Pupillary and behavioral markers of alerting and orienting: An individual difference approach

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\textbf{A B S T R A C T}

Measuring task-evoked pupillary (TEP) responses as an index of phasic activity in the locus coeruleus (LC), we examined two competing hypotheses regarding the alerting and orienting mechanisms of attention. According to a dual mechanism account (Fernandez-Duque & Posner, 1997), two separate noradrenergic and cholinergic mechanisms modulate, respectively, the alerting and orienting effects. However, Corbetta and colleagues (2008) proposed that LC phasic activity may also be involved in orienting effect through its functional relationship with the ventral attentional network. We recruited seventy-five healthy Norwegian participants to perform a Posner cueing task. Both behavioral and pupillary responses revealed the alerting effect. Also, both behavioral and pupillary responses indicated that cued attention is affected by age. Behavioral responses also revealed orienting effect. However, we found no TEP differences between valid, invalid, and neutral conditions, suggesting that TEP effects were driven by the alerting effect of cue presentation. Moreover, both behavioral and pupillary estimates of alertness and orienting were uncorrelated. Finally, individual differences in general cognitive abilities did not appear to affect the orienting and alerting mechanisms. This pattern of results is consistent with the dual mechanism account of attention. However, the LC involvement in the (re)orienting attention may be driven by state-specific factors.

1. Introduction

The locus coeruleus norepinephrine (LC-NE) system is a small subcortical nucleus composed of noradrenergic (norepinephrine, NE) neurons, which projects to the majority of brain areas, including the whole cortex (Sara, 2009) and modulates cognitive processes. Researchers distinguish two polarities of its activity, known as the tonic and phasic modes (Aston-Jones & Cohen, 2005). The LC tonic (sustained) activity appears to regulate arousal and transitions between behavioral states, i.e. wakefulness, alertness, exploration, or stress (Hofmeister & Sterpenich, 2015). The phasic mode is characterized by bursts of high-frequency neuronal discharge in response to relevant external or internal stimuli. Several hypotheses are proposed to explain the role of LC activity in the regulation of changes between behavioral and brain states (e.g. Aston-Jones & Cohen, 2005; Berriidge & Waterhouse, 2003; Bouret & Sara, 2005; Yu & Dayan, 2005, Corbetta, Patul, & Shulman, 2008; Reimer et al., 2014; Shine, Aburn, Breakspear, & Poldrack, 2018). A common view is that the phasic LC activity modulates the goal-directed attentional processing and behavioral performance (Hofmeister & Sterpenich, 2015). However, compared to other neuromodulators (e.g. dopamine and acetylcholine), the role of the LC-NE system in sub-components of visuospatial attention is less understood (Noudoost & Moore, 2011). There are two competing accounts regarding the role of LC-NE in spatial attention.

Posner and Boies (1971) divided the attentional system of the human brain into three separate but interacting neural networks that are now termed as: alerting (readiness for an incoming event), orienting (shifting one’s focus) and executive (conflict resolution; Callejas, Lupiáñez, & Tudela, 2004; Fan et al., 2009, 2002; Petersen & Posner, 2012; Posner & Peterson 1990; Raz & Buhle, 2006; Rueda, Fan, McCandliss, Halparin, & Posner, 2004). According to “dual mechanism account” (Fernandez-Duque & Posner, 1997), which has support from both pharmacological, animal and human studies (Petersen & Posner, 2012), the “alerting” network is modulated by the locus coeruleus’ norepinephrine (LC-NE) system, whereas the “orienting” system is modulated by cholinergic signals (Coul1, Nobre, & Frith, 2001; Petersen & Posner, 2012; Witte & Marrocco, 1997).

Corbetta and Shulman (2002), however, divided the attentional system into two other interacting networks, known as the dorsal network, which is activated by our current expectations in a top-down way.
manner, and the ventral network, which is driven in a bottom-up manner to reorient the attention towards significant events that, spatially or temporally, appear unexpectedly (Fan et al., 2009; Vossel, Geng, & Fink, 2014). Later, Corbetta et al. (2008) proposed that the main role of LC phasic activities is to facilitate adaptive responses by triggering a functional shift of activity between dorsal, goal-driven and ventral, stimulus-driven attentional networks. That is, the LC phasic activity may also be involved in reorienting of attention through its functional relationship with the ventral attentional network. Here, we refer to this view as the “singular account”.

Here, we test the dual and singular accounts of LC phasic activity involvement in alerting and orienting components of visuospatial attention using pupillometry and a self-developed version of the Posner cueing identification task. That is, we investigated whether pupillary responses indicate an involvement of LC’s phasic activity also in the reorienting of attention (Corbetta et al., 2008), or they only implicate the involvement of noradrenergic modulation in the alerting mechanism, as the dual mechanism account proposes (Fernandez-Duque & Posner, 1997). Moreover, we investigate if individual differences in the level of general cognitive abilities (i.e., working memory capacity, WMC; and g factor) or level of overall task performance modulate pupillary indices of alerting and orienting effects, as an indirect index of LC phasic activity. Individual differences in the level of task performance, compared to the level of general cognitive abilities, can be an index of situation-specific triggers of pupillary responses driven by different factors like task-specific skills, mental effort, motivation, fatigue, or stress. We also examine the effect of individual differences in age.

