

Beyond eye gaze: What else can eyetracking reveal about cognition and cognitive development?



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ABSTRACT

This review provides an introduction to two eyetracking measures that can be used to study cognitive development and plasticity: pupil dilation and spontaneous blink rate. We begin by outlining the rich history of gaze analysis, which can reveal the current focus of attention as well as cognitive strategies. We then turn to the two lesser-utilized ocular measures. Pupil dilation is modulated by the brain's locus coeruleus-norepinephrine system, which controls physiological arousal and attention, and has been used as a measure of subjective task difficulty, mental effort, and neural gain. Spontaneous eyeblink rate correlates with levels of dopamine in the central nervous system, and can reveal processes underlying learning and goal-directed behavior. Taken together, gaze, pupil dilation, and blink rate are three non-invasive and complementary measures of cognition with high temporal resolution and well-understood neural foundations. Here we review the neural foundations of pupil dilation and blink rate, provide examples of their usage, describe analytic methods and methodological considerations, and discuss their potential for research on learning, cognitive development, and plasticity.

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1. Introduction

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A remarkable insight from the field of psychology is the fact that we can probe the inner workings of the mind by measuring

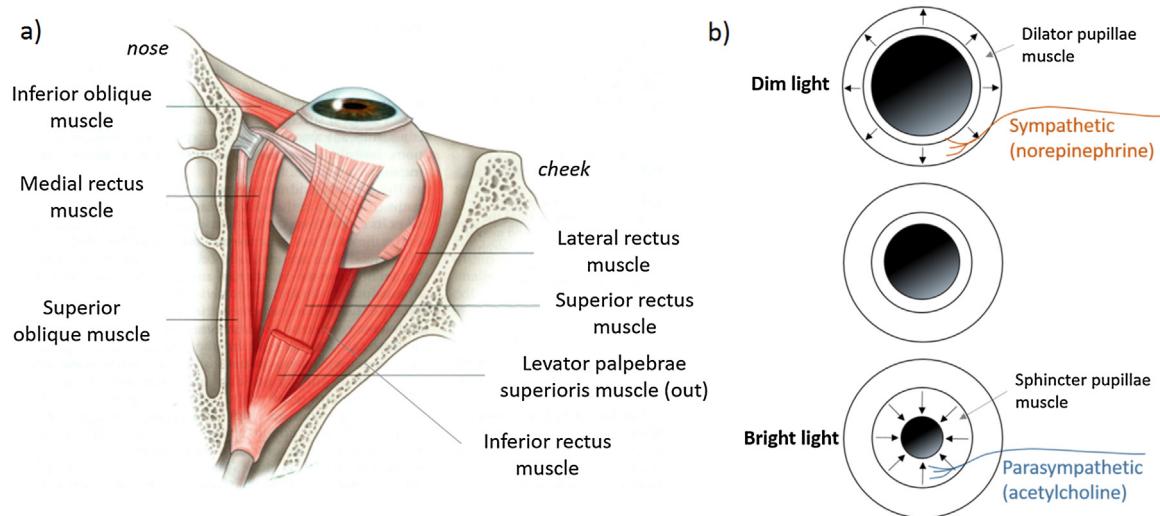


Fig. 1. Eye muscles responsible for eye movements and pupil dilation and contraction. a) Superior view of the eye. The superior and inferior rectus muscles are responsible for the eye's vertical movements, whereas the lateral and medial rectus muscles control horizontal movements. Adapted with permission from Eds. [Levin et al., \(2011\)](#). b) Top: The dilator pupillae muscle dilates the pupil and is controlled by sympathetic fibers. Bottom: The sphincter pupillae muscle contracts the pupil and is controlled by parasympathetic fibers. The balance between the activation of the dilator and sphincter pupillae muscles dictates pupil diameters.

how various eye muscles contract (Fig. 1). Cognitive psychologists have exploited this fact for over two centuries (e.g., Wells, 1792; Hering, 1879; cited by Wade, 2015). Over the last two decades, however, eyetracking has largely taken a backseat to brain imaging research as a way to study the mechanisms that underlie behavior. Now, thanks to notable improvements in eyetracking hardware, software, and analytic approaches, as well as increased recognition of the limits of what we can learn from brain imaging, eyetracking is regaining its former status. The overarching goals of this review paper are threefold: first, to provide an overview of ocular measures and what we have learned from studies in adults about their neurobiological underpinnings and behavioral correlates; second, to discuss methodological approaches and considerations; and third, to discuss how eyetracking has been and could be extended to study cognitive development. The most commonly utilized ocular measure is that of eye gaze; we will provide only a brief overview of this approach before focusing primarily on task-evoked pupillary responses and spontaneous eyeblink rate. This review focuses on the applicability of these measures to our understanding of cognitive functioning in neurotypical children and adults; however, this methodology is also useful in clinical research (e.g., Blaser et al., 2014; Burkhouse et al., 2015; Caplan and Guthrie, 1994; Chan and Chen, 2004; Fried et al., 2014; Hallett, 2000; Karson, 1988; Rommelse et al., 2008; Tulen et al., 1999).

One might think of eyetracking as either an impoverished measure of brain function or a rich measure of cognition. However, it can complement both behavioral and brain measures. Indeed, it has been argued that oculomotor studies provide an ideal neuroscience model to investigate association between brain mechanisms and behavior (e.g., Luna et al., 2008). Ocular measures can provide additional information over and above accuracy and response times as a result of their high temporal resolution, making it possible to measure how people respond to task demands on a moment-by-moment basis. Indeed, eyetracking sampling rates range from 25 to 2000 measurements per second, which means that the faster eyetrackers achieve sub-millisecond temporal resolution, similar to EEG. Despite being an indirect measure of brain function, eyetracking has several advantages compared to EEG and fMRI, which make it the better choice for a number of paradigms and research questions. First, given that participants can be seated comfortably at a table during data collection (or can move freely, with a

head-mounted eyetracker), testing can happen in a more natural environment than the noisy and space-restricted environment of the MRI scanner. Second, most eyetrackers are portable, making it possible to take them to schools, hospitals, and other venues. As such, it is possible to reach a larger and more diverse population than the small pool of participants who are willing and able to travel to research facilities. Third, the rapid calibration procedures available on modern eyetrackers make it possible to begin an experiment quickly. This is particularly helpful for developmental researchers seeking to minimize testing time.

In many studies, ocular data are captured for the sole purpose of ensuring that participants maintain fixation at the center of the screen. However, the measurement of eye position can also provide a moment-by-moment assessment of thought processes in a wide variety of contexts (e.g., Shepherd et al., 1986; Theeuwes et al., 2009; Van der Stigchel et al., 2006). Yarbus (1967) provided a simple illustration of this idea, asking subjects different questions as they viewed the same painting. When asked to judge the age of each character, the sample participant looked primarily at the depicted faces; when asked to judge the material wealth of the family, he looked primarily at the characters' clothing and some of the surrounding objects.

In the decades since Yarbus' vivid demonstration, numerous studies have corroborated the fact that one's eyes are generally directed towards the object of one's thoughts (Ferreira et al., 2008; Just and Carpenter, 1980, 1976; Theeuwes et al., 2009; Thomas and Lleras, 2007; Van der Stigchel et al., 2006). Indeed, although it is possible to attend covertly to a spatial location without moving one's eyes to it, it is not only more common but also more effective to fixate what we are attending to (Deubel and Schneider, 1996; Shepherd et al., 1986). Further, fMRI and cortical stimulation research corroborate the close link between attention and gaze, showing that the frontal eye fields (FEF), which control eye movements, are also implicated in the deployment of covert visual attention (Awh et al., 2006; Corbetta et al., 1998; Grosbras et al., 2005; Müller et al., 2005).

Multiple gaze metrics that have been used to study cognition in adults are derived from eye position data. Fixations are used to calculate time spent looking at a particular location, which in turn is thought to reflect engagement of attention and the time needed to process the stimulus at that location. This metric has been used

to gain insights into what we remember (e.g., Hannula et al., 2010), how we perform mental computations (e.g., Green et al., 2007), how we read (e.g., Rayner, 1998), how we solve problems (e.g., Grant and Spivey, 2003), and how we learn (Rehder and Hoffman, 2005; Lai et al., 2013). Saccades, the rapid eye movements that allow us to shift between fixations, can reflect shifts in attention that are either controlled (e.g. a voluntary eye movement or saccade towards a target) or automatic and stimulus-driven (e.g., a reflexive saccade towards a sudden stimulus) (Luna et al., 2008). The accuracy and latency of saccades have provided insights for example about cognitive control capacity (e.g., Funahashi et al., 1989; Luna and Velanova, 2011; Munoz and Everling, 2004). The number of saccades between task-relevant stimuli, which is assumed to reflect the process of comparing specific stimuli or integrating several pieces of information, has been used to study reasoning (Demarais and Cohen, 1998; Thibaut and French, 2016; Vigneau et al., 2006); Some research questions require analysis of scan paths, rather than simple quantification of fixation and saccade measures. In these types of investigations, the subject of interest is how people approach a problem space, so the measure must encapsulate multiple fixations and the path of movements between them (Bochynska and Laeng, 2015; Dewhurst et al., 2012; Hayes et al., 2011; Yoon and Narayanan, 2004).

We have identified three broad classes of eye movement studies of cognitive development (Fig. 2). The first of these is comprised of studies that measure reflexive orienting to a stimulus (i.e., reflexive saccades). The second class involves tasks in which the target response is a voluntary eye movement (i.e., voluntary saccades), wherein measurement of saccades is needed to measure task accuracy and response latency. Finally, the third class involves measures of spontaneous eye gaze patterns (i.e., scan paths) during analysis of a complex stimulus or a set or series of stimuli, for example in studies of higher-order cognitive abilities like reading or reasoning.

The first class of studies has been particularly useful for studying cognitive processes in infancy, since the brain pathways that control reflexive saccades are relatively mature at birth, whereas those controlling voluntary eye movements are immature at birth but develop rapidly during the first six months of infancy (Richards and Hunter, 2002).

In an effort to understand what they know or remember, researchers measure how long infants look at a novel or unexpected stimulus. This implicit measure of attention is analogous to 'looking time' measures of head turns towards an object, but is considered more precise (Aslin and McMurray, 2004; Feng, 2011; Franchak et al., 2011). Eye movement analyses have already been used extensively to characterize the expectations and cognitive processes of infants (for a review see Gredebäck et al., 2009).

In a study of language comprehension, for example, Lewkowicz and Hansen-Tift (2012) showed that 8–10-month-old infants looked longer at a speaker's mouth than at her eyes, whereas younger infants and older children and adults both showed the opposite preference (Fig. 2a). All infants looked more at the speaker's mouth during infant-directed speech as opposed to adult-directed speech. The authors' interpretation is that infants direct their attention to the mouth as they learn to produce sounds, whereas older children and adults tend to focus on the eyes to glean social cues (Lewkowicz and Hansen-Tift, 2012). A separate longitudinal study showed that the transition from focusing on a speaker's eyes to her mouth happened between 6 and 9 months of age (Tenenbaum et al., 2013). This approach has also been used to probe infants' sustained and joint attention, object representation, perceptual completion, and relational memory (Gredebäck et al., 2009; Johnson et al., 2003; Richmond and Nelson, 2009; Yu and Smith, 2016, in press).

The second class of studies can only be successfully administered on older children and adults, wherein they must perform a

task that explicitly requires them to make specific eye movements in accordance with task rules. Perhaps the best example is a measure of cognitive control known as the antisaccade task (Hallett, 1978; Munoz and Everling, 2004). On this task, participants are asked to fixate at the center of the screen and wait for a stimulus to flash. On prosaccade trials, they are asked to move their eyes rapidly to the target; on antisaccade trials, they must move their eyes to the mirror-opposite location of the screen. As noted previously, orienting towards a stimulus is reflexive; thus, moving one's eyes to the opposite location on the screen requires inhibitory control, as well as maintenance of the relevant task rule. Using this task, Luna et al. have shown that cognitive control improves gradually over childhood and adolescence, leading to fewer and fewer errors on antisaccade trials (Luna et al., 2004). In fact, this task reveals a more protracted developmental trajectory for cognitive control than most tasks involving hand movements, likely because it is particularly difficult to break the strong link between attention and gaze (Deubel and Schneider, 1996; Shepherd et al., 1986). This second class of oculomotor studies also includes investigations of the development of processing speed (Luna et al., 2004), planning (Asato et al., 2006), language (e.g., atypical patterns in dyslexia; Tiadi et al., 2016), mental imagery (Johansson et al., 2006), and spatial working memory (Luna and Velanova, 2011; see also Theeuwes et al., 2009).

The third class of studies involves analysis of sequences of saccades around a complex stimulus. There is a smaller developmental literature using this approach than the others, but there are some examples. For example, eye movement analysis has been used to characterize differences in the way in which beginning and skilled readers approach a text. Typically, while reading, very short words are not fixated at all, while longer words almost always are, and people often go back and fixate again on words that have more letters or are more difficult to comprehend (Rayner, 1998). Beginning readers or less-skilled readers exhibit longer fixations, shorter saccades, and more refixations than skilled readers (Rayner, 2009). Delving more deeply into sources of individual differences in eye movement patterns during reading, several researchers have found that working memory capacity is an important factor (Calvo, 2001; Traxler et al., 2005). Thus, combining eye gaze analysis with independent cognitive measures can help us to isolate key processes underlying a complex behavior.

Researchers have also begun to use gaze measures to study the development of the ability to reason about novel problems (Chen et al., 2016; French and Thibaut, 2014; Gladý et al., 2012; Thibaut et al., 2011; Thibaut and French, 2016). We are beginning to understand the neural underpinnings of developmental improvements in reasoning ability (Dumontheil et al., 2010; Wendelken et al., 2016), but these studies provide only limited insights into the underlying cognitive changes. Gaze path analyses can provide detailed insights into the strategies and approaches people use as they solve complex problems. In one recent study, Chen et al. (2016) investigated the difference in reasoning strategies between younger and older children, and also the change in strategies as children received feedback throughout the session (Fig. 2b). Using a visuospatial matrices task, they identified specific gaze patterns that they proposed reflect necessary task operations, and counted the number of times those occurred in a trial, as opposed to other eye gaze patterns. They found that older children, better-performing children, and those who received helpful feedback during task performance all demonstrated more task-specific operations than children who performed less well due to their age, skill level, or lack of feedback.

