversed-U shape: both the lowest LC tonic activity (i.e., smaller changes in pupil size) and the highest (i.e., larger changes in pupil size) are associated with a detrimental impact on performance, chiefly ascribed to drowsiness in the first case, or explorative behavior (e.g., distractibility) in the latter (Murphy et al., 2011), whereas the optimal spot would be somewhere in the middle. In short, the study of anticipatory alertness appears key for anxiety research, and pupil dilation is likely the optimal proxy measure for this construct.

Finally, one long-lasting matter of contention in the more performative domains of anxiety (e.g., test anxiety; Hembree, 1988) is the role of fear of negative evaluations, which can either be conceptualized as a cause or as a consequence of impaired performance. At any rate, the perception of feedback as particularly negative, or emotionally distressing, can have long-reaching effects on subsequent occurrences of the same situations, feeding into a vicious loop of increased anticipation anxiety and further avoidance. In this case, monitoring the changes in pupil size during the presentation of feedback would be particularly informative because the corresponding affective, arousing effect could be quantified precisely and then used in the context of the statistical modeling of behavioral data. In this regard, it is fascinating to note how several studies have linked the pupil-linked arousal system to the maintaining of internal belief systems, for example concerning perceptual confidence (Colizoli et al., 2018). Changes in pupil size following the feedback have been linked, in particular, to surprise (Preuschoff et al., 2011) and the computing of prediction errors that have an active role in shaping behavioral performance via the updating of the mental representation of the tasks (Braem et al., 2015), although the research in this specific domain is currently still active.

To summarize, even in the case of a rather heterogeneous class of disorders and clinical manifestations, pupillometry, in conjunction with suitable methodological arrangements, may provide an integrated, but reliable biomarker that, in some circumstances, might also tease apart specific cognitive processes as well as individual differences in their instantiation. This implies that pupil size has the potential to go beyond broad classifications of mental states or conditions (e.g., anxiety), to reach more circumscribed and narrow domains. For example, within the broad domain of anxiety, math anxiety can be defined as excessive fear and worry about math-related performance or situations which includes elements of avoidance (Caviola et al., 2017; Maldonado Moscoso et al., 2020, 2022). While several common traits may accompany math anxiety and general anxiety, the two constructs are relatively independent (Hill et al., 2016). Math anxiety is a debilitating condition in that it decreases self-confidence in students and creates a barrier that hampers successful learning (Ashcraft et al., 2021), hence an improved identification of math anxiety is highly needed (Primi et al., 2014). Yet, to date math anxiety is only assessed via questionnaires (i.e., the AMAS; Hopko et al., 2003). Crucially, the existence of possible biomarkers to bridge this gap, e.g., related to pupil size, has so far received little consideration, with very few exceptions. Layzer Yavin et al. (2022), for example, showed that math-related words (e.g., "estimate") are processed more similarly to words with a negative (e.g., "missiles") than neutral valence (e.g., "drawer"), thus substantiating the notion that stimuli related to mathematics can evoke fear and pupil dilation (Layzer Yavin et al., 2022). Throndsen et al. (2022), on the other hand, found that math anxiety,

measured in young adults, did not moderate cognitive effort (measured via pupil dilation) when performing complex multiplications (Throndsen et al., 2022). Thus, while to date very few studies have tackled this issue, the ground seems fertile for further investigations on the matter: we suggest that pupil size has the potential to return objective signatures of (math) anxiety in a very inexpensive, precise way, and future studies should leverage on this capability to reach an enhanced classification of young students.