The reason for introducing such an individual differences approach is that some studies have indicated that the level of general cognitive abilities can have an effect on the behavioral responses in the Posner task, on the functional connectivity in the frontoparietal attentional network, and on the pupillary responses. For example, some researchers have found a relationship between intelligence scores and response times (RT) in the Posner letter matching task (Neubauer, Biemann, Mayer, & Angleitner, 1997), also between IQ and memory performance in the Posner cueing task (Markant & Amso, 2014), and between visual WM and attentional orienting mechanism (Wang, Yan, Wang, Oliviers & Theeuwes, 2017). However, Redick and Engle (2006) found that high (HS) and low span (LS) individuals differ in their executive control network (i.e., LSs were more slowed by incompatible flankers than HSs), and not in the alerting or orienting networks.

Human imaging studies have also shown that the same neural structure (i.e., frontoparietal network) is involved in both WMC and attentional orienting (Ku, 2018), and that there is an association between intelligence, attention, and functional connectivity in the frontoparietal network (Hearne, Mattingley, & Cocchi, 2016; Pamplona, Santos Neto, Rosset, Rogers, & Salmon, 2015; Schultz & Cole, 2016; Song et al., 2008). Besides, there is evidence for the modulatory effect of LC-NE system on the frontoparietal network (Szabadi, 2013), as well as on individual differences in both WMC and attention control (Unsworth & Robinson, 2017), and on the functional connectivity throughout the brain (Moore & Bloom, 1979). The strength of functional connectivity is found to be associated with changes in pupil sizes (Eldar, Cohen, & Niv, 2013; Warren et al., 2016).

Some pupillometry studies suggest that TEP responses are modulated by individuals’ general cognitive abilities (Heitz, Schrock, Payne, & Engle, 2008; Peavler, 1974; Tsukahara, Harrison, & Engle, 2016; van der Meer et al., 2010) but also their levels of task performance (Aminihajibashi, Hagen, Andreassen, Laeng, & Espeseth, 2019, under review). Thus, it is possible that (only) individuals with high performance in the Posner cueing task or those with high general cognitive abilities can have different LC activity and functional connectivity within the relevant brain areas, and benefit more from either warning signals (alertness) or the validity of spatial signals (orienting).

Measuring pupillary responses seems a promising and reliable method to track the activity of the LC’s noradrenergic system because both direct recordings from LC neurons in animals (Joshi, Li, Kalwani, & Gold, 2016; Rajkowski, Kubiak, & Aston-Jones, 1994; Varazzani, San Galli, Giraldeau, & Bouret, 2015) and neuroimaging studies in humans (Alnæs et al., 2014; Murphy, O’Connell, O’Sullivan, Robertson, & Balsters, 2014; Schneider et al., 2016; Yellin, Berkovich-Ohana, & Malach, 2015) have shown a tight link between the fluctuations of pupil diameter and the LCs level and pattern of activation (Aston-Jones & Cohen, 2005; Devilbiss & Waterhouse, 2011). Phasic LC activations driven by behaviorally relevant targets are always associated with pupil dilations. From cognitive psychology studies, it is also known that pupillary changes are a reliable index of mental effort and the intensity of attentional processes (Kahneman, 1973; Wilhelm, Wilhelm, & Lüdtke, 1999; for reviews see: Beatty & Lucero-Wagoner, 2000; Eckstein, Guerra-Carrillo, Singley, & Bunge, 2017; Granholm & Steinhauser, 2004; Laeng, Sirois, & Gredebäck, 2012; Mathot, 2018b; Steinhauser, Siegle, Condray, & Pless, 2004; van der Well and Steenbergen, 2018), which are assumed to be controlled by the noradrenergic arousal system of the locus coeruleus (Alnæs et al., 2014).

Using pupillometry and the attention networks test (ANT), Geva, Zivan, Warsha, and Olichik (2013) provided evidence for the involvement of the LC-NE system in both alerting and orienting and executive networks (with differing onset and rate of firing). Similarly, through pharmacological manipulations, Reynaud et al. (2019) found that high dose of atomoxetine, a NE reuptake inhibitor that increases NE availability in the brain, increases pupil size and modulates both alerting and orienting in ANT in a context-dependent manner. Dragone et al. (2018) also found an effect of orienting on pupil responses in a Posner cueing task, only when the centrally presented cues were highly predictive (80%). Mathôt, van der Linden, Grainger, and Vitu (2013) also found that covertly attending to a bright area, compared to a dark area, induce pupillary light reflex, which was associated with behavioral cueing effects in a Posner cueing task.