The breadth and depth of cognitive insights gleaned from gaze analyses motivates the expansion of eye-tracking methodology in several directions. Regarding gaze analyses, longitudinal studies examining the development of cognitive skills are relatively rare (exceptions include Huestegge et al., 2009; Schneider et al., 2004).

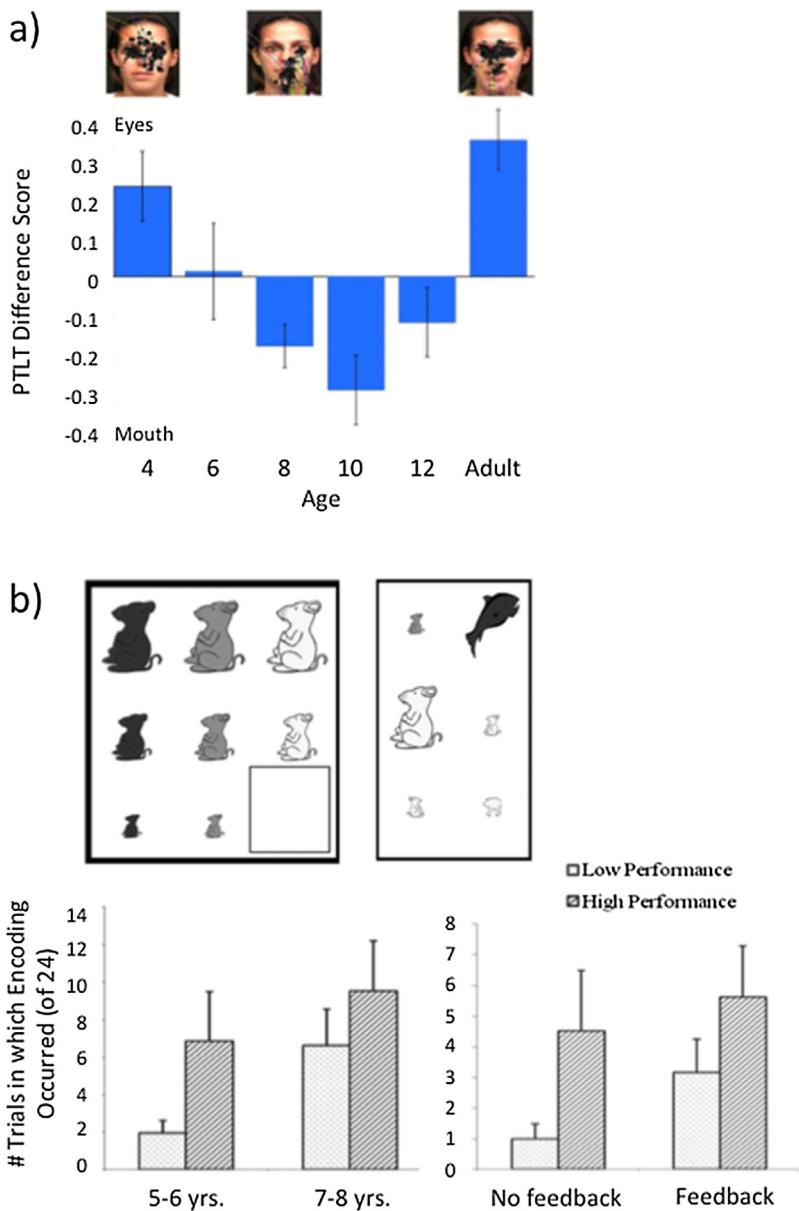


Fig. 2. Gaze analyses in developmental research on attentional capture in infancy and visuospatial reasoning in children. a) While viewing speakers' faces, four-month olds spent a greater proportion-of-total-looking-time (PTLT) on a speaker's eyes, whereas 8- to 12-month olds spent greater PTLT on a speaker's mouth. In adulthood, the balance shifts back to a speaker's eyes. Reprinted with permission from Lewkowicz and Hansen-Tift (2012). b) In a developmental comparison of matrix reasoning, the authors defined an "encoding" sequence as three subsequent fixations along a row or column of the matrix problem space. Using a median split by performance, higher-performing 5–6 year-olds demonstrated approximately the same encoding prevalence as 7–8 year-olds (left). Similarly, children who received feedback on how to complete the puzzles demonstrated more encoding behavior than those who did not (right). Reprinted with permission from Chen et al. (2016).

Such studies would enable us to illuminate the shift in strategies as children and adults construct new concepts, build new skills, and gain expertise across a variety of cognitive domains. Additionally, two methodologies now widely available via standard eye-tracking technology have the potential to augment the insights of gaze analyses: pupillometry and spontaneous blink rate. The analysis of pupil dilation has been used for over a century in the scientific study of cognitive processes (Kahneman and Beatty, 1966; Löwenstein, 1920; Schweitzer, 1956), but obtaining these data required hand-measurement of photographs taken of the pupil every 0.5–1 s, or the use of infrared pupillometers that obscured the participant's vision. Similarly, measures of blink rate have informed cognitive and clinical studies since the 1920s (e.g., Ponder and Kennedy, 1927), but required hand-counting of visually observed blinks, the use of electrooculography (EOG), or other custom-made devices.

Now that both of these measures can be obtained with modern eye-trackers and analyzed with automated data processing software, we recommend the expansion of their use in developmental studies.

As the use of eyetrackers becomes more widespread, it is important that researchers who are just beginning to use this methodology understand both its affordances and its limitations. Just as fMRI indirectly measures brain activity by measuring blood oxygenation, necessitating that researchers mitigate and account for the effects of the physiological and idiosyncratic factors that affect blood flow, there are also many potential influences on ocular responses that must be considered (Gredebäck et al., 2009). Below, we provide an introduction to these ocular measures, the neural mechanisms they reflect, and the opportunities they present for new insights into cognition and cognitive development.

2. Pupil dilation

Changes in pupil size are caused by two antagonistic muscles (Fig. 1b): the dilator pupillae, which is located in the outer parts of the iris and dilates the pupil, and the sphincter pupillae, located in the central parts and constricting it. The constricting sphincter muscle receives input from brain systems involved in the pupillary light reflex (Loewenfeld and Lowenstein, 1993), but both pupillary muscles also receive inputs from brain systems involved in cognitive and autonomic functions (Samuels and Szabadi, 2008). As a result, changes in cognitive and autonomic activity influence pupil diameters. Pupil dilations cannot be inhibited voluntarily, although it is possible to dilate one's own pupils, for example by doing mental arithmetic (Loewenfeld and Lowenstein, 1993). Neuroscientists and cognitive psychologists have exploited the pupillary response to cognitive effort to study the unfolding of cognitive processes over time by observing fluctuations in pupil diameters. A large number of studies has used this method for at least 6 decades in human adults (e.g., Lowenstein and Loewenfeld, 1958) and – to a lesser extent – in infants (for a review, see Hepach and Westermann, 2016). But despite its many advantages, pupillometry has been underrepresented in the study of children and adolescents so far.

Below, we first provide a detailed overview of the neural systems underlying the relationship between cognition and pupil dilation. We do so for two main reasons: First, the close relationship between task-evoked pupil dilation and its underlying neural mechanisms provides a strong argument that this method can be used with participants of any age. Second, knowledge about this relationship allows researchers to translate results about the neural system into cognitive studies, and to interpret results of cognitive studies in terms of underlying neurophysiological processes. After reviewing the neural substrates of the pupillary response, we will detail how this method has been used to study cognitive processes in adults, and how it could be used in children.

2.1. Pupil dilation as a proxy of noradrenergic activity in the brain

The pupils of the eye not only constrict in response to light and dilate in response to darkness; in children as well as adults, they also dilate during autonomic arousal (Beatty and Lucero-Wagoner, 2000; Granholm and Steinhauer, 2004; Samuels and Szabadi, 2008) and mental activity (Beatty, 1982; Granholm and Steinhauer, 2004; Loewenfeld and Lowenstein, 1993; Sirois and Brisson, 2014). The reason that the pupil responds to arousal and mental activity is that pupil dilation is modulated by the noradrenergic locus coeruleus (LC), as shown in Fig. 3 (Rajkowsky et al., 1993). The LC is a small nucleus in the brainstem that plays a central role in the regulation of physiological arousal (Samuels and Szabadi, 2008) and cognitive functioning (Sara, 2009). Below, we will first describe the neural structures underlying the tight relation between pupil dilation and LC activity and then turn to the role of the LC system in arousal and cognition.

The LC is a cluster of neurons that release norepinephrine (NE; also called noradrenaline), a neuromodulator with widespread influences on central and peripheral nervous system activity that will be described later. NE is essential for normal brain development; it is expressed in the brain even before the brain's neurons are differentiated (Herlenius and Lagercrantz, 2001). NE projections to the LC's cortical target structures are already in place at birth (Marshall et al., 1991). Baseline levels of NE continue to change during development, increasing steadily before birth, reaching their maximum shortly after birth, and remaining largely stable throughout childhood (Herlenius and Lagercrantz, 2001; Robinson, 1975).

The relationship between the pupillary system and LC-NE activity has been established through numerous anatomical and physiological studies in both adult humans and animals. The

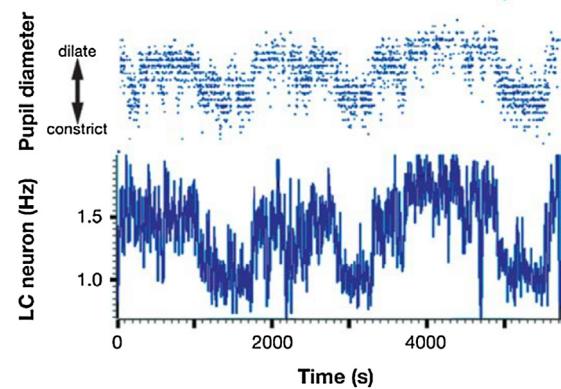


Fig. 3. Temporal coupling between pupil diameter and firing of a single LC neuron of a monkey during performance of a signal-detection task. The relationship between LC firing and pupil diameter is mediated through the projection of the LC to the Edinger-Westphal nucleus, the origin of the pupil's parasympathetic constricting fibers, and through the influence of the LC-NE system on sympathetic nervous activity, which promotes pupil dilation. Reprinted with permission from Rajkowsky et al. (1993).

strength of temporal coupling between LC firing frequencies and pupil diameter in monkeys is striking (Fig. 3; Costa and Rudebeck, 2016; Joshi et al., 2016; Rajkowsky et al., 1993; Varazzani et al., 2015), and fMRI studies have shown corresponding links between LC BOLD signals and pupil diameter in humans (Alnaes et al., 2014; Murphy et al., 2014). A recent study involved simultaneous recording in rhesus monkeys of pupil diameter, neuronal firing of the LC, and neuronal firing of the substantia nigra pars compacta (SNc), which is the production site of the neuromodulator dopamine (DA). This study showed that LC activity was linked to pupil dilation and the monkeys' exerted effort, providing evidence for links between LC activity and pupil dilation and between pupil dilation and cognition (Varazzani et al., 2015). LC-NE activity leads to pupil dilation because the LC has direct inhibitory projections to the parasympathetic Edinger-Westphal nucleus, where the pupil's constricting fibers originate. By inhibiting the Edinger-Westphal nucleus and the pupil's constricting muscle, LC activity therefore indirectly dilates the pupil (Beatty and Lucero-Wagoner, 2000; Loewenfeld and Lowenstein, 1993; Samuels and Szabadi, 2008). LC activity also increases activity in the sympathetic system (Samuels and Szabadi, 2008), including sympathetic fibers that innervate the pupil, resulting in additional pupil dilation (Fig. 4; see also Loewenfeld and Lowenstein, 1993). A pharmacological study in humans has shown that both inhibition of the parasympathetic constricting fibers and excitation of the sympathetic dilating fibers contribute to the cognitively-evoked pupil response (Steinhauer et al., 2004).

Samuels and Szabadi (2008) have provided a comprehensive review of the anatomical structures underlying the LC's role in arousal and autonomic function. NE release promotes wakefulness through the LC's dense excitatory projections to the majority of the cerebral cortex and to other structures related to alertness. At the same time, LC activity suppresses sleepiness through its substantial inhibitory projections to sleep-promoting GABAergic neurons in the basal forebrain and to other structures related to low arousal throughout the central nervous system (Samuels and Szabadi, 2008). LC activity also increases sympathetic activity and decreases parasympathetic activity via direct projections to the sympathetic and parasympathetic divisions of the spinal cord and indirect projections to various nuclei influencing the autonomic system.