3.2. A perspective for substance use disorders

As discussed above, pupil size may provide a finely grained readout of one's physiological state, in terms of the balance between the sympathetic and parasympathetic autonomic systems. Thus, it appeals to the measurement of a broad range of physiological processes and their dysfunctions, and one particularly pressing example is craving within the context of addiction (Kronberg & Goldstein, 2023). Craving is defined as a strong desire to consume a substance, from food to drugs: being framed in motivational terms, thus, it involves a state of heightened arousal that, as detailed above, can potentially be fruitfully measured by changes in pupil size. Craving is another example of a construct that is currently mostly measured via self-reports or questionnaires (e.g., the Questionnaire of Smoking Urges, QSU, for smoking Cox et al., 2001), while multiple authors have stressed the importance of having more objective biomarkers (Kronberg & Goldstein, 2023). Recent fMRI (Koban et al., 2023) and EEG studies (Parvaz et al., 2016) have started bridging this gap by exploiting the fact that, to some extent, craving can be elicited by relevant visual cues (e.g., a particular food or items connected to one's addiction). Thus, autonomic reactions can be probed by presenting salient images to participants or patients, and their extent can provide in principle a proxy for current craving levels. The problem remains, however, that most studies have still relied on self-reports to guide the search for optimal biomarkers. In one common paradigm, for example, pictures of addiction-related cues are shown while some kind of physiological recording is acquired. In detail, following each stimulus, patients were asked to rate their current desire to consume that item via a Likert scale. These quantitative responses were exploited to search for the relevant signal in physiological recordings (e.g., fMRI; Koban et al., 2023). However, for how sensitive biological biomarkers can be, one can only look for them where self-reports suggest one to look, thereby exposing one to the risk of being misled by demand characteristics or limitations in the individual's level of insight (Kronberg & Goldstein, 2023). To overcome this limitation, few studies have exploited one core feature of cue-induced craving, which is its automaticity. First of all, the cues are salient because the repeated exposition to them in real life was often accompanied by their consumption (and thus the resulting physiological alterations), therefore eliciting associative learning and conditioning processes; as detailed above, pupil size is a robust marker of classic conditioning. Second, it is long known in cognitive psychology that intrinsically rewarding stimuli can “grab” attentional resources quite powerfully (Blini et al., 2018; Chelazzi et al., 2013). Likewise, cues related to one's addiction have been found to capture spatial attention with a very specific time course (e.g., both early on and in later stages; Della Libera et al., 2019). These stimuli gain high attentional priority in everyday life situations, creating a vicious loop believed to help maintain addiction (Volkow et al., 2010), and to the point of hampering inhibitory and monitoring processes (Blini et al., 2020; Cox et al., 2006). While the causal role of attentional bias in addiction is still debated, it has been nevertheless pointed at as a valid marker of the underlying, fluctuating motivational state (Christiansen et al., 2017), including clinically meaningful information such as current craving level (Field et al., 2014). Studies that have explored this feature via pupillometry are still, however, very scarce. In mice, olfactory stimuli that were previously paired with cocaine injections lead to transient pupil dilation (Smith et al., 2016). A similar dilation is seen, upon presentation of meaningful visual cues, in smokers (Chae et al., 2008), or cocaine-users (Rosse et al., 1995). Pupil dilation to alcohol-related cues, furthermore, can be exploited as a valid prognostic factor in predicting the odds of alcohol relapse during treatment, suggesting it may reflect craving (Kvamme et al., 2019). At any rate, pupil size has been found capable of predicting the status (e.g., smoker or not) of out-of-sample, young individuals in that different for addiction-related visual cues (e.g., people smoking) than for the respective, matched control images (Blini & Zorzi, 2023). In this case, however, the most predictive feature was a constriction of the pupils occurring very early in the course of visual analysis. The behavioral paradigms that accompany physiological recordings, once again, can largely account for this different pattern of changes in pupil size. In Blini and Zorzi (2023), for example, the main task was to await and respond quickly to a rare probe that was occasionally presented following the presentation of the experimental images. As discussed above, the pupils in this condition dilate steadily and steeply due to an enhanced alert state, and the temporal predictions that a probe may soon appear. Having observed constriction for salient images, in this setting, was interpreted as nicotine-related cues subtracting attentional resources to this main task (e.g., being more distracting, because capturing attention more strongly). Another potential explanation of the finding was a modulation of the PLR given, once again, by attentional orienting processes that would be more pronounced in the case of salient images. An explanation in terms of spatial attentional resources was partially supported by the correlation between pupillary constriction and an independent task aimed at measuring precisely this construct (i.e., a dot-probe task, akin to Posner's paradigm to assess spatial attention). To summarize, even in the case of a construct as diverse as craving in addiction, pupillometry has the potential, still largely unexplored, to offer high predictive power and return relevant information. However, predictive power is rarely effective on its own without proper control, control being in this case the use of the most suited behavioral paradigm, that is one in which the most likely cognitive processes at play are duly identified.

4. Technical challenges and limitations

Despite the increasing availability of affordable and reliable eye-tracking tools, designing rigorous pupillometry experiments remains challenging and demands careful attention to various technical and methodological details. As Steinhauer and Hakerem (1992) aptly noted, while modern technology enables rapid data collection, there is a risk that the speed of experiment generation may lead to more routinized, rather than well-conceived paradigms (Steinhauer & Hakerem, 1992). This issue is not unique to pupillometry but extends to many research techniques that have become more accessible in recent years.