However, the findings have not been consistent. For example, while results from some pharmacological studies have revealed the effect of NE manipulation on both alerting and orienting (Clark, Geffen, & Geffen, 1989; Coull et al., 2001; Reynaud et al., 2019), others found only a neuromodulatory effect of NE on alerting in a Posner cueing task (Witte & Marrocco, 1997a; Witte, Davidson, & Marrocco, 1997b). Moreover, behavioral studies have shown that individual differences in alerting and orienting processes are not correlated (Fan et al., 2009) and pharmacological studies with humans, monkeys, and rats have found that the manipulation of norepinephrine (NE) release influences alerting and the acetylcholinergic (Ach) drugs influence orienting in a double dissociated manner (Davidson & Marrocco, 2000; Everitt & Robbins, 1997; Fan, McCandliss, Sommer, Raz, & Posner, 2002).

One reason for this discrepancy can be methodological differences. For example, pharmacological manipulation of the LC-NE system can influence its interaction with other neuromodulatory systems and have a differing influence on neural activity of different brain areas (Szabo & Blier, 2001). It is also possible that some other state-specific and task characteristics or individual difference factors trigger the involvement of the LC-NE system in orienting. For example, the ANT involves exogenous cues, and performance on the ANT task, compared to Posner cueing task, is influenced by congruency effects in addition to alerting and orienting effects (Newson, 2018), which may influence the involvement of underlying neuromodulatory systems, especially in combination with other factors. Therefore, here we used the Posner cueing task, rather than ANT. Surprisingly, there are very few pupillometry studies on covert orienting of attention with the Posner cueing task.

The Posner cueing task is one of the paradigms that have been frequently used to study the development and neurophysiological basis of attentional networks (Posner, 2014). In the Posner paradigm (1980), non-spatial and spatial cues are used to study the effect of warning signals (alerting) and (re)orienting of visuospatial attention on performance (Chica, Martin-Arevalo, Botta, & Lupianez, 2014; Posner, 2014).
The main idea is that attending to a location, overtly or covertly, facilitates the processing of incoming information in a given location, which consequently decreases our response time (Posner, Snyder, & Davidson, 1980, but also see Green & Woldorff, 2012 for a non-attentional explanation). The valid cue (when a target is presented in the position indicated by the cue) facilitates task performance by providing the correct information about when and where the target will appear. This behavioral advantage in the valid, compared to invalid, trials is called the orienting effect. The other cue types (i.e. invalid and neutral cues) are only temporally informative and, relative to valid trials, they lead to less optimal performances (e.g., slower response times and/or more errors), but relative to trials with no cue, when no temporal information is available, performance will be better. The behavioral advantage in cued trials, relative to no-cue, is called alerting effect. Several factors are found to be influential in attention orientation and performance in the Posner task. For example, in addition to cue’s validity (i.e. the probability of valid cues), cue’s type (i.e. endogenous versus exogenous) can affect performance and the involved neural structures (Chica, Bartolomeo, & Lupiáñez, 2013). How long the cues and targets are shown, the interval duration between cue’s onset and target onset (stimulus onset asynchronies; SOA) and the type of task (detection vs. identification) are also shown to change the physiological (e.g. pupil responses) and behavioral outcome (Chica et al., 2013).

Gabay, Pertzov, and Henik (2011) found, for instance, that only a demanding identification task (in comparison to a detection task) induced a phasic pupil dilation locked to the behavioral response time.

To test the dual and singular accounts, we reasoned that if the dual mechanism account is true, then pupillary responses should only express the involvement of the noradrenergic alerting mechanism, which operates globally to prepare the individual for responding to the coming target. That is, all cued trials should trigger a larger pupil dilation compared to no-cue trials in both SOA conditions, without any significant difference in TEP dilations between cued conditions. In contrast, behavioral responses (i.e. response times and accuracy) should express the involvement of both alerting and orienting mechanisms. That is, as shown also in previous studies, we expect a higher accuracy and faster response time (RT) in the valid trials compared to all other trial types (orienting effect) and higher accuracy and faster RT in neutral than in no-cue trials (alerting effect) in both SOA conditions. Moreover, this account suggests that the orienting effect seems to be independent of the level of alertness because it is driven by cholinergic neuromodulation of attentional focus and behavioral responses activated by spatial cues (Fan, McCandliss, Sommer, Raz, & Posner, 2002). Therefore, behavioral and pupillary indices of alertness (no-cue – neutral) and orienting (invalid – valid) effects should be uncorrelated (Fan et al., 2002).

However, if the singular account is true, then the detection of invalidly cued targets (i.e., reorient the attention) is also associated with an increased phasic LC activity accompanied by larger pupil dilations in invalid compared to valid trials. Moreover, the behavioral and pupillary indices of alertness and orienting effects should be positively correlated. However, we predicted that the effect of spatial cues on behavioral and pupillary responses will be influenced by SOA manipulation (i.e., longer RT along with larger TEP responses in SOA1300, especially in older subjects). Some previous findings (Hayward & Ristic, 2013) have shown an increased RT in cued trials when SOA was long (931 ms compared to 106 ms) and the probability of target presentation was low (75%). Moreover, RT benefits and costs increased with age only when SOA was very long (2000 ms) and the cue was presented centrally in a discrimination task (Greenwood, Parasuraman, & Haxby, 1993, but also see Chica et al., 2014; Yamaguchi & Kobayashi, 1998).