As a neuromodulator of brain activity, NE influences cortical processing globally and has a crucial influence on cognitive processes. The LC is the only source of NE in the cerebral cortex (Sara, 2009), projecting to widespread but highly specific sites

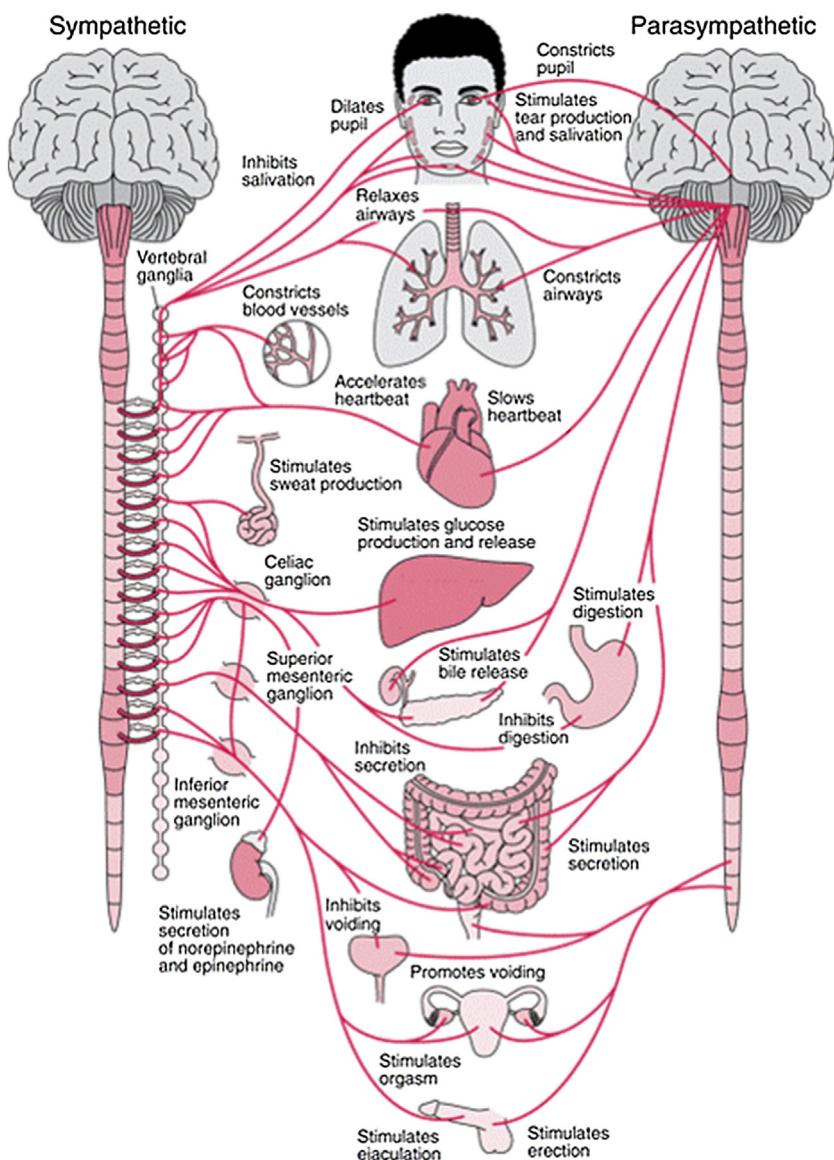


Fig. 4. Anatomy of the autonomic nervous system and its sympathetic (fight-or-flight) and parasympathetic (rest-and-digest) branches. Post-ganglionic activity is mostly mediated by NE in the sympathetic branch and by acetylcholine in the parasympathetic branch. Many organs receive inputs from the sympathetic and parasympathetic branches, in which case functions are often reciprocal, as with pupil dilation (sympathetic dilates, parasympathetic constricts) or heart rate (sympathetic accelerates, parasympathetic slows). Reprinted with permission from the Merck Manual Professional Version, known as the Merck Manual in the US and Canada and the MSD Manual in the rest of the world, edited by Robert Porter. Copyright 2016 by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co, Inc, Kenilworth, NJ. Available at <http://www.merckmanuals.com/professional>. Accessed April 27, 2016.

(Fig. 5a). [Sara \(2009\)](#) and [Ramos and Arnsten \(2007\)](#) have provided comprehensive reviews on NE, focusing specifically on its role in attention and memory ([Sara, 2009](#)) and executive function ([Ramos and Arnsten, 2007](#)). NE's function is elucidated by its effects on sensory processing. When NE is applied to primary sensory neurons in the auditory or somatosensory cortex, spontaneous firing rates ("noise") decrease, while responses to sensory stimulation ("signal") are spared ([Foote et al., 1975; Waterhouse and Woodward, 1980](#)). In other words, NE boosts the signal-to-noise ratio of incoming sensory information. This effect has been called "gating" because it determines which input will be processed further. Similar gating effects have been found for many target areas of the LC, including the cerebral cortex, hippocampus, midbrain, thalamus, and spinal cord ([Foote et al., 1983](#)). NE also "tunes" neuronal responses; for example, it boosts the firing rates of neurons that are selective for a line's orientation that is held in working memory, while decreasing the firing rates of neighboring neurons that rep-

resent slightly different orientations. In other words, NE narrows the tuning curve of the responding neurons, resulting in a steeper decrease in activation from the memorized line orientation compared to slightly different line orientations ([Ramos and Arnsten, 2007](#)). In frontal regions, NE's gating and tuning effects crucially influence how narrow or broad the attentional focus is. This underlies a variety of complex cognitive functions, ranging from working memory to learning, memory, reward processing, decision making, and behavioral adaptation ([Sara, 2009](#)). Tracking pupil diameter over time allows researchers to study these processes by indirectly measuring the timing of norepinephrine release in response to a challenge.

The role of the LC-NE system in physiological arousal and its specific role in signal processing and cognition are intrinsically linked. This point is illustrated by a study by [Aston-Jones et al. \(1999\)](#). Nearly all of the 300+ monkey LC neurons recorded from in this study responded selectively to target stimuli in a visual dis-

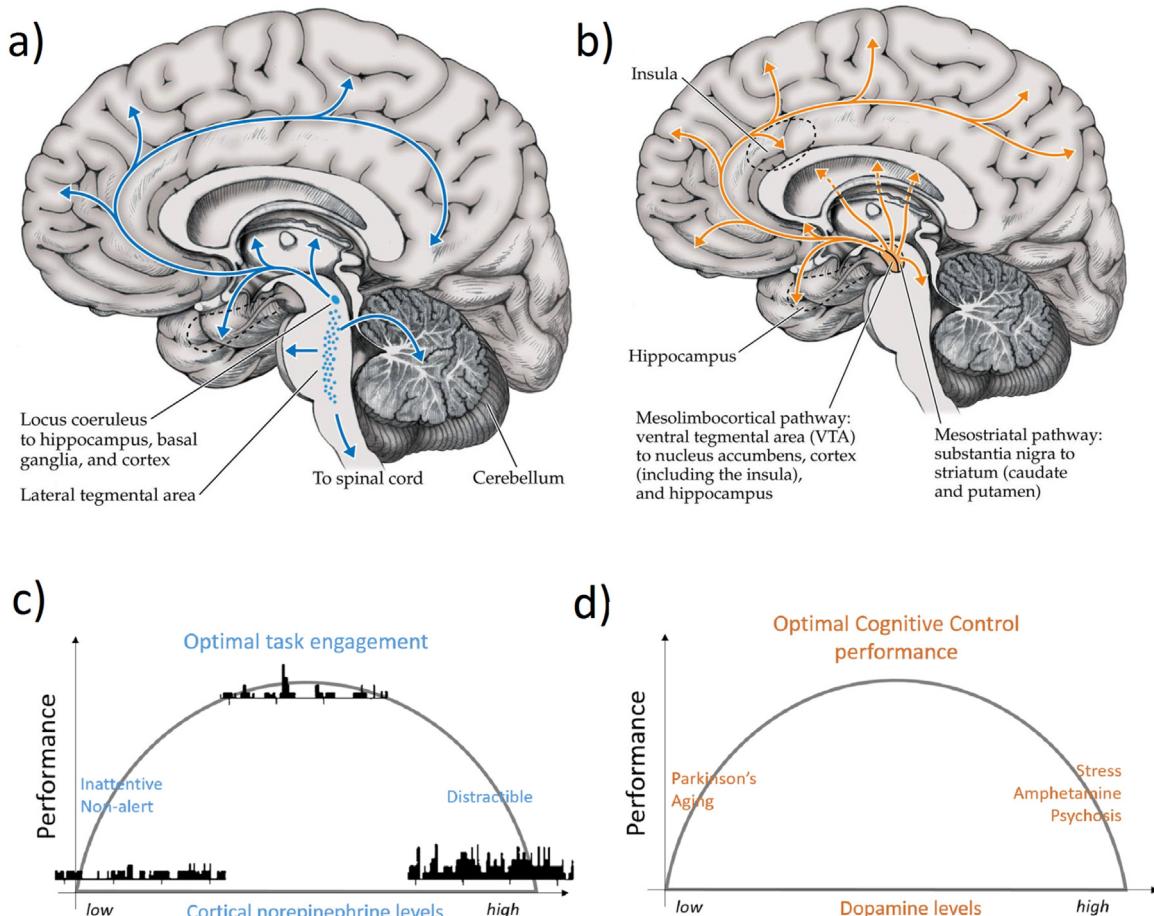


Fig. 5. NE and DA pathways in the brain and their relationship to cognitive performance. a) The LC is the only source of cortical NE but has widespread and highly specific connections throughout the entire nervous system. The LC-NE system promotes physiological arousal and is crucial for a variety of cognitive functions, such as attention, memory, and decision making. b) DA cells in ventral tegmental area (VTA) innervate the mesocorticolimbic pathway that projects to limbic and cortical regions. In the mesostriatal pathway, the striatum receives input from DA cells of the substantia nigra. Reprinted with permission from Breedlove et al. (2010). c) Task performance is optimal at intermediate levels of NE, at which task-relevant stimuli elicit pronounced phasic LC responses. Low levels of NE are associated with inattentive behavior and drowsiness, and high levels with distractibility. Adapted with permission from Aston-Jones et al. (1999). d) Just as for NE, the relationship between DA levels and cognitive control performance can be described by a quadratic function. Specifically, this inverted U-shape relationship has been widely documented for D1 receptor activity and working memory performance. Adapted with permission from Goldman-Rakic et al. (2000).

crimination task, but not to distractors, suggesting that the LC-NE system selectively boosts the processing of relevant, but not irrelevant, sensory information. As might be expected, this preferential processing of task-relevant stimuli is reduced at both extremely low and high levels of arousal. Consequently, periods of extremely reduced and extremely elevated baseline activity in the LC, resulting in drowsiness and physiological arousal, respectively, were accompanied by larger variability in the monkeys' response times, elevated false alarm rates, and largely diminished LC responses to task-relevant stimuli. Only intermediate levels of tonic LC activity, resulting in alertness and attentional focus, seem to allow for phasic LC responses to task-relevant stimuli (Fig. 5c). Taken together, both extremely low and high levels of tonic LC activity are accompanied by a lack of task-dependent phasic LC responses as well as poor task performance, whereas intermediate levels are accompanied by phasic responses to task-relevant stimuli and good task performance. On a behavioral level, this inverse-U relationship has been famously described by Yerkes and Dodson (1908). The same relationship between LC-NE activity and task performance has since been shown in humans, using pupil dilation as a measure of LC-NE activity. Intermediate levels of LC activity, accompanied by phasic pupil dilation in response to task-relevant stimuli, were associated with better performance than both low and high tonic

dilations, which were associated with diminished phasic responses (Gilzenrat et al., 2010; Murphy et al., 2011).

Two different theories have been proposed regarding the role of the LC-NE system in attention and behavior: the adaptive-gain theory (for a review, see Aston-Jones and Cohen, 2005) and the unexpected-uncertainty theory (for a review, see Yu and Dayan, 2005). The adaptive-gain theory postulates that the LC-NE system balances the evolutionary trade-off between the exploration of unknown but potentially superior resources on the one hand, and the exploitation of well-known but potentially inferior ones on the other. According to this theory, intermediate levels of tonic LC activity, leading to focused attention and task engagement, are linked to exploitation, whereas high levels of tonic LC activity, resulting in distractibility and task disengagement, are linked to exploration (Aston-Jones and Cohen, 2005). The unexpected-uncertainty theory, on the other hand, postulates that tonic LC activity reflects uncertainty about the probability of upcoming events. According to this theory, high levels of tonic LC activity reflect high uncertainty and intermediate levels reflect a certain degree of predictability; phasic LC activity is evoked at intermediate levels, when new sensory inputs radically diverge from the participant's prevailing expectation, which is usually the case for behaviorally relevant

stimuli and initiates the updating of the prior interpretation (Yu and Dayan, 2005).

2.1.1. Relation between pupillometry and other measures of brain activity

2.1.1.1. Functional magnetic resonance imaging (fMRI). Studies employing concurrent fMRI and pupillometry have shown that human pupil dilation and BOLD signals in the LC are temporally coupled, as mentioned above, supporting the use of pupil dilation as a measure of LC activity in humans (Alnaes et al., 2014; Murphy et al., 2014). Based on a review of the combined pupillometry-fMRI studies available to date, it seems that pupil dilation is also correlated with the activity of the brain regions engaged by the current task demands. We provide three examples here based on different tasks. First, on a digit-sorting fMRI task, pupil dilation was used as a regressor for the BOLD signal, and was found to be temporally correlated with activation of regions in left lateral prefrontal cortex and bilateral parietal cortex that have been implicated in working memory and cognitive control (Siegle et al., 2003). Similarly, on a gambling task, pupil dilation was found to be temporally correlated with activation of regions in bilateral posterior inferior prefrontal cortex and pre-supplementary motor area that have been implicated in decision-making (Satterthwaite et al., 2007). Third, in a multiple object-tracking paradigm, individual differences in pupil dilation between different numbers of tracked objects predicted activity in the dorsal frontoparietal attention network, including the FEF, anterior and posterior intraparietal sulcus, and superior parietal lobule, assessed in a separate session, above and beyond the number of tracked objects (Alnaes et al., 2014).

In addition to the task-related findings above, it has been shown that pupil dilation during resting-state fMRI or mental imagery is temporally correlated with activation of default-mode areas (medial prefrontal cortex, inferior parietal lobule, and junction of precuneus and posterior cingulate), and negatively correlated with activation of sensorimotor areas (Yellin et al., 2015). In this study, a slow buildup of activity in default-mode areas preceded pupil dilation, along with widespread BOLD suppression in the sensorimotor cortex. Given these findings, Yellin and colleagues suggested that elevated tonic LC activity, reflected in pupil dilation, is linked to the suppression of sensorimotor processes and the production of spontaneous thought. As a possible neural mechanism of this complex interplay, the authors propose a lagged connection between posterior inferior parietal lobule and the LC, acting as a neural accumulator regulating tonic LC activity and the balance between exploration and exploitation. Taken together, these studies show that the pupillary response not only correlates with LC activity, but also with any other type of cortical activity associated with ongoing thought processes.

We posit that these pupillary-brain correlations can be explained in at least two ways: (1) Pupil dilation reflects attentional focus and mental effort, and should therefore naturally correlate with the brain regions carrying out an attended task. In other words, pupil dilation and the activity of specific brain regions should be temporally coupled: as a task unfolds, arousal and mental effort, reflected in pupil dilation, wax and wane and are temporally coupled to the activity of implicated brain regions. (2) There is also a more mechanistic explanation, although the two are not mutually exclusive. NE boosts the signal-to-noise ratio in task-relevant brain regions, which is reflected in an increased task-related BOLD signal. In parallel, NE also dilates the pupils. In other words, the amplitude of pupil dilation and BOLD signal should be correlated, with higher levels of neural gain and task engagement reflected in greater pupil dilation.

Most of the studies on cognitive tasks described above used average measures of pupil dilation as regressors in their fMRI analysis, whereas the resting state study used the raw dilation

time course. The correlation between the raw pupil dilation and the BOLD signal reveals an aspect of temporal coupling, but the correlation between BOLD and average pupil dilation also points to a coupling of amplitudes. When task-related pupil responses averaged over multiple trials and several seconds still show a correlation with BOLD signals, this cannot be explained in terms of temporal coupling alone. The evidence therefore seems to be consistent with both explanations.