Despite some important, recent attempts (Fink et al., 2024; Mathôt & Vilotijević, 2022), there is still little consensus on the optimal pipeline for processing pupillary time series. Handling these data can be tricky in light of the artifacts spawning within each experimental trial. First of all, blinks are inevitable in any setting and must be dealt with accordingly: beyond the data loss occurring while the eyes are closed, the estimation of pupil diameter by eye trackers in the proximity of a blink is also affected and imprecise due to the partial occlusion of the eyes by the eyelids. Thus, robust data-cleaning techniques of the time series must be in place, often requiring interpolation and/or smoothing. Overall, the analysis of pupillary data typically requires substantial pre-processing, including signal averaging and baseline correction procedures, to reduce trail-level single-subject variability and obtain reliable group-level results.

The most challenging aspects of pupillometry, however, are not related to data analysis as much as to experiment design. Pupil diameter changes first and foremost to adapt to different light levels. It is therefore paramount that different experimental conditions do not covary with different light levels (e.g., all experimental stimuli should have the same luminance), in order to avoid misleading interpretations. The same is, however, also true for a broad range of low-level features such as, e.g.,

spatial frequency, density, and contrast (Barbur et al., 1992; Cai et al., 2024). Second, the position of the eyes should ideally be constant across the experiment, since their position in the ocular globe may impact the estimation of pupil size by the eye trackers' infrared cameras. Third, participants should ideally be as constrained as possible and attempt to stay still, in that motor activity does impact pupil diameter. Indeed, in all cases in which manual/motor responses are required, it has to be taken into account that these would almost certainly impact the time course of the changes in pupil size with a robust dilation – probably occurring following a quick, light-induced, constriction due to changes in the context – which will dominate the signal leaving less room for more subtle, cognitive effects to be detected, at least in the early stages of the trial. This leads to the final caveat of the technique: changes in pupil size are determined by the synergic action of two muscles and thus are rather slow when compared to the time scale of neural activity. The earliest effects, e.g., due to changing light levels, may emerge after 200–300 ms, and continue for several seconds afterward. More cognitively-driven effects can emerge later, with the additional complication that, of course, different cognitive processes have their distinctive latency (Blini et al., 2024). Thus, experimental designs would ideally be sufficiently long to allow the evaluation of an extended time window, but also sufficiently separated (in terms of inter-trial interval) to allow the pupils to return to baseline levels. At any rate, due to the short-lived and subtle nature of many pupillary reactions, a very precise time-synch between experimental stimuli and eye recordings is warranted.

Finally, the most pressing limit at a conceptual level is that pupillometry, with respect to other techniques such as EEG, lacks the depth and dimensionality to easily tease apart the source(s) of specific effects (e.g., neural areas). As reviewed above, pupil dilation rather reflects the integrated output of several, distinct attentional and emotional/motivational networks. So, at state, without further advances in computational models to clarify the generative processes behind pupil changes, the specific subsystem that gets activated as a response to a given stimulus cannot be easily ruled out and such duty has to be largely demanded to the experimental design.

5. Concluding remarks

Despite the technical limitations exposed above, pupillometry remains a valuable tool in both research and practical applications (e.g., clinical settings). In particular, while it may not be easy to separate the contributions of specific networks solely by assessing pupil size, the ability to obtain a rich, integrated view of the various processes underlying specific cognitive states is certainly valuable in the context of mental chronometry and in the search for reliable biomarkers of specific dysfunctions. Particularly appealing is the capability to provide indications about automatic processes, not as heavily reliant on the development of verbal and global reasoning abilities. It is thus time to move past, whenever feasible, coarse questionnaire-based assessments of behavioral traits or states to adopt more graded, objective, and physiologically informed methods. The advancements in the eye tracking industry brought about the availability of inexpensive, non-invasive, and reliable tools to measure eye movements and changes in pupil size, often with a sampling rate much superior to what would be necessary for this aim. Thus, it is likely that pupillometry will increasingly gain traction - in the near future - as an appealing tool to investigate mental cognitive functions and dysfunctions.

CRediT authorship contribution statement

Serena Castellotti: Writing – review & editing, Writing – original draft. **Elisa Castaldi:** Writing – review & editing. **Elvio Blini:** Writing – review & editing, Writing – original draft. **Roberto Arrighi:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Data availability

No data was used for the research described in the article.

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