Finally, we examined if there is a significant relationship between pupillary indices of orienting and alerting and estimates of both general cognitive abilities (i.e., WMC and g factor) and task performance (total RT in the correctly performed trials). To our knowledge, this is the first study that tests these competing accounts using Posner cueing task and pupillometry along with investigating the modulatory effect of individual differences in cognitive abilities.

2. Method

2.1. Participants

A Statistical Power analysis was run using the G*Power tool (Faul, Erdfelder, Lang, & Buchner, 2007), and based on Geva et al. (2013), who using the ANT, reported an effect size of $\eta_p^2 = 0.59$ for the interaction between Component x Condition. This revealed that with an alpha level of 0.05, and eight number of groups (2 SOA x 4 Trial Type conditions), a sample size of 13 was required when power was set to 0.90. However, since a different paradigm was used in Geva et al.’s study, and we also investigated the effect of general cognitive abilities, we required and recruited more participants.

Seventy-five participants (27 females; $M_{\text{age}} = 33$ years, $SD_{\text{age}} = 8.4$; Min-Max$_{\text{age}} = 18$–52) were recruited from a sample pool screened at the Oslo University Hospital for a separate genetics project. The inclusion criteria were being a healthy ethnic Norwegian, aged between 18 and 70 years. The project’s exclusion criteria were to have any neurological disorders, previous head injury, substance abuse, or severe mental disorders (evaluated by the Primary Care Evaluation of Mental Disorders interview; PRIME-MD: Spitzer et al., 1994). Participants were invited to the Department of psychology at the University of Oslo to participate in several pupillometry experiments. All participants had a normal or corrected-to-normal vision, signed a consent form, and received monetary compensation. The final sample size differed across the different measures since data from 5 individuals were missing for WMC, 6 for the g factor, 1 for the behavioral data, and 3 for the pupillary data due to technical problems.

2.2. Materials and procedure

2.2.1. Posner cueing task

Behavioral and pupillary indices of alerting, orienting, along with overall task performance (which indicate the degree in which individual benefits from any warning signal, as well as shifting the orientation of visuospatial attention to effectively detect a target) were measured using a self-developed version of Posner cueing task.

2.2.1.1. Stimuli. Using E-prime software (2.0.10.353), we developed a Posner paradigm in which there were four types of trials, cues were presented centrally and cue’s validity was manipulated (180 out of a total 300 trials (60%) were valid). In invalid trials ($N = 40$, 13%), in contrast to valid ones, the target letters are not presented at the place (square box) that cue had pointed to (Fig. 1). In neutral trials (13%), all corners of the central square box were thickened indicating that target can appear in any place. Finally, in uncued trials (13%), participants did not receive any cue and the target could appear in any place. All trials were presented in a semi-counterbalanced manner to all participants. We also manipulated the Stimulus Onset Asynchrony (SOA) having two conditions with either a short (800 ms) or long (1300 ms) SOA with equal frequency. These SOA conditions were chosen based on the fact that pupillary responses need time to develop and to get back to the baseline level (e.g., Eckstein et al., 2017) and based on previous findings in the pupillometry studies (Dragone et al., 2018; Gabay et al., 2011). Behavioral literature has shown that the effects of endogenous cues are observable at SOAs of ~ 300 ms, and last for several seconds (Chica et al., 2014).

2.2.1.2. Design. Each trial began with presenting a fixation slide (1000 ms) and, following a “covert” attentional orienting procedure, participants were instructed to focus their gaze on a circle located at the center of the screen throughout the whole task (see Fig. 1) and only shift the mind’s eye or attention. Mean pupil size during this fixation
period was used to provide a baseline measurement. At the center of the screen, there was also a square box. To present the cue (100 ms), one of the corners in this central square became thicker (Fig. 1) to indicate where the target would be likely to appear. After an either 800 ms or 1300 ms time interval, the target stimuli, i.e., a black A or Q letter, appeared on a gray background.

The target was presented (in 2500 ms) in one of the four square boxes located in each corner of the screen (3 degrees visual angle) with equal distance from each other and from the center of the screen where the cue was presented (see Fig. 1). The task was to identify the target and, regardless of which square the letter was presented in, to press, as fast and accurate as possible, the outer left button on the response box when seeing the Q letter and the outer right button when seeing an A. The response keys were counterbalanced between participants. After responding, a fixation slide appeared on the screen until the participant pressed one of the bottoms on the response box to go to the next trial (following a self-paced procedure).

2.2.1.3. Procedure. After signing the consent form, participants read the instruction for the task. The experiment was also explained verbally to the participants, who were shown where to fixate their gaze. Before the experiment, all participants performed six practice trials and received visual feedback each time they answered incorrectly. They were tested in the same, soundproof room (eye lab), where the only light source in the room was one fluorescent ceiling lamp, providing a constant environmental luminance.