2.1.1.2. Electroencephalography (EEG). As a measure of activity of the LC-NE system, pupil dilation is related not only to BOLD signals, but also to EEG signals. This section will review evidence for this relationship, with the goal of convincing readers that pupil dilation is, like EEG, a reliable measure of certain aspects of brain function. The second goal of this section is to allow readers who are already familiar with EEG to relate the two measures. A number of studies have combined pupillometry with EEG in adults, in an effort to characterize the overlaps and differences between the processes measured by the two methods. No such studies have been conducted in children so far, and more research is necessary to prove that the findings obtained with adults hold at all ages. The positive-going event-related potential (ERP) labeled the P3 has – just like task-evoked pupil dilation – been proposed as a marker of LC-NE activity (Murphy et al., 2011; Nieuwenhuis et al., 2005). The P3, one of the most studied ERPs, peaks 300–600 milliseconds after the presentation of a task-relevant stimulus and is most prominent at frontal-central midline electrodes (Sutton et al., 1965). The notion that the P3 reflects (phasic) LC-NE activity is supported by a number of human and animal studies (for a comprehensive review, see Nieuwenhuis et al., 2005). For example, a primate neurophysiology study found that both LC neuronal firing and the simultaneously measured P3 were selectively elicited by target stimuli in a visual “oddball” task (Aston-Jones et al., 1991).

The specific relationships between the LC-NE system, P3, and pupil dilation have only recently been investigated in greater depth (Hong et al., 2014; Kamp and Donchin, 2015; Murphy et al., 2011). In one study, tonic pupil dilation prior to stimulus presentation on an auditory oddball task showed an inverse-U relationship to both the evoked P3 amplitude and to task performance, supporting the claim that P3 amplitude reflects phasic LC-NE activity and task engagement (Murphy et al., 2011), similar to what we have described for tonic pupil dilation. In addition, P3 amplitude as well as stimulus-evoked pupil dilation decreased substantially over the course of the experiment, pointing to decreasing task engagement, while pre-stimulus pupil diameters and response times increased, revealing increasing distractibility. A similar but more data-driven study showed comparable relationships between pre-stimulus pupil diameter, stimulus-evoked dilation, and a P3-like EEG component (Hong et al., 2014). This study also showed a link between stimulus-evoked pupil dilation and pre-trial EEG alpha band activity (8–12 Hz), in that reduced alpha, indicative of elevated attention, coincided with increased stimulus-evoked pupil dilation, associated with elevated task engagement (Fig. 5c). These results suggest a strong link between phasic pupil dilation and the P3, making pupillometry a promising alternative (or addition) to EEG studies about attention, novelty, and surprise.

However, despite the many similarities between the two measures, neither of the abovementioned studies (Hong et al., 2014; Murphy et al., 2011) found a direct correlation between them. In fact, an even more recent investigation has revealed additional discrepancies (Kamp and Donchin, 2015), suggesting that the measures reflect at least partially distinct underlying mechanisms. This is not, perhaps, surprising, given that pupillometry provides a more indirect and global measure of brain function than a specific ERP component. Taken together, both pupil dilation and P3 amplitude have been used as measures of LC-NE activity and task-directed

attention and are typically elicited by similar cognitive tasks. Nevertheless, the two are not interchangeable, and further research is needed to clarify how the two measures, independently or jointly, elucidate cognitive processing.

In summary, research in human adults has started to reveal the precise relationship between pupillometry and EEG and fMRI, and demonstrates that pupillometry may augment these methods. For example, including pupil dilation as a regressor in whole-brain fMRI analysis has increased the sensitivity and specificity of the results (Siegle et al., 2003), and has revealed finer temporal patterns than would be possible with fMRI alone (Yellin et al., 2015). Additional research involving simultaneous pupillometry and brain imaging data collection is warranted to articulate more clearly the relationships between them, but the evidence to date is sufficient to conclude that pupil diameter is an indirect measure of brain function.

2.2. Cognitive processes studied with pupillometry

Most cognitive experiments that employ pupillometry focus on the fast, task-related LC-NE response reflected in phasic pupil dilation, while studies focusing on alertness and arousal also consider the slower, autonomic, tonic modulations reflected in baseline pupil diameters. Here, we provide only a broad overview of the topics and phenomena that have been studied by measuring phasic pupil dilation, and refer the interested reader to more detailed reviews. So far, pupillometry has been used extensively in the study of adult cognition (reviews: Andreassi, 2000; Beatty, 1982; Goldinger and Papesh, 2012; Granholm and Steinhauer, 2004; Loewenfeld and Lowenstein, 1993), and an increasing number of publications reflects its gain in popularity in infant research (for reviews, see Hepach and Westermann, 2016; Sirois and Brisson, 2014). To date, however, pupillometry has only been used in a handful of studies to investigate child cognition (e.g., Chatham et al., 2009; Chevalier et al., 2015; Johnson et al., 2014; Karatekin et al., 2007).

Pupil dilation is often used as a measure of a person's mental effort when working on a task, or, on the flipside, a task's intrinsic processing demands (Beatty, 1982). A more recent computational framework has proposed that pupil dilation reflects capacity utilization, the balance between task demands and individual cognitive resources (Just et al., 2003). Other suggestions of how to relate the physiological pupillary response to cognitive descriptions have been proposed in terms of adaptive gain and unexpected uncertainty, as described above (Aston-Jones and Cohen, 2005; Yu and Dayan, 2003).

Although the labels for the cognitive processes underlying the pupillary response differ between theories, it is clear that pupil dilation reflects a specific, intensity- and attention-related aspect of cognitive processing. For example, a large number of studies has shown that pupil dilation scales with levels of difficulty across a wide range of tasks, including short-term memory (Fig. 6a; Kahneman and Beatty, 1966; Klingner et al., 2011), arithmetic operations (Fig. 6b; Ahern and Beatty, 1979; Hossain and Yeasin, 2014; Klingner et al., 2011), digit sorting (Siegle et al., 2003), sentence comprehension (Ahern, 1978), and perceptual matching (Ahern and Beatty, 1979). Across all of these tasks, more difficult problem-solving conditions elicited larger pupil dilations than easier conditions. The same has been shown in children (Boersma et al., 1970), making pupillometry a promising method with which to quantify differences in task difficulty. The relationship between the intensity of cognitive processing and pupil dilation also holds across tasks, with simpler paradigms eliciting smaller pupil dilations than more complex ones, even when the tasks stem from unrelated domains, such as when comparing a perceptual task to mental calculation and sentence comprehension (Beatty, 1982). Taken

together, the fact that pupil diameter scales with task demands makes it a valuable tool for objectively measuring the intensity of cognitive processing in participants of any age.

Pupil dilation also reveals which trials in a task elicit the greatest cognitive effort, such as target tones in a target detection task (Fig. 6c; Book et al., 2008) or incongruent trials in a cognitive control task (Fig. 6d; Laeng et al., 2010; Siegle et al., 2004). Similarly, adults and infants show elevated pupillary responses to deviant tones embedded in a sequence of identical tones, in an auditory oddball paradigm (Wetzel et al., 2016). In children, proactive and reactive cognitive control (Chatham et al., 2009; Chevalier et al., 2015) and working memory (Karatekin et al., 2007) have been studied using pupil dilation to reveal the intensity of cognitive processing at every time point in a trial.

In addition to reflecting differences in cognitive processing between tasks, pupil dilation also reflects cognitive characteristics of the individual participant. In one study, adults with higher scores on intelligence tests showed smaller pupil dilations during a number of cognitive tasks (mental multiplication, digit span, sentence comprehension) than those with lower scores (Beatty, 1982), suggesting that more skilled participants exerted less effort to complete the task. This study highlights the relation between the pupillary response and individual differences in cognitive processing. We do not know of similar studies in children, but note that pupillary responses are a promising objective measure of cognitive effort for children who are too young to provide reliable self-assessments. Taken together with the abovementioned studies that examined the effects of manipulating task difficulty, pupil dilation seems to reflect how intensity and attention unfold over time during the cognitive process, which is shaped by task demands as well as individual differences in cognitive functioning.

Although we emphasize here studies in which pupillometry has been used to study cognition, it can also be used to study responsiveness to motivationally salient stimuli (for a review, see Sirois and Brisson, 2014). Indeed, pupil dilation has been shown to be a sensitive index of pain perception, negative emotions, sexual attraction, and subjective preferences across a range of stimuli, highlighting the point that pupil dilation reflects arousal across a range of contexts, and is not specific to cognitive challenges. Thus, tight experimental control is required to avoid potential confounds.

2.3. Potential of pupillometry to inform developmental research

The rich literature on task-evoked pupillometry in adult humans and in animals reviewed above lays a solid foundation for research on learning and development. While few studies have applied this technique in research with children thus far, we introduce below two lines of research that show how pupillometry has already been used to provide mechanistic insights into cognitive development. We first introduce the experimental paradigm, analyses, and results from both lines of research, and then discuss the applicability of pupillometry in developmental cognitive research.

In one line of research (Jackson and Sirois, 2009; Laeng et al., 2012; Sirois and Jackson, 2012), pupillometry has been used to shed light on object permanence in infants, a topic that has provoked decades of debate. In one study (Sirois and Jackson, 2012), infants' pupils were recorded while they looked at events that did or did not violate the principles of object permanence: a drawbridge that either passed through an occluded box or stopped upon touching the hidden object, similar to Baillargeon and colleagues' classic experiment (Baillargeon et al., 1985). In Sirois and Jackson's control conditions, the drawbridge moved in similar ways as in the experimental conditions, but no box was present (for a more detailed description, see Fig. 7a). The authors employed functional data analysis (see following section) to precisely characterize the effects of the two experimental factors (presence of the box and

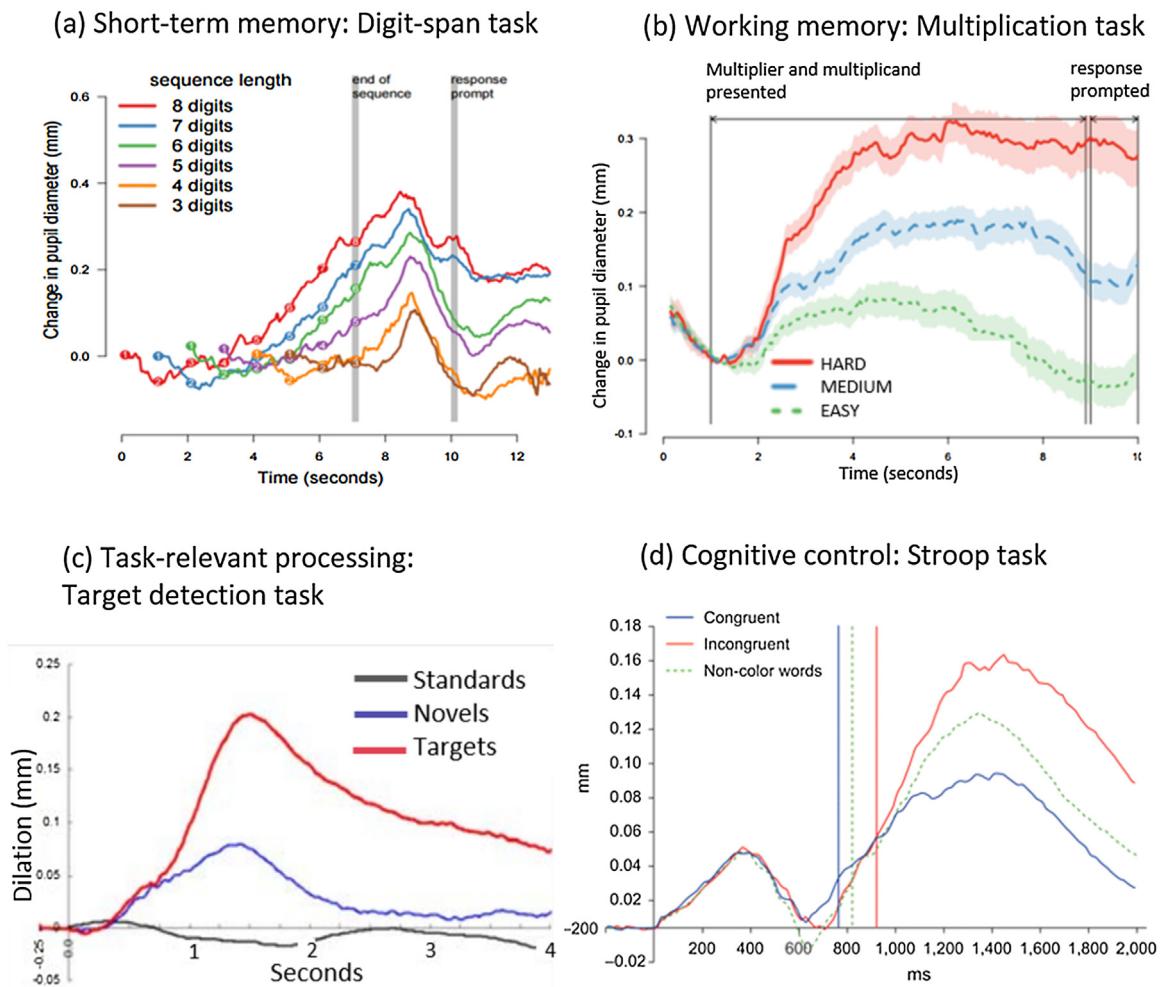


Fig. 6. Pupil dilation scales with task difficulty in a variety of cognitive domains. a) Short-term memory: Digit-span task. Subjects saw 3–8 digits, presented sequentially for one second each, and attempted to recall all digits after a retention interval of 3 s. Pupil dilation increased as a function of short-term memory load. Reprinted with permission from Klingner et al. (2011). b) Working memory: Multiplication task. Subjects were asked to mentally multiply two visually presented numbers. The numbers were smallest in the “easy” condition, bigger in the “medium” condition, and biggest in the “hard” condition. Pupil dilation scaled with task difficulty and remained elevated for several seconds after stimulus presentation. Reprinted with permission from Klingner (2010). c) Task-relevant processing: Oddball task. Subjects listened to a stream of auditory stimuli and were instructed to press a button in response to target tones only. Target tones (1500 Hz) made up 10% of the presented stimuli, 80% were standard stimuli (1000 Hz), and 10% were novel stimuli (bells, whistles, horns, etc.). There was no sign of pupil dilation in response to standard stimuli. Novel stimuli elicited a pronounced pupil dilation of more than 0.5 millimeters, but target tones elicited a much larger response of 2 millimeters, reflecting selective orientation toward task-relevant stimuli. Reprinted with permission from Book et al. (2008). d) Cognitive control: Stroop task. Subjects were asked to name the color of 320 letter combinations presented for 2 s. In congruent trials, the colored letters formed the name of the color, whereas in incongruent trials, the letters formed the name of another color. Non-color words were used as a control condition. Pupil dilation was reduced in congruent trials relative to non-color words and was increased in incongruent trials, suggesting that pupil dilation is a sensitive measure of cognitive control. Reprinted with permission from Laeng et al. (2010).

rotation angle of the drawbridge) on the infants' cognitive processes at any time in the trial. The effect of the presence of the box on pupil dilation was confined to the moments at the beginning and end of the trial when the box was visible in one condition, but not in the other (Fig. 7a, dashed line), and the effect of the rotation angle of the drawbridge was confined to moments that were similarly relevant in terms of the drawbridge's movement (Fig. 7a, thin solid line). These findings suggest that the infants paid attention to the relevant features and events in this paradigm, and also that pupil dilation is a sensitive measure of cognitive processing even within the first 10 months of life. Next, in order to test the infants' knowledge of object permanence, Sirois and Jackson tested for an interaction between presence of the box and rotation angle of the drawbridge (Fig. 7a, thick solid line), which would indicate that the infants processed the impossible event differently from the possible events. The fact that there was no interaction between the two factors cast doubt on the infants' knowledge that the box continued

to exist after it was occluded – and of their knowledge about object permanence in general.