2.2.2. Measuring general cognitive abilities

General cognitive ability is typically measured by standardized intelligence tests (Colom, Karama, Jung, & Haier, 2010; Hunter, 1986), but it can also be estimated by statistically-derived parameters like the g factor (Deary, Penke, & Johnson, 2010; Spearman, 1904) or by using estimates of working memory capacity (Unsworth & Robinson, 2017). Indeed, there is a high correlation between WMC and g factor (Conway, Kane, & Engle, 2003), and between WMC and fluid intelligence ($r = 0.66$, Fukuda, Vogel, Mayr, & Awh, 2010). Similar to the g factor, WMC can predict performance on a wide range of cognitive tasks (Unsworth & Robinson, 2017; Wilhelm, Hildebrandt, & Oberauer, 2013). Here, we measured individuals’ WMC, using the Letter-Number-Sequencing (LNS) task, a subtest from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 2003). The task is to organize strings of unsorted numbers and letters that are in varying lengths so that the numbers to be in ascending order and the letters in alphabetic order. The test has high reliability ($\alpha = 0.85$) at each age group (Sattler & Ryan, 2009), and is the most widespread measure of WMC among European psychologists (Evers et al., 2012). It also correlates highly with laboratory measures of WMC, and with a composite score of three separate operation span tasks, $r = 0.53$ (Hill et al., 2010).

In addition, we computed individuals’ g factor scores by running principal component analysis (PCA) based on participants’ scores on three cognitive tests; Matrix Reasoning subtest of the WASI (Wechsler, 1999) that estimates the fluid and reasoning abilities, Color-Word Interference Test (CWIT; Delis, Kramer, Kaplan, & Ober, 2000) that estimates the processing speed and inhibition ability, and the Hopkins Verbal Learning Test (HVLT; Brandt, 1991) that measures the ability of verbal learning and memory, following a similar procedure used in previous studies (Christoforou et al., 2014; Házsz et al., 2013). See supplementary material, section 1, for a detailed explanation of these tests.

2.3. Apparatus

Measurements of pupil size and eye gaze positions were recorded by a binocular Remote Eye-tracking Device (R.E.D.; SMI-SensoMotoric Instruments, Teltow, Germany) set to a sample rate of 60 Hz. Head movements were stabilized using a chin-rest to keep the eye-to-monitor distance constant at 57 cm. The experiment was shown on a 47 × 29.4 cm color, LED monitor with a resolution of 1920 × 1080 pixels, and a 60 Hz refresh rate.

2.4. Pupillometry procedure

A standard calibration procedure was conducted at the beginning of a session (to calibrate the eye-tracker). Participants were asked to keep their gaze on the gray fixation circle at the center of the screen (Fig. 1) while performing the task. The psychometric tests and pupillometry experiments were administered on different days.

2.5. Data processing

2.5.1. Psychometric data

Working Memory Capacity. Individual WMC was measured as a total score obtained from the Letter-Number Sequencing task ($M = 14.91$, $SD = 2.61$; Min-Max = 9–22).

g factor. To estimate g factor scores based on individuals’ scores on three cognitive tests, we first made a composite score for each test and ran a principal component analysis (PCA). To create a total composite score for CWIT, we first ran a separate PCA on RTs obtained from four conditions of CWIT. To make these scores comparable with scores from the other two tasks, we inverted RTs in the CWIT task so that a higher score indicates better function. Moreover, scores from the three learning and recall trials of the HVLT task were aggregated to compute a sum score. Finally, these measures along with raw scores from MR (Matrix Reasoning) task were used in a PCA. The first unrotated component was used (eigenvalues: $1.33, 0.94, 73$) as an estimate of the g factor scores ($M = 0.004$, $SD = 1.01$; Min-Max = $-2.47$ to $2.41$).

2.5.2. Behavioral data

One subject did not complete the Posner task and therefore the sample size for these behavioral data was $N = 74$. The percentage of correct responses was measured for each trial type (i.e., valid, invalid, neutral, and uncued trials), each SOA condition (800 ms & 1300 ms),
and each individual using the analysis tool provided by the E-prime software. We also computed the median response time (RT) for each individual using the same procedure, except that trials with incorrect responses and RTs faster than 250 ms were first excluded. These data were used to examine the effect of trial types and SOA conditions on performance. The behavioral alerting (RT in no-cue – RT in neutral trials) and orienting (invalid - valid) indices were first measured separately for each SOA condition. We averaged the Z scores of orienting and alerting indices from each SOA condition to estimate a total orienting and alerting estimate for each individual. A high alertness score indicates that performance is more influenced by the warning signals so that it takes more time to respond when there are no warning cues. A high orienting score indicates that performance is strongly influenced by the validity of cue and it takes more time to respond when a cue is invalid.

Finally, we calculated a total RT score for each participant by collapsing mean RTs across all four conditions. This total RT score was considered as an estimate of each individual’s overall task performance (‘Posner skill’).

2.5.3. Pupillary data

Time intervals containing blinks were replaced using linear interpolations, beginning five samples before and five samples after a blink. Then, a Hampel filter (Pearson, 1999) was used to exclude the instrumental noises (Klingner, Kumar, & Hanrahan, 2008). However, the analysis was also repeated with unfiltered data, but the conclusions did not change. That is, all p-values below and greater 0.05 were also below and greater 0.05 when using unfiltered data. This explanation holds whenever we report that the pattern of results did not change. Any significant changes are otherwise reported. All pre-processing of pupillary data was done using R (R Core Team, 2018). Analysis scripts are available from https://github.com/thohag/pupilParse. The pupillary data of two subjects were not recorded due to technical problems, and one subject who did not finish the task, so the final sample size in the pupillary analysis was N = 72.

2.5.3.1. Pre-trial baseline pupil size. The average pupil size during the 1000 ms at the beginning of each trial was used as a measure of pre-trial baseline size. After calculating the mean baseline, baseline values that were larger and smaller than 1.5 interquartile range (IQR, Seo, 2006) from the median were considered as an outlier and filtered out.

2.5.3.2. Task-evoked pupil (TEP) size. We had two types of event-related pupillary responses, one after cue presentation, and one after target presentation. The subtractive correction method (Mathôt, Fabius, Van Heusden, & Van der Stigchel, 2018a) was used to derive baseline-corrected TEP sizes in each trial for each participant. That is, the average pre-trial baseline pupil size was subtracted from the pupil size measured at each sample. Similar to RT measurements, only trials with correct responses were included.

To calculate the cue- and target-evoked pupil sizes (respectively, CEP & TaEP), we used findings from the literature to choose time windows during which the experimental effects on pupil responses can be expected to appear. Evidence from the literature indicates that the real effects of manipulations on pupil size require at least 220 ms to develop (Mathôt, van der Linden, Grainger, & Vitu, 2015). Moreover, when performing tasks that require motor responses, peak dilations, under normal room lighting, tend to occur from 600 to 900 ms (Steinhauer & Hakerem, 1992) to 1400 ms (Geva et al., 2013; Laeng, Ørbo, Holmlund, & Miozzo, 2011) after stimulus presentation. Accordingly, we selected two time-windows to measure the average pupil sizes induced by cues (i.e., mean pupil size from 200 ms after cue presentation until target presentation), and by targets (i.e., mean pupil size during 200 ms to 1400 ms after target presentation.

However, since we had two SOA conditions, the time window used to measure the cue-related TEP sizes was longer in SOA1300 (1000 ms) than in SOA800 (500 ms). Therefore, we measured and ran two series of analyses, similar to Dragone et al. (2018). First, the time window from 200 ms after the cue presentation until the target presentation was used to analyze the pupillary changes as a function of cue duration. We refer to these measurements as CEP 1. In the second series of analyses, the time window from 1400 to 1900 ms was used to measure the cue-evoked mean pupillary responses because this duration (500 ms) was shared by both SOA800 and SOA1300 conditions. These measurements are referred to as CEP 2.

In contrast, the time duration used to measure target-related TEP sizes was the same in both SOAs (i.e., 1200 ms). Target-evoked pupil responses were also used to estimate alerting (no-cue – neutral) and orienting (invalid - valid) effects in each SOA condition. We averaged the Z scores of these indices (e.g., an average of Z scores of target-evoked orienting indices in SOA800 and SOA1300) to estimate the total orienting and alerting scores.

Finally, we used a Monte Carlo autocorrelation method (Guthrie & Buchwald, 1991; Rigato, Rieger, & Romei, 2016; Siegle, Ichikawa, & Steinhauer, 2008) to explore the temporal profile of the orienting and alerting effects during their evolution, without specifying a priori time window. The temporal profile refers to the onset of the effects and the time course over which the target-evoked pupillary changes differed between the compared conditions significantly. This analysis along with its results are presented and discussed in Supplementary material, part 7.

2.5.4. Gaze deviation data

The amount of gaze deviation from the central fixation was measured to check if participants oriented their attention covertly during the cue-target period. To measure gaze deviations in each trial, the mean eye movements that did not exceed the 4 degrees of visual angle from the fixation point was coded as 0 whereas deviations > 4 degrees (in the direction of cued positions) were coded as 1. Then, the average and median gaze deviation was calculated for each trial type and SOA condition. The four degrees of visual angle was chosen based on the amount of visual acuity around the foveal fixation in humans, which drops to one third in 4 degrees away from the fovea (Strasburger, Rentschler, & Jüttner, 2011; Österberg, 1935). As presented in Supplementary Material section 10, descriptive statistics showed larger deviations in non-directional trials than in directional trials, which indicates that participants were actually complying with instructions. More importantly, there was not a significant difference in gaze deviations from the fixation point between valid and invalid or between neutral and no-cue trials (Supplementary Material section 10), which is important for pupillary results with alerting and orienting scores.