The second study outlined here aimed to evaluate the extent to which differences in allocation of attention at encoding could explain differences in short-term memory (STM) between children and adults. It is well-known from previous research that pupils dilate while to-be-remembered digits are presented in a digit span paradigm, plateau while the digits need to be retained, and slowly constrict as they are recalled (Fig. 6a; Cabestrero et al., 2009; Granholm et al., 1996; Kahneman and Beatty, 1966). In the developmental study featured here, 10-year-olds and adults performed a task in which they were asked to memorize a number of digits that exceeded their STM capacity – i.e., a STM ‘overload’ task (Johnson et al., 2014). Children's pupils did not dilate throughout the digit presentation but plateaued around the sixth digit and constricted during the later ones (Fig. 7b), suggesting that their attention waned prior to the end of the stimulus sequence. Adults

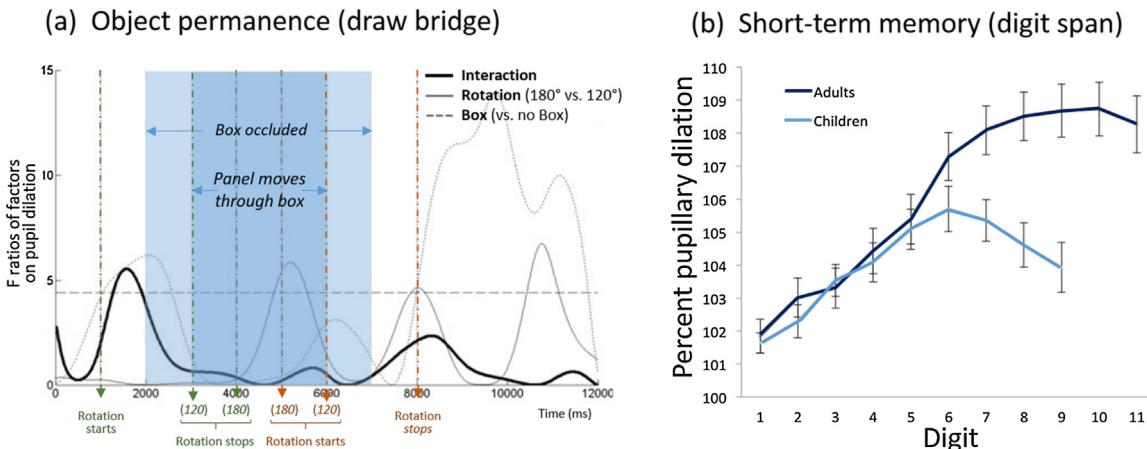


Fig. 7. Examples for the use of pupillometry in development. a) Object permanence. Ten-month-old infants saw drawbridges that, by rotating, occluded a box behind. Infants' pupils responded to the rotation of the drawbridge, revealed by a main effect of rotation (180° or 120°), and to the presence of a box, revealed by a main effect of the presence or absence of the box, but did not respond to the violation of the principles of object permanence (box present and 180°), as would be revealed by an interaction between both. Adapted with permission from Sirois and Jackson (2012). b) Short-term memory. Differences in pupil dilation between children and adults while listening to long sequences of to-be-recalled digits. The premature drop in children's pupil diameters before the end of the sequence suggests that their worse recall performance might be caused by a lack of attention during encoding and a failure to allocate sufficient cognitive resources. Reprinted with permission from Johnson et al. (2014).

reached a similar plateau significantly later. Notably, the position of the digit at which the dilation peak was reached predicted a child's or adult's STM capacity, measured on the standard digit span task, over and above STM capacity as measured with the eyetracking task. The authors concluded that the allocation of cognitive resources at encoding is an important factor in the development of STM (Johnson et al., 2014). With behavioral measures collected at the end of a trial, it would not have been possible to directly measure cognitive processing during encoding; by contrast, with eyetracking, it was possible to collect moment-by-moment measurements throughout the trial.

Taken together, both of the studies featured here show how much detail pupil dilation can provide about cognitive processes, even when these processes have already attracted decades of scientific attention. The effects of the different trial events (movement of the bridge and occlusion of the object in the first study; presentation of each digit in the second study) could be characterized individually by measuring pupillary dilation in response to each event. The same would not have been possible with summary measures of behavior, such as looking times or behavioral responses, which reflect the final outcome of various mental processes operating at different points in a trial. Further, interpreting pupil dilations is more straightforward than looking times because of its close link to a single brain system (Aslin, 2007; Jackson and Sirois, 2009).

2.4. Methodology of pupillometry

Pupil diameter is measured automatically by most conventional eyetrackers because pupil tracking is necessary to determine gaze position. Some eyetrackers are directly integrated into computer screens; others are external devices and set up below a screen or other medium of interest. Modern eyetrackers include calibration software, and pupil diameter is provided in millimeters (rather than pixels, as with older-generation eyetrackers).

Pupil diameters vary between 1.5 mm in bright light and 9 mm in total darkness. Whereas they can double or halve in size due to changes in luminance, cognitively-evoked responses are usually smaller than 0.5 mm (Beatty, 1982; Sirois and Brisson, 2014). Nevertheless, these changes can be detected reliably when luminance is held constant or when the data have been cleaned from the effects of changing luminance, for example using the method proposed by Pomplun et al. (2009). Some researchers conduct pupillometry

experiments in dimly lit rooms with the goal of obtaining maximum amplitudes of pupil dilation. Contrary to this intuition, cognitively-evoked pupil dilation is larger in moderate light than in darkness (Steinhauer et al., 2004). (Figs. 1b and 4). We therefore recommend conducting cognitive experiments in moderately lit rooms.

Pupil dilation can be measured at the sub-millisecond time scale, but researchers should keep in mind the response latency of the pupillary system when designing experiments. The pupil takes up to 1.5 s to reach maximum constriction after a sudden flash of light (Loewenfeld and Lowenstein, 1993), and tracks slow changes in luminance with a lag of about 1 s (Yellin et al., 2015). In cognitive studies, the pupil usually begins dilating immediately after stimulus presentation, but takes approximately 1–1.5 s to reach its maximum elicited dilation, depending on the nature and difficulty of the task (Murphy et al., 2011; also compare the different pupil dilation time courses in Fig. 6). In order to reduce overlaps between consecutive stimuli and trials, most researchers temporally separate subsequent stimuli by about 1 s, and insert inter-trial intervals of at least 3 s. Nevertheless, analysis methods also exist for much faster task designs at the border of conscious perception (Wierda et al., 2012).

Of relevance for developmental studies, pupil diameter changes with age. Diameter increases rapidly during the first decade of life (when measured in dim light, starting at 5.66 mm in 1-month olds), plateaus at the age of 11–15 years (with diameters between 7.10–7.45 mm in dim light), and slowly but consistently shrinks thereafter (reaching 4.5 mm in 80-year olds) (Loewenfeld and Lowenstein, 1993; MacLachlan and Howland, 2002). These changes coincide partially with changes in cerebral levels of NE (Herlenius and Lagercrantz, 2001; Robinson, 1975). For the purposes of interpreting age-related differences, relative measures of pupil dilation as compared with a baseline should therefore be used instead of absolute diameters, as described below.

Taken together, possible confounds of the task-evoked pupillary response include testing-related factors such as varying stimulus luminance, rapid presentation of stimuli, and varying lighting conditions, as well as a variety of participant-related factors, such as age, wakefulness, anxiety level, and use of pharmacological agents that affect NE levels (e.g., caffeine, marijuana, and various medications). Testing-related factors are easier to control than participant-related ones, although participants can be asked to refrain from taking stimulants or other drugs prior to testing, and a

friendly testing environment can help reduce anxiety. Fortunately, many of these factors are thought to influence baseline pupil diameter rather than the phasic, task-evoked responses that are usually of interest in cognitive studies, so their effects are usually recorded but only taken into account in extreme cases. A more detailed practical guide on designing eyetracking and pupillometry experiments has been provided by Holmqvist et al. (2011).

The first step in analyzing pupillometry data is data cleaning. Dilation values reflecting measurement errors need to be identified and removed and short gaps of missing data, usually caused by blinking, can be interpolated (refer to Sirois and Brisson, 2014 for a practical guide). In the next step, absolute pupil diameters are usually transformed into relative pupil dilations. To obtain trial-wise relative pupil dilations, the pupil diameter prior to trial onset is subtracted from each data point in the trial. In the next step, trials of the same experimental conditions are averaged within subjects. EEG analysis software can be used to preprocess pupillometry data in this way, although many researchers develop their own in-house preprocessing procedures.

In the next step, data can be compared between groups or between conditions using standard statistical software. The easiest way to compare pupillary responses is to calculate average pupil dilations for a small number of pre-defined time windows (for example, stimulus presentation and response) and compare these using *t*-tests, ANOVA, or regression. More sensitive results can be achieved with other methods, for example functional data analysis. Here, the time course of the pupillary response is fit by a mathematical function, which is then submitted to a statistical test. The resulting test statistic is also a function over time, making it possible to determine the exact time points when a critical value is exceeded, without the need of controlling for multiple comparisons due to the number of time points. No data are lost due to averaging over large time windows, which makes functional data analysis a sensitive and precise method for analyzing pupil dilations. More detailed descriptions of this technique have been provided elsewhere (Jackson and Sirois, 2009; Ramsay, 2016; Ramsay and Silverman, 2002; Sirois and Brisson, 2014).

Many alternatives exist for analyzing pupil dilation data. As briefly mentioned above, automated deconvolution has been used to analyze a task that was at the border of conscious perception in terms of speed (Wierda et al., 2012). Principal component analysis (PCA) has been used to decompose the pupil dilation waveform and isolate dilation components associated with task performance and general cognitive abilities (Verney et al., 2004). Time-frequency analyses, such as Fourier transform and short-time Fourier transform, have revealed specific frequency bands in the pupil dilation signal that relate to alertness (Nowak et al., 2007). The Hilbert analytic phase has been used to extract signals from the pupillary response that reflect cognitive overload (Hossain and Yeasin, 2014). A variety of methods, such as independent component analysis (ICA) (Calhoun et al., 2009), has also been proposed to facilitate the combination of pupillometry with fMRI, EEG, genetic, or other data.

As detailed above, pupil dilation provides a rich measure of neuro-cognitive processing in children and adults, and is suitable for a variety of data analysis techniques, ranging from the classic comparison of means to more data-intensive methods, such as PCA and time-frequency analysis, to cutting-edge statistical methods from the areas of machine learning and big data. However, several key points must be kept in mind with regard to study design and interpretation. First, various factors aside from cognitive demands can, if not properly controlled, influence pupil size. However, it is possible, with tightly controlled experiments, to isolate task-evoked pupillary responses that are sensitive to cognitive manipulations. Secondly, researchers must bear in mind that pupil dilation provides only an indirect measure of LC-NE activity.

However, the relationship between the LC-NE system and pupil dilation has been established with a variety of methods, including human and animal studies with pharmacological manipulations and brain imaging techniques (Samuels and Szabadi, 2008; Sara, 2009), allowing researchers to draw inferences about neural processes from pupillometry data.

3. Spontaneous eyeblink rate

Dopamine (DA) is an important neurotransmitter involved in learning, working memory, and goal-oriented behavior (for a recent review see Westbrook and Braver, 2016). Despite decades of research on animal models and adult samples, we currently lack suitable methods for directly measuring DA activity in children and adolescents.

It has been proposed that spontaneous eyeblink rate, or the frequency at which the eyelids open and close, can serve as a non-invasive, indirect measure of DA activity in the central nervous system. In this section we review evidence that establishes the link between blink rate and the dopaminergic system, as well as studies showing the feasibility of using this marker to examine the modulatory role of DA in cognitive development and learning.

3.1. Spontaneous eyeblink rate as a proxy of dopaminergic activity

Blinking serves various functions, ranging from the maintenance of ocular health to non-verbal communication. There are three main types of blinks – voluntary, reflexive, and spontaneous – which differ in their purpose and underlying mechanisms. Both reflexive and spontaneous blinks occur without volition. Reflexive blinks occur mainly as a response to environmental stimuli and cause the eyelids to shut quickly, for instance to protect the eyes from a foreign particle. Spontaneous blinks, by contrast, occur in the absence of such triggers and are characterized by a highly synchronized and transient closing and reopening of the eyelids, a movement that helps to distribute the tear film uniformly over the eye (Cruz et al., 2011).