2.5.5. Statistical analysis

All pre-processing of pupillary data was done using R (R Core Team, 2018). Analysis scripts are available from https://github.com/thohag/pupilParse. The standard SPSS version 25 (IBM SPSS Statistics for Windows and Macintosh, Version 25.0. Armonk, NY: IBM Corp) was used to analyze the data. When the sphericity assumption was violated, Greenhouse–Geisser correction was used and reported. We also investigate and report the results with and without age as a covariate for several reasons. First, the age range in our sample (18–52) was three times larger than that in the other pupillometry studies (Gabay et al., 2011; Geva et al., 2013; Dragone, Lasaponara, Pinto, Rotondaro, De Luca, & Doricchi, 2018). Moreover, previous findings have revealed a negative relationship between age and cognitive functions (Glisky, 2007), between age and pupil size (indicating that older individuals show smaller pupil sizes at any luminance level; Guillon et al., 2016), along with a positive relationship between age and behavioral latencies in Posner task (Greenwood et al., 1993; Langley, Friesen, Saville, & Ciaramelli, 2011). Also, correlation analysis in the current study confirmed a positive relationship between our participants’ ages and their RTs with older participants performed the task more slowly (Supplementary...
material, Table 1). We found also a negative relationship between age and TEP sizes, indicating that older participants had smaller TEP sizes (Supplementary material, Table 2). Since the aim of the present study was to examine the modulatory effect of individual differences in cognitive abilities and aging on behavioral and psychophysiological markers of the Posner cueing effect, the analyses were rerun while the effect of age was statistically partialled out. One-tailed p values were used in the analyses that we had prior predictions about the direction of relationships (e.g., age effects) while two-tailed p values were used when we did not have any prediction and the findings in the literature were inconsistent (e.g., the relation between alerting and orienting estimates). We also used JASP (v.0.9) software (https://jasp-stats.org/) to obtain a precise likelihood estimate of the ‘conclusiveness’ of findings with the Bayesian analyses.

3. Results

The descriptive statistics of all dependent variables in each experimental factor are presented in Table 1.

3.1. Behavioral results

Bivariate correlation analyses did not show a significant relationship between response time and accuracy in any of the trial types in each SOA condition, all p values > 0.05. As expected, correlational analysis revealed a positive correlation between WMC and g factor scores, r = 0.37, p = .002. However, there was no significant relationship between total RT (overall performance) and WMC (r = 0.04, p = .74), or between total RT and g factor (r = -0.20, p = .10). WMC and g factor scores did not significantly correlate with age (p > .25).

3.1.1. Accuracy

A repeated-measures ANOVA with Accuracy as dependent variable, and Trial Type (valid, neutral, no-cue, invalid) and SOA (800 and 1300 ms) as within-subject factors revealed a main effect of Trial Type, Greenhouse-Geisser F(2.43, 175.08) = 3.06, p = .04, ηp2 = 0.04 (Fig. 2). Accuracy was high in all trials (over 90%). However, pairwise comparisons showed that the mean accuracy in the valid trials was significantly better than in all other trial types (all p values < 0.01). Accuracy in neutral trials was also higher (mean difference = 0.013) than accuracy in no-cue trials, p = .05. The main effect of SOA (p = .17) and the interaction between SOA and Trial Type (p = .99) were not significant.

An ANCOVA with Age as covariate showed an interaction between Age and Trial Type, Greenhouse-Geisser F(2.43, 175.08) = 3.07, p = .04, ηp2 = 0.04. A correlation analysis showed a negative relationship between age and accuracy only in neutral trials in SOA1300 (r = -0.23), indicating that older people benefited less from temporally warning signals.

3.1.2. Response time

We repeated the same ANOVA with median RT as the dependent variable. Results revealed a significant main effect of SOA, F(1, 73) = 58.00, p < .001, ηp2 = 0.44, main effect of Trial Type, F(3, 219) = 5598, p < .001, ηp2 = 0.43, and a significant interaction between SOA and Trial Type, Greenhouse-Geisser F(2.49, 181.44) = 4.70, p = .006, ηp2 = 0.06 (Fig. 2). Planned comparisons with paired-samples t-tests showed that, except in no-cue trials, RTs in all other trial types were faster when SOA was longer; i.e., 1300 ms (all p < .01, Table 1). Another paired samples t-tests were run for Trial Type factor. Results showed that when SOA was longer (1300 ms), RTs in both valid and neutral trials were faster than RT in no-cue and invalid trial types (all p values < 0.001), but RT in invalid trials did not differ significantly from RTs in no-cue trials (p = .26). In SOA800 condition, however, the median RT was faster in the valid trials than all other trial types (all p < .001, see Table 1). RTs were also faster in neutral than in invalid trials but there was not a significant difference between RTs in no-cue trials and RTs in invalid and neutral trials. These results indicate that

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**Table 1**

Descriptive statistics for dependent variables in each trial type and SOA.

|          | SOA800 |          | SOA1300 |          |
|----------|--------|----------|----------|----------|
|          | Valid  | No-Cue   | Neutral  | Invalid  |
| Accuracy | 0.96 (0.04) | 0.93 (0.07) | 0.94 (0.06) | 0.95 (0.06) | 0.96 (0.04) | 0.93 (0.06) | 0.95 (0.06) | 0.93 (0.06) |
| RT       | 519.52 (88.03) | 554.74 (93.84) | 545.36 (98.02) | 566.80 (113.80) | 489.47 (87.42) | 549.18 (108.11) | 517.42 (94.45) | 548.95 (100.25) |
| CEP 1    | -0.04 (0.05) | -0.05 (0.05) | -0.04 (0.05) | -0.04 (0.04) | -0.02 (0.04) | -0.03 (0.06) | -0.02 (0.05) | -0.02 (0.05) |
| CEP 2    | -0.04 (0.05) | -0.05 (0.05) | -0.04 (0.05) | -0.04 (0.04) | -0.03 (0.04) | -0.04 (0.06) | -0.04 (0.05) | -0.04 (0.05) |
| TaEP     | 0.09 (0.06) | 0.08 (0.06) | 0.10 (0.06) | 0.10 (0.07) | 0.14 (0.08) | 0.11 (0.07) | 0.14 (0.09) | 0.14 (0.09) |