The muscles that control the opening and closing of the eyelids are the levator palpebrae superioris and orbicularis oculi muscles, respectively (Fig. 1a). The neural processes that control the movement of these muscles during spontaneous blinking are not yet well characterized (Cruz et al., 2011; Jongkees and Colzato, 2016). Neuroimaging studies in non-human primates suggest that spontaneous blinking produces broad activation patterns across the cortex, but interestingly not in areas that respond to voluntary blink production, such as the FEF and the lateral intraparietal cortex (Guipponi et al., 2015). Research in a rodent model points to the spinal trigeminal complex of the medulla, which has been previously associated with the production of reflexive blinks, as a key region in the circuit that controls spontaneous blinking (Kaminer et al., 2011).

It has been hypothesized that DA modulates the frequency of spontaneous blinks indirectly, by regulating the inhibition of the spinal trigeminal complex (Kaminer et al., 2011). Although the precise neural circuitry that controls blink rate still requires further investigation, several lines of research have demonstrated a link between spontaneous blink rate and dopaminergic activity in the central nervous system. In the following two sections, we summarize key pharmacological manipulation studies and findings from populations with DA-related disorders. For a more comprehensive review on the relationship between DA activity and spontaneous blinking, we refer readers to Jongkees and Colzato (2016).

3.1.1. Pharmacological manipulations

Studies of pharmacological manipulations in non-human animals have provided the most compelling evidence of the relationship between blink rate and DA activity. This work demonstrates that blink rate rises steeply after the administration of DA receptor agonists such as apomorphine. Conversely, administering DA receptor antagonists leads to a notable decrease in blink rate (Karson et al., 1981). This effect is specific to DA, and not simply a byproduct of general sedation (Karson, 1983).

Subsequent research has aimed to characterize the selective roles of different DA receptors in blink rate modulation, since this information would elucidate the mechanisms of blinking and also provide vital information for using blink rate as a marker of dopaminergic function. DA is transmitted to various areas of the brain (Fig. 5b) that have receptors of varying structural, biochemical, and functional properties. The two main families of DA receptors in the brain are D1-class receptors, abundant in prefrontal cortex, and D2-class receptors, primarily expressed in subcortical structures like the striatum (Beaulieu and Gainetdinov, 2011). The cognitive functions associated with these receptor classes will be discussed in more detail in Section 3.2.

In an effort to pinpoint the receptors that underlie blink rate, researchers have examined the effects of pharmacological agents that affect D1 and/or D2 receptor function. This work has yielded mixed evidence as to which receptor class is most closely involved in modulating blink rate (Fig. 8). Some pharmacological studies suggest D2 as the primary modulator of blink rate (e.g., Groman et al., 2014; Taylor et al., 1999). For instance, the administration of a D2 agonist, but not D1 agonist, results in increases in blink rate that correlate with PET (Fig. 8a and b) and post-mortem measurements of D2-like receptor availability in the striatum of rhesus monkeys (Groman et al., 2014).

In contrast, other studies point to D1 as the primary modulator of blink rate (e.g., Kotani et al., 2016; van der Post et al., 2004). The most compelling evidence comes from a study where the systematic administration of a D1-agonist produced dose-dependent increases in blink rate in marmosets (Kotani et al., 2016). A similar dose-dependent blink rate response (Fig. 8c) was observed after the administration of a D1/D2 non-selective agonist that has been used on previous seminal blink rate studies (e.g. Karson, 1983). Importantly, the effect on blink rate of this D1/D2 agonist was selectively reversed only with the administration of a D1-antagonist (Fig. 8d). Lastly, other studies posit an interaction or common effect of D1 and D2, in addition to independent modulatory effects of each receptor (Elsworth et al., 1991; Karson, 1983; Kleven and Koek, 1996). These conflicting results underscore the complex relationship between blink rate and DA activity (for a review, see Jongkees and Colzato, 2016). Much of the evidence suggests that both D1 and D2 receptors can modulate spontaneous blinking, and Jongkees and Colzato propose that the effects of D1 receptors on spontaneous blink rate might only be produced at certain dosages of pharmacological manipulations, whereas tonic blink rate might be more closely related with D2 activity in the basal ganglia more generally. However, this account may not be consistent with the developmental trajectories of DA tone, expression of D2 receptors, and spontaneous blink rate: DA tone and expression of D2 receptors in the basal ganglia peak during adolescence (Ernst et al., 2009), whereas blink rate, as far as we can tell from cross-sectional samples, increases from infancy to adulthood (Zametkin et al., 1979). Given these conflicting accounts about D1 and D2 receptor involvement, we can conclude only at this point that spontaneous blink rate is modulated by central dopaminergic activity.

3.1.2. Clinical studies

Patients with conditions that are known to compromise the dopaminergic system show irregularities in blink rate. For instance,

low blink rate is seen in patients with Parkinson's disease (PD), a disorder that results from the loss of dopaminergic cells in the substantia nigra (Agostino et al., 2008). Medications that raise DA levels also increase blink rate in these patients (Bologna et al., 2012). By contrast, schizophrenia and Tourette's syndrome – conditions linked to elevated dopaminergic activity (Chan and Chen, 2004) – are associated with elevated blink rate (Tharp et al., 2015). The severity of the symptoms in these conditions is positively correlated with blink rate, a relationship that is also present in pediatric patients with early-onset schizophrenia (Caplan and Guthrie, 1994).

Although the precise influence of each dopamine receptor on the neural circuitry that controls spontaneous blink rate remains an open area of research, findings from studies with pharmacological manipulations and clinical samples with compromised dopaminergic function support the viability of blink rate as a biomarker of central dopaminergic activity. The fact that we can acquire blink rate data non-invasively makes it possible to assess DA-related cognitive functions in adulthood and development.

3.2. Cognitive processes studied with blink rate

Blink rate has been used as a peripheral measure of DA involvement in various cognitive and affective functions (e.g., Colzato et al., 2009; den Daas et al., 2013; Fukuda, 2001; Karson et al., 1981; Oh et al., 2012; Smilek et al., 2010; Tharp and Pickering, 2011; Wiseman and Nakano, 2016). Cognitive control and learning have been heavily represented in the literature, and thus will be the focus of this section.

Our ability to control impulses, maintain long-term goals, and flexibly adapt to changing rules from the environment are all important aspects of cognitive control. DA is an important neuromodulator of fronto-striatal circuits that support these functions. It has been proposed that during goal-oriented behavior, DA aids in the maintenance of abstract goals in higher levels of the cognitive control hierarchy, while also allowing flexibility in updating lower-level rules guiding attainment of subgoals (Puig et al., 2014; Westbrook and Braver, 2016). Just as for NE (Fig. 5c, see pupillometry section), the relationship between cognitive control and DA is often described with an inverted U-shape function (Cools and D'Esposito, 2011), as shown in Fig. 5d. There is some evidence that this relationship can be captured with blink rate, for example in the context of cognitive flexibility on a divergent thinking task (Chermahini and Hommel, 2010), as well as performance on an attentional task subsequent to cognitive depletion (Dang et al., 2016). Most of the research in this domain has associated baseline blink rate with cognitive control, often showing a positive linear relationship.

Different functional roles related to cognitive control have been ascribed to the two DA receptor families. For instance, D1 signaling is traditionally associated with maintenance of representations of long-term goals, while D2 signaling in the striatum is associated with an increase in flexible processing and distractibility (Puig et al., 2014; Takahashi, 2013; Westbrook and Braver, 2016). In a recent study, Zhang et al. (2015) tested the relationship between baseline blink rate and these dimensions of cognitive control in a sample of young adults. They found that higher blink rates predicted better performance on set-shifting and Stroop tasks, but worse performance on an updating task that taxes working memory (3-back). These and other findings indicate that higher baseline blink rate is associated with better cognitive flexibility but worse maintenance (Dreisbach et al., 2005; Müller et al., 2007; Tharp and Pickering, 2011). However, other research has shown that higher blink rate at baseline is related with lower distractibility on tasks that place high demands on working memory (Colzato et al., 2009). Research isolating cognitive flexibility, updating, and maintenance processes

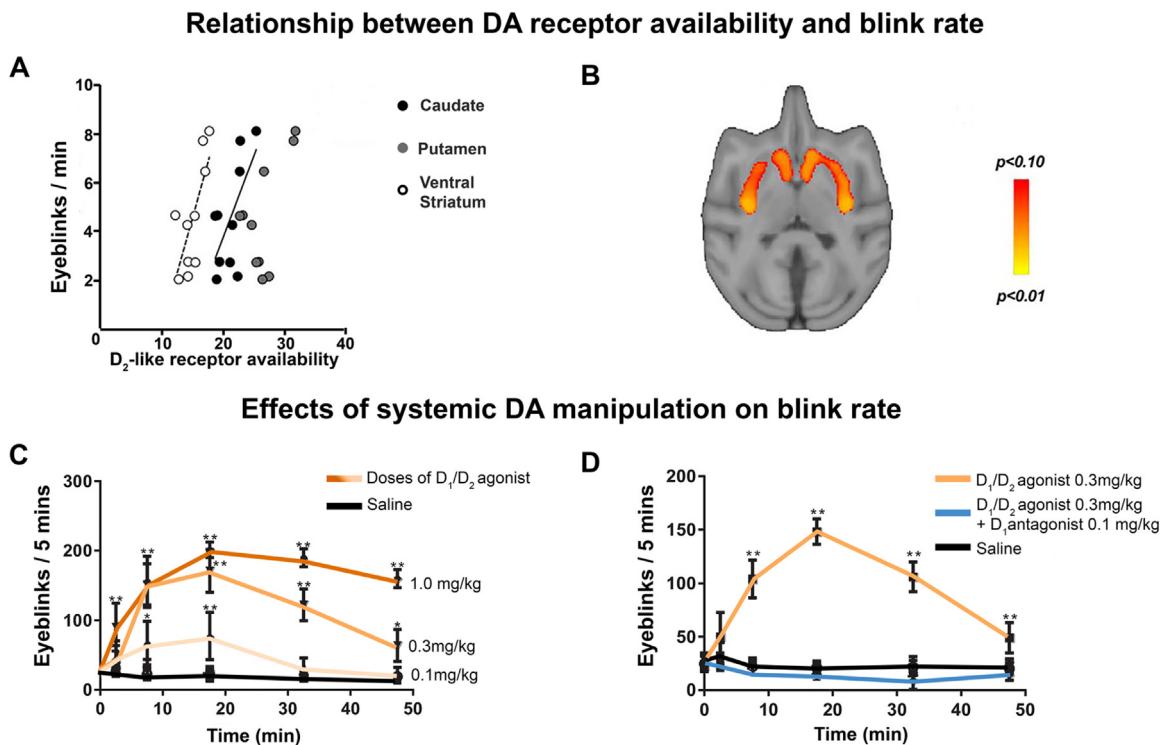


Fig. 8. Relationship between blink rate and DA receptor activity. a) Blink rate is positively related with PET measures of D₂-like receptor availability in the ventral striatum (white circles) and caudate nucleus (black circles), but not putamen (gray circles). These relationships were not observed with D₁-like receptors (not shown). b) Statistical map (*p*-values) of the voxelwise linear regression of blink rate on D₂-like receptor availability from (a) overlaid on the striatal volume of the rhesus monkey's MRI template. Adapted with permission from Groman et al. (2014). c) Systemic administration of apomorphine, a non-selective DA agonist, increased blink rate in a dose-dependent manner (orange lines) above baseline levels (saline administration, black line) in marmosets. d) This effect was only reversed with the administration of SCH39166, a D₁-antagonist (blue line), but not with the administration of haloperidol, a D₂-antagonist (not shown). Adapted with permission from Kotani et al. (2016).

is needed to better understand which aspects of the modulatory effect of DA on cognitive control can be captured with blink rate, which will be essential for examining how DA influences the developmental trajectories of these different processes.

In addition to resting blink rate, some paradigms lend themselves to measure task-evoked blink rate, which could act as an indirect measure of phasic DA and could provide additional insights into the relationship between DA and cognitive control. For example, phasic DA release is associated with "Go" signals that increase the selective updating of contextual features that are relevant for ongoing goal-directed behavior (Frank et al., 2001; Westbrook and Braver, 2016). A similar phenomenon has been captured with task-related blink rate on a Flanker task, wherein the occurrence of spontaneous blinks on one trial predicted the exertion of greater control on the subsequent trial (van Bochove et al., 2013). These findings suggest that task-evoked blink rate can capture functions typically associated with phasic DA release, and point to the feasibility of using similar paradigms to examine, on a moment-by-moment basis, how differences in the functioning of the DA system contribute to age-related differences in cognitive control – in particular, the ability to proactively update the level of control needed given changing task demands.

Beyond cognitive control, DA also supports learning. Striatal DA activity has been linked to reinforcement learning, as it signals reward prediction errors, exhibiting a large phasic DA release when rewards are greater than expected, and firing rates below baseline when rewards are smaller than expected (Bayer and Glimcher, 2005; Glimcher, 2011; Schultz et al., 1997). Additionally, lower levels of tonic DA have been related to better ability to learn from negative outcomes (Pessiglione et al., 2006; van der Schaaf et al., 2014). This DA-related effect has been studied using blink rate. Slagter et al. (2015) found that, compared to participants with a

higher blink rate at rest, participants with a lower one learned more from negative than positive outcomes in a probabilistic learning task. In another study, positive feedback was found to mediate the relationship between PET measures of D₂-like receptor availability and performance on a reversal-learning task (Groman et al., 2014). Blink rate mediated the relationship between the availability of D₂-like receptors and ex-vivo measures of D₂-like receptor density, thus providing a crucial link between these measures of DA and behavioral measures of reward sensitivity. Taken together, these studies show that blink rate can be used as a measure of DA-related learning, and could help bridge neuroimaging and direct measurement of DA activity.

One view of DA's role in learning is that it codes the consequences of prediction and learning signals, and not the prediction errors themselves. Instead, bursts of phasic DA release signal the salience of an incentive and enhance the 'wanting' of a reward (Berridge, 2007). This hypothesis has not been assessed with blink rate in the context of learning, but Peckham and Johnson (2015) showed the feasibility of using event-related blink rate as an indirect measure of phasic DA, in the context of reward processing in bipolar patients and healthy controls. In both groups, receiving a reward increased blink rate above resting levels, but to a lesser extent in anticipation of having to exert effort to obtain a reward (Peckham and Johnson, 2015). This study shows an exciting possibility of using task-evoked blink rate as a proxy for phasic DA release during reward processing, which could inform current hypotheses about the functional role of DA in learning. In addition, this study shows the possibility of examining mechanisms underlying developmental differences in decision-making, for example during adolescence.

In summary, there is converging evidence that blink rate can be a sensitive measure of DA involvement in certain aspects of cognitive

control (e.g., cognitive flexibility) and learning, producing findings that are consistent with PET and research with laboratory animals. Designing paradigms that would allow us to measure both resting and task-evoked blink rate could help to further elucidate whether blink rate can be used to measure the effects of phasic DA release on DA tone, and to better understand individual differences and age-related changes in goal-directed behavior.

3.3. Potential of blink rate to inform developmental research

The developmental trajectory of blink rate from infancy to adulthood has been primarily characterized with cross-sectional samples (for reviews, see Cruz et al., 2011; Jongkees and Corzato, 2016). Based on the findings to date, even a fetus is capable of producing spontaneous blinks starting during the third trimester of pregnancy. Neonates and infants have a very low blink rate, blinking on average less than 3 times per minute. Blink rate increases during childhood (6–8 blinks/min) (Lavezzo et al., 2007; Zametkin et al., 1979), and stabilizes at adult levels by late adolescence (10–20 blinks/min).

The fact that blink rate can be obtained at different ages has enabled cross-sectional comparisons and the (non-invasive) study of the role of DA in typical and atypical cognitive development. The following studies represent areas of research that have used blink rate in this manner, and that can be most closely related to the adult literature; these include cognitive control, decision-making, and learning.

As highlighted in the previous section, DA is strongly implicated in cognitive control, which undergoes important changes in childhood and adolescence (Bunge and Wright, 2007; Casey et al., 2016; Luna et al., 2015). The development of the prefrontal-striatal networks in part drives age-related improvements in these abilities (Casey et al., 2016). Dynamic changes occur in the DA system in childhood and adolescence that may contribute to the development of cognitive control. For example, an increase in striatal DA activity during adolescence (Padmanabhan and Luna, 2014) could be related in part to enhanced flexibility in learning that has been observed during adolescence (Johnson and Wilbrecht, 2011).

Although no studies to date have used blink rate to measure DA and the development of cognitive control longitudinally, Tharp et al. (2015) provided evidence that blink rate can be used as a measure of DA function in childhood. They used blink rate both at rest and during performance of a task that required rule switching to differentiate between typically developing children and children with Tourette syndrome (TS), a condition associated with elevated levels of DA (Albin and Mink, 2006; Singer et al., 1982). Compared to controls, TS patients in Tharp et al. study were more likely to apply incorrect rules when required to switch flexibly between two rules from trial to trial. Patients also exhibited uniformly high blink rates, wherein they failed to show the pattern that typically developing children showed, of a gradation of increase in blink rate as a function of task difficulty (Fig. 9a). This effect was observed even in unmedicated children, and was selective to blink rate since no associations were found with the amplitude or timing of pupil dilation. This study provides evidence that blink rate can be used to examine individual differences in DA functioning and engagement of cognitive control in various pediatric populations.

Research on rodents and non-human primates has shown that cortico-striatal circuits that are influenced by DA undergo dramatic, non-linear changes during development. Adolescence is a period of heightened plasticity of the DA system, with a marked proliferation of D2 receptors in the prefrontal cortex and striatum (Ernst et al., 2009). It has been proposed that the peak in striatal DA activity during puberty influences reward processing and sensation seeking (Padmanabhan and Luna, 2014). Barkley-Levenson and Galván (2016) provided the first evidence that blink rate could

be a powerful measure of age-related differences in reward sensitivity between adolescents and adults. Specifically, they used a risky decision-making task to test whether blink rate would predict how often a participant would choose options that would maximize their gains, irrespective of the probability of winning. Even though baseline levels of blink rate did not differ between adolescents and adults, higher blink rate only predicted more use of gain-maximizing strategies in the adolescent group. Considering that there was no group difference in baseline blink rate, it would be intriguing to test in future studies whether task-related blink rate could capture DA contributions, as well as age-related differences in the ability to update decision-making strategies based on past gains or losses.

The type of learning that could guide shifts in decision-making would in part require building associations between cues, actions, and outcomes over time – in other words, learning rules. Werchan et al. (2015) have provided one of the first demonstrations that blink rate could be a valuable tool to test DA involvement in rule learning. They found that eight-month-olds were capable of learning implicit hierarchical rules, and that trials with higher-order rule switches elicited higher blink rates. Importantly, this relationship with blink rate was only present in the second half of the experiment, when the rule sets had been learned. This learning process relies on DA-innervated pathways in adults and other species (Money and Stanwood, 2013; Rothmond et al., 2012; Weickert et al., 2007). Even though the blink rate results of this study suggest that the DA system has a functional role in infancy similar to its role in adults, the functional properties or development of the DA system in the first years of human life is not well understood (Money and Stanwood, 2013; Rothmond et al., 2012; Weickert et al., 2007). There is indirect evidence from longitudinal research that there might be rapid changes occurring in this system, given the observation of an increase in resting blink rate between four and 12 months of age (Bacher, 2014). These findings are encouraging in that they suggest that blink rate can be used as a marker of DA across development, beginning in infancy.

In conclusion, these studies show the feasibility of using blink rate to indirectly measure the involvement of DA in cognitive development in both typically developing children and pediatric patient populations. Given the widespread contributions of DA to cognition, there are several lines of research that could benefit from the measurement of blink rate. An extension of the prior literature cited here could be to characterize the involvement of DA in the development of cognitive flexibility, which has been found to follow a non-linear developmental trajectory, with adolescents outperforming adults (Johnson and Wilbrecht, 2011; Simon et al., 2013).

Blink rate measurement could also inform the study of the development of decision-making and learning. As shown by Barkley-Levenson and Galván (2016), blink rate is associated with age-related differences in reward-seeking behavior. Future research could evaluate whether task-evoked blink rate in decision-making paradigms has the temporal resolution needed to capture phasic changes in DA release, which are known to occur during reward processing (Schultz, 2013). If so, this metric could prove useful for assessing changes in decision-making flexibility (i.e., change in decision-making strategies) as well as for characterizing reinforcement learning (e.g. how past outcomes affect future strategy use) during different points in development. In addition, blink rate could be a suitable method to examine individual differences in motivation during learning. It has been hypothesized that DA translates incentives into motivation, which can direct working memory allocation (Westbrook and Braver, 2016). Blink rate could also be a useful method to assess whether incentive-related changes in DA (as measured by phasic blink rate) during academic learning are predictive of future learning success. If so, blink rate

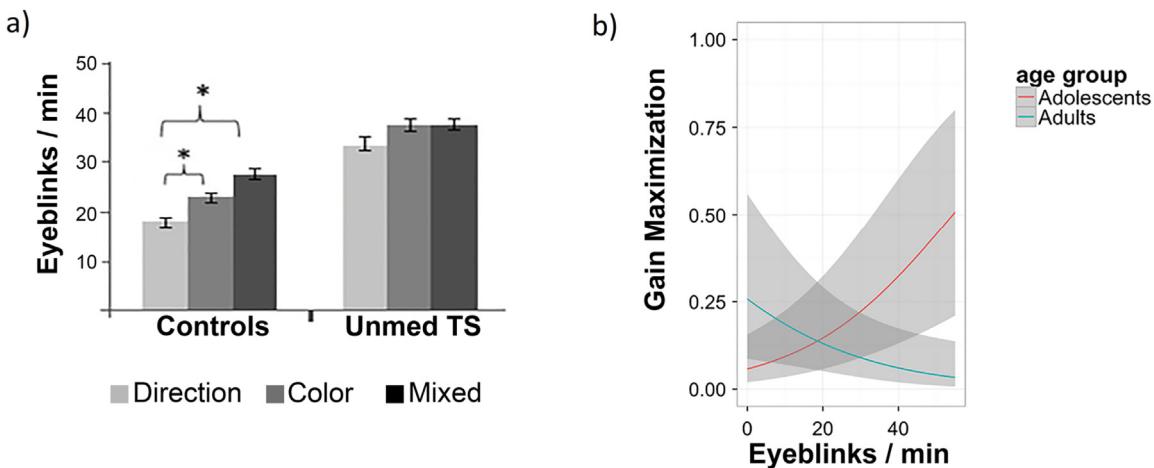


Fig. 9. Measurement of spontaneous eyeblink rate in developmental studies. a) Blink rate during performance of a task that requires rule switching flexibility can be used to differentiate between typically developing children and children with Tourette syndrome (TS), a condition associated with elevated levels of DA. Patients showed higher average blink rate at rest as did the control subjects, and also did not show task difficulty-related increases in blink rate. Adapted with permission from Tharp et al. (2015). b) Relationship between blink rate at rest and age-related differences in reward-seeking behavior on a risky decision-making task. Higher blink rate predicted increased use of a gain-maximizing strategy for adolescents but not for adults. Adapted with permission from Barkley-Levenson and Galván (2016).

could be a complementary ocular measure to improve currently available gaze-based computer tutors (e.g., Gütl et al., 2005), and a valuable method for education-based research.

Although blink rate is a promising measure for studying the development of DA-related cognitive processes, there is a strong need for a longitudinal study to assess the developmental trajectories of blink rate from childhood to adulthood. To date, only a handful of studies have measured blink rate longitudinally, and these have involved time points that were rather close in time (e.g., Bacher, 2014). Longitudinal studies would not only enrich our understanding of typical development, but could also be useful to measure outcomes of psychiatric treatment in pediatric populations, and also potentially facilitate earlier detection of risk factors for later substance abuse problems, such as enhanced sensitivity to cues of rewards and blunted D2 activity (Berridge, 2007; Goldstein and Volkow, 2011; Yin and Knowlton, 2006).

3.4. Methodology of spontaneous blink rate

The studies reviewed thus far suggest that blink rate, as measured during paradigms known to be sensitive to DA modulation, can be a promising tool to capture DA function throughout development and adulthood. Below, we describe how spontaneous blink rate can be estimated with an eyetracker.

Some of the most popular methods to record blink rate are infrared eyetrackers, EOG, electromyography (EMG), EEG, and video cameras. Besides video cameras built into a computer, eyetrackers are arguably the most cost effective and convenient method to use with special samples. Since blinks are often characterized as a gap in data recording, traditional eyetrackers have not enabled researchers to differentiate with good fidelity whether loss of data is due to blinks, muscular artifacts (e.g. as caused by yawning) or head movements away from the visibility of the eyetracker lens. However, newer models have built-in technology to account for these issues, such as automatic adjustments for small head movements, concurrent measurement of pupil dilation, and video cameras that can be used to perform manual inspections of eyelid closures in a subset of the data (e.g., Pedrotti et al., 2011). Even though combining these features can improve blink detection accuracy, it is still possible to misclassify blinks that are reflexive or voluntary as spontaneous blinks. The development of detection algorithms with higher precision, as those employed with other ocular recording methods (e.g., Gehricke et al., 2002; Królik and

Strumiłło, 2012), is needed to increase the validity of the calculation of blink rate from data that can be obtained from eyetrackers.

Eyeblinks are defined in eyetracking data as continuous periods of approximately 100–500 ms (corresponding to the typical range of spontaneous eyeblink durations) during which the coordinates or pupil diameters of the eyes are not recorded. This threshold could vary depending on the sampling rate of the apparatus or other methodological considerations (Jiang et al., 2013; Siegle et al., 2008). Blink rate is then calculated as the number of blinks occurring over a specified time interval and is usually expressed in terms of number of blinks per minute (Holmqvist et al., 2011). An inverse measure, which is used less often, is the interblink interval, which refers to the time between blinks.

Another important consideration is when to measure blink rate. The studies we have reviewed have measured blink rate either at baseline or during performance of a task. Baseline blink rate is used as a proxy of tonic DA levels, whereas blink rate recorded during performance of a task is considered to reflect phasic DA. A typical paradigm for acquiring baseline or tonic measures involves having participants look at a fixation cross on the center of a dark computer screen for 5–6 min (Holmqvist et al., 2011) and as little as 3 min (Zaman and Doughty, 1997) to be able to capture fluctuations in blink rate that can naturally occur. Phasic or task-related blink rate is captured in response to a task manipulation, either in an event-related or block design, and the data are averaged over static or moving windows of varying lengths, and as little as 30 s (e.g., Peckham and Johnson, 2015; Siegle et al., 2008; Tharp et al., 2015; Werchan et al., 2015). Alternatively, some studies have also treated blink rate as time series data, which facilitates examining event-related blink rate modulations during natural viewing (e.g., Shultz et al., 2011).

Several methodological factors need to be taken into consideration in order to maximize the interpretability of spontaneous blink rate measures. These include controlling for environmental and subject-specific variables that could affect blinking behaviors. Specifically, factors that affect the moisture level of the eye, such as dry eye conditions, seasonal allergies, temperature and humidity of the room, and use of contact lenses directly affect how much a person blinks to restore optimal levels of eye moisture (Al-Abdulmunem and Briggs, 1999; Cruz et al., 2011; Doughty, 2001). In addition, the presence of air pollutants, like cigarette smoke, elicit reflexive eyeblinks (Holmqvist et al., 2011). These factors can be controlled by maintaining the room's temperature and air qual-

ity stable, asking participants to wear glasses instead of contact lenses, and if possible rescheduling sessions for participants who are suffering from seasonal allergies or colds. Blink rate can also be affected by sleep deprivation (Barbato et al., 2000), as well as certain medications and stimulants that affect the DA system, like caffeine, cannabis, and antipsychotics (Holmqvist et al., 2011). It is recommended to ask participants to get a good rest before a session and to abstain from use of these drugs to minimize the acute effect of usage. In situations when it is not feasible for the participant to withhold medical treatment, the inclusion of unmedicated patients or a dose-response analysis would be needed (e.g., as done in Tharp et al., 2015).

Blink rate is also susceptible to confounds that can arise from experimental design. For example, blinking frequency increases as a factor of time in long experiments because it can affect the moisture of the eyes and also produce fatigue, both factors that modulate blink rate (Stern et al., 1994). Frequent breaks can eliminate these problems (Holmqvist et al., 2011). Also, visual designs that prompt large saccades or involve complex visual processing could increase blink rate irrespective of the mental workload (Al-Abdulmunem and Briggs, 1999; Cruz et al., 2011). Thus, if measuring event-related blink rate, we recommend presenting visual stimuli centrally on the screen to minimize the number of saccades. Finally, the time of day when the session takes place can also affect results, since blink rate increases in the evening (Barbato et al., 2000). It is typically recommended that sessions take place before 5 p.m.

Even when controlling for environmental and experiment design factors, a special population for whom blink rate is still challenging to obtain are infants and young children. Changes in behavioral states could alter the rate of blinking and data validity could also be affected by artifacts or gaps in the data caused by excessive motion (see Bacher and Smotherman, 2004 for a review of blink rate on infants). Recent technical advances such as automated body-movement adjustments and lighter, head-mounted gear can alleviate certain challenges associated with head movements (e.g. Smith et al., 2015), but the temporal requirements of maintaining fixed gaze for a tonic measurement may still render the data unreliable. It is therefore recommended to also carefully monitor the behavioral state of the infant or child during ocular data acquisition. Despite these cautionary notes, blink rate is still a measure that could further our understanding of the development of the dopaminergic system, as well as DA contributions to goal-oriented behavior and learning during development.

4. Conclusion

We have presented evidence that pupillometry and blink rate are, like eye gaze, sensitive measures of specific aspects of cognitive processing. All three ocular measures can be collected in a single session and with the same equipment, and can provide complementary information about cognitive processing. Although pupillometry and blink rate have been used extensively in adults, and to a lesser extent in infants, they have been used much less in children and adolescents – and even then, only rarely for the study of cognition. These gaps in the literature provide an opportunity to augment behavioral and brain imaging methods in studying how the mind changes over a broad developmental window.

4.1. Complementarity of ocular measures

Broadly, eye gaze can provide a moment-to-moment measure of the focus of attention, and can reveal which cognitive strategies are employed in complex tasks. Pupil dilation provides a window into the brain's LC-NE system, and reveals the subjective difficulty of cognitive tasks and the intensity of current cognitive processing.

Blink rate is modulated by DA, and has been used to study cognitive control, learning, working memory, and decision making. The differences and commonalities between these measures are described further below.

Eye gaze metrics are especially suited to revealing aspects about attentional focus during visual processing. Saccades and fixations can reveal what parts of the displayed information are most salient, and to what extent and in what order information is processed within a complex stimulus set. Eye gaze can also reveal how several pieces of information are integrated or compared during a task. Unlike eye gaze measures that are well suited for visually complex tasks, pupil dilation and blink rate are best captured in tasks with auditory stimuli or simple visual design that minimize sources of artifacts, such as eye movements and large luminance contrast.

Pupil dilation and blink rate can be recorded simultaneously, given that the same task designs can be optimized for both; thus, it is possible to ask how the two measures are related. DA and NE are closely related catecholamines that modulate neural activity in overlapping brain regions (Fig. 5a and b) and are associated with overlapping functional roles in cognition (Arnsten and Li, 2004; Meindertsma, 2014; Sara, 2009). Given the strong relationship between these neuromodulators, could we expect to tease apart DA and NE effects with blink rate and pupil dilation? Various research suggests that pupil dilation and blink rate do in fact reflect different processes that are uniquely associated with DA and NE (Siegle et al., 2008; Tharp et al., 2015; van Bochove et al., 2013). For example, phasic changes in pupil dilation have been associated with sustained processing of information, often associated with NE (e.g. Siegle et al., 2008), whereas phasic blink rate may respond to changing needs for flexible updating of representations, associated with DA (e.g., Tharp et al., 2015). In a working memory task, during which pupil dilation and blink rate were recorded concurrently (Siegle et al., 2008), pupil dilation but not blink rate scaled with the working-memory load of the task, as has been observed previously (e.g. Johnson et al., 2014; Kahneman and Beatty, 1966), whereas the timing of blinks but not pupil dilation was related to the presentation of new information, as has also been observed previously (e.g. Tharp et al., 2015).

Although the studies described above show that blink rate and pupil dilation are not redundant measures, there are likely cases in which they parallel one another closely, given that DA and NE release occur in tandem in many circumstances. Indeed, tonic levels of both catecholamines vary as a function of arousal, with low levels during drowsiness, intermediate levels during 'alert interest', and high levels during extreme stress (Robbins and Arnsten, 2009; see also Fig. 5c and d). Although NE is released in response to task-relevant or surprising stimuli (Aston-Jones and Cohen, 2005; Yu and Dayan, 2003), whereas DA is released in response to reward-predicting stimuli or unexpected rewards (e.g., Glimcher, 2011), these conditions co-occur in many tasks. For example, a pupillary response is observed when participants receive an unexpected reward (Einhäuser et al., 2010) – the classic scenario for DA release. However, the pupillary response in these situations can also be explained as the response to a surprising event. Thus, although pupil diameter and blink rate have different biological underpinnings and can be dissociated in many circumstances, this is not to be expected under conditions that elicit both NE and DA release.

Studies employing both pupillometry and measurement of eye blink rate should be conducted in developmental samples, with the goal of shedding light on the developmental trajectories of the NE and DA systems. It is conceivable that the two neurotransmitter systems mature at different rates (see Sections 2.1, 3.1, and 3.3) and that the balance between them changes during development. Longitudinal or cross-sectional studies with surprising as well as reward-predicting elements might be able to shed light on such developmental trajectories through the measurement of pupil dilatation.

tion and blink rates. In addition, such studies would be crucial to determine the extent of overlap between the NE and DA systems during development.

Although eye gaze, blink rate, and pupil dilation seem to be able to provide complementary information about cognitive processing, only a small number of studies has used more than one measure simultaneously so far (e.g., Siegle et al., 2008). Employing multiple eye-tracking measures in the same task would provide the unique opportunity to assess mutual relationships between them and also to directly compare the assessments of similar cognitive processes. This is especially important because all three measures have independently been used as measures of attention, employed strategies, and effortful cognitive processing. More studies are needed to identify circumstances under which these measures may reveal either complementary or redundant information about cognitive development.

4.2. Next steps: foundational research

Much foundational research is still needed before we can fully interpret developmental changes in pupil diameter or blink rate. For example, additional longitudinal studies tracking individuals between infancy, childhood, and adolescence are needed to characterize developmental changes in these measures, and how they relate to changes in cognitive performance. So far, studies have shown cross-sectional differences in tonic pupil dilation (Loewenfeld and Lowenstein, 1993; MacLachlan and Howland, 2002), the saccade system (e.g., Luna et al., 2004), and for blink rate (Zametkin et al., 1979; Cruz et al., 2011). But far less is known about systematic differences in task-evoked pupillary responses and blink rates. Only studies that examine these changes longitudinally will be able to characterize the precise developmental trajectory of the three ocular systems and to reveal individual differences. This research is necessary as a foundation for studies comparing age groups because differences in ocular responses need not necessarily arise from differences in cognitive processing, as which they are usually interpreted in cognitive studies. Only knowledge about the typical development of these responses will allow for an adequate interpretation of differences between age groups.

Longitudinal studies combining ocular measurements with cognitive tasks are needed to characterize the relationships between cognitive processing and changes in the underlying neurophysiology during development. This research is crucial for several reasons. First, the close links between the LC-NE system and pupil dilation and between the DA system and spontaneous blink rate have been established solely based on adult (and animal) work, and need to be replicated in children and adolescents. Second, several differences in ocular responses are conceivable between children and adults. These differences need to be characterized, explained, and related to cognitive processing. For example, the magnitude of the task-evoked pupillary response may change during development merely as a result of the dramatic changes in baseline pupil dilation; the same is true for spontaneous blink rate. It is important to study in what ways these changes, likely reflecting the maturation of the underlying neural system, are related to changes in cognitive processing. Third, the question needs to be answered as to how far developmental changes in the ocular measures are driven by age, pointing to a role of physiological maturation, versus how much they are driven by cognitive abilities, pointing to a role of experience. Very simple paradigms for which performance can be well-matched across ages (e.g., basic sensory discrimination paradigms, such as the auditory oddball task in Wetzel et al., 2016), should be used to answer this questions. Lastly, no non-invasive measures of the NE and DA neuromodulatory systems have been developed for use in humans yet (i.e., not requiring injection of radioactive isotopes, as is done for positron emission tomogra-

phy (PET) studies of dopamine receptor binding). In the absence of such tools, pupil dilation and blink rate are our best available options for probing neurochemical underpinnings of cognition in pediatric populations. These methods can facilitate the study of the early development of abilities such as attention, working memory, cognitive control, decision making, and learning.

4.3. Future directions: application to the study of cognitive development

The adult cognitive literature employing ocular measures has revealed a number of promising avenues for research, some of which we have reviewed above. Many of the used paradigms lend themselves to investigations in younger participants, shedding light on the development of the cognitive abilities in question. We will first focus on using pupillometry to study attention and using blink rate to study motivated behavior. After that, we will turn to more general topics and discuss how ocular measures can be used to identify cognitive processes that underlie developmental changes and how learning progress or the effects of interventions can be tracked using these measures.

One example of adult research that could reveal new aspects of neurocognitive development has focused on the influence of LC-NE activity on attention, as measured via pupillometry (Eldar et al., 2013). In this study, participants with different levels of LC-NE activity (or “neural gain”, in the terms of the adaptive-gain theory; Aston-Jones and Cohen, 2005) were identified based on their task-evoked pupillary responses. Participants with the largest neural gain were found to show a strong correlation between attention during the task and their attentional predisposition. In other words, participants who were predisposed to attend to certain image features, independently of the task at hand, attended to these same features during the task. Participants with smaller neural gain, on the other hand, showed no such correlation, or even a negative one. These participants attended to any image features, independent of their own predisposition. This relationship reveals that high levels of neural gain led participants to rely heavily on their attentional predispositions, whereas lower levels led participants to relax these predispositions and to explore features more equally. The correlation between levels of neural gain and reliance on attentional predispositions was almost perfect ($r=0.96$). Employing a similar task design in children could reveal if the LC-NE system is equally important for guiding attention during development. If the relationship were indeed found to be similarly strong, the pupillary response alone could be used as a quantitative measure of this aspect of attention, making obsolete verbal responses and thereby facilitating research on attention in even younger children, including preverbal infants.

The use of blink rate to study motivated behavior is another example of adult research for which translation into developmental studies seems promising. DA release in the striatum typically occurs in response to rewards and reward-predicting cues (Schultz, 2013). In reward-motivated behavior, the initial valuation of a reward or reward-predicting cue is thought to drive the allocation of effort to a task. The striatum is implicated in this stage of processing, which can occur without awareness of the signal or presence of the reward. In contrast, later reward processing stages can inform strategic decision-making and engage cortical areas (Bijleveld et al., 2012). Using blink rate as a proxy of striatal DA activity, Pas et al. (2014) found that individuals with higher tonic blink rate exerted more effort in a finger-tapping task when they were presented with cues that indicated higher pay-off of their work, but this effect only occurred in response to reward cues presented subliminally (i.e., an extremely fast and masked cue). Prior to this work, studying the neurobiological underpinnings of the initial phase of reward processing in humans was more difficult due to tempo-

ral and/or spatial constraints of neuroimaging methods (e.g., van Hell et al., 2010). Thus, blink rate can provide an invaluable way to examine reward processing. In particular, it could be used to characterize age-related differences at different stages of reward processing, which could inform current models and theories of decision-making during adolescence.

More broadly, ocular measures can be helpful in determining which of several candidate processes determine age-related differences in performance. If the experimental protocol achieves a separation in time of the processes in question, for example through sequential phases of encoding, retention, and recall in a memory experiment, the ocular responses for each can be assessed and compared independently. Such paradigms are useful in developmental research whenever it is necessary to pinpoint which cognitive processes are affected in a complex task, or to determine what the underlying reasons are for differences in behavior.

Another potential application of ocular measures is to track learning progressions and to specify the underlying mechanisms of behavioral change. For example, reduced cognitive effort associated with task performance (i.e., greater efficiency) could be evident in reduced task-evoked pupillary responses and blink rates. Reduced numbers of saccades would also suggest increased efficiency, and the same is true for fixation patterns that are more concentrated on the crucial elements of a task. In other words, quantitative changes in the ocular responses often reveal changes in cognitive efficiency, rather than qualitative changes in strategy. If an intervention led to changes in strategy, qualitatively different ocular response patterns would be expected, such as pupil dilations and blink rates whose intensities have shifted from some task components to others, or eye movements with qualitatively different patterns of saccades and fixations. Ocular measures are therefore a promising tool for determining whether a behavioral improvement reflects continuous or discontinuous, quantitative or qualitative change in underlying mechanisms.

5. Summary

Summing up, three different measures of the eyetracking toolbox, eye gaze, pupil dilation, and blink rate, have the promise of accessing crucial aspects of cognitive processing, such as attention, working memory, decision making, and cognitive control, across age groups. In this review, we have described the neural systems underlying pupil dilation and spontaneous blink rate, the LC-NE and DA systems, respectively. Amongst others, these systems play central roles in a number of complex cognitive functions, such as attention and working memory (LC-NE), and reward processing and cognitive control (DA). Building on a characterization of these neural systems, we next exemplified the range of cognitive studies in which these methods have been applied so far. Due to gaps in the literature in the use of these measures in the study of cognitive development, these sections focused mainly on adult work. The subsequent sections introduced a small number of selected examples from the developmental literature to show what kinds of analyses can be done with each measure and what results have been obtained in a developmental setting. We then explained the methodological details and considerations of each method.

In the final section, we compared eye gaze, pupil dilation, and blink rate in terms of appropriate task designs and underlying cognitive processes, and showed that these measures can be used as complementary measures of different aspects of cognitive processing. We also highlighted gaps in the current literature that need to be addressed to provide a solid foundation for developmental studies and studies comparing different age groups with these methods. Lastly, we pointed out several directions in which future research using ocular measures could advance the study of cognitive devel-

opment. Research on attention and motivated behavior might be areas that will especially benefit from these methods, but the methods also have the potential to unveil aspects of neurophysiological processes underlying a much broader range of cognitive functions. Finally, we argued that qualitative and quantitative changes during learning and development could be differentiated with these measures. In closing, we expect that the eyetracking toolbox – the measurement of eye gaze, pupil dilation, and blink rate – will yield novel insights about cognitive development over the coming years.

Conflict of interest

None.

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Update

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Erratum

Erratum

The purpose of this publisher correction is to inform readers that the final version of the articles linked with this correction were replaced with a corrected version in April 2019. The corrected version contains a

Declaration of Interest statement which the publisher inadvertently omitted from the original version.

The Publisher apologizes for any inconvenience this may cause."



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