Note. Mean and standard deviation (in parentheses) of all dependent variables; i.e., accuracy (%), RT = response time (ms), CEP 1 = cue-evoked pupil size estimated using the shared equal period from 1400 to 1900 ms by both Stimulus Onset Asynchrony (SOA) conditions, and TaEP = target-evoked pupil sizes.

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**Fig. 2**. Behavioral results. Effect of Trial Type and Stimulus Onset Asynchrony (SOA) conditions on accuracy (left panel) and response time (right panel). Error bars represent SE.
the simple main effects of Trial Type and SOA conditions were not significant. When the effect of age was controlled in an ANCOVA, results revealed that only the main effect of SOA was significant, F(1, 72) = 12.23, p = .001, η² = 0.15, indicating that RTs were faster when SOA was longer; i.e., 1300 ms.

3.1.3. Relationship between behavioral indices of alerting vs. Orienting effects

Finally, a bivariate correlation analysis showed that total estimates of alertness (RT in no-cue – RT in neutral) and orienting (invalid - valid) effects were uncorrelated, r = 0.04, p = .76, which is consistent with the dual mechanism hypothesis. Similar analyses were run to investigate the relationship between alertness and orienting scores in each SOA condition separately, but these indices were still uncorrelated (Supplementary material, Table 3).

3.2. Pupillary results

3.2.1. Task-evoked pupil sizes after cue presentation

A repeated measures ANOVA with mean CEP 1 sizes as dependent variable, and Trial Type (4 levels) and SOA (2 levels) as within-subject factors, revealed a significant main effect of SOA, F(1, 71) = 41.42, p < .001, η² = 0.37, and main effect of Trial Type, Greenhouse-Geisser F(2.45, 173.62) = 3.67, p = .02, η² = 0.05. Pairwise comparisons indicated that cue-evoked pupil sizes were larger in longer (1300 ms) than shorter (800 ms) SOA (mean difference = 0.02 mm), p < .001. Moreover, TEP sizes in no-cue trials were smaller than all other trial types, all p values < 0.05 (Fig. 3, left panel & Fig. 4). The interaction between factors was not significant, p = .19. An ANCOVA with Age as covariate revealed only a main effect of SOA, F(1, 70) = 6.33, p = .014, η² = 0.08.

The data were also examined by Bayesian repeated-measures ANOVA to obtain a precise likelihood estimate of the ‘conclusiveness’ of findings. The prior was based on the default JASP Cauchy distribution for the likelihood of the data under H1 (Dienes, 2014). The BF10.0 for the effect of SOA was 6.071e + 12, which provides ‘very strong evidence’ for the likelihood of the data under H1. (Dormann et al., 2012) The BF10.0 for the Trial Type model alone was 0.34, which is inconclusive evidence (0.33 > BF > 1) and more on the side of ‘anecdotal evidence’ for the null hypothesis. Post hoc comparisons, however, showed strong evidence for the difference between valid and no-cue conditions, and anecdotal evidence in the comparison between no-cue and the other two cue types (Supplementary material, Table 4).

A similar repeated measures ANOVA was repeated with mean cue-evoked pupil sizes estimated using the same period in both SOAs (CEP 2) as the dependent variable. The main effect of SOA was not significant longer, F(1, 71) = 3.40, p = .07, η² = 0.05, but the main effect of Trial Type was significant, Greenhouse-Geisser F(2.49, 177.16) = 3.58, p = .02, η² = 0.05. However, controlling for the effect of age in an ANCOVA revealed neither the main effect of SOA (p = .45) nor the main effect of Trial Type (p = .88).

3.2.2. Task-evoked pupil sizes after target presentation

A similar repeated measures ANOVA was run to investigate the effect of within-subject factors on target-evoked pupil sizes. Results revealed a significant main effect of SOA, F(1, 71) = 109.03, p < .001, η² = 0.61, and main effect of Trial Type, Greenhouse-Geisser F(2.58, 182.92) = 8.75, p < .001, η² = 0.11. Pairwise comparisons indicated that target-evoked pupil sizes were larger (mean difference = 0.04 mm) when SOA was longer (1300 ms; p < .001). Moreover, TEP sizes in only no-cue trials were smaller than all other trial types, all p values < 0.006 (Fig. 3, right panel & Fig. 4). An ANCOVA with Age as covariate revealed only a main effect of SOA, F(1, 70) = 20.11, p < .001, η² = 0.22. The data were also examined by Bayesian repeated-measures ANOVA. The obtained Bayes factors for both the effect of SOA (BF10.0 = 1.99e + 27) and Trial Type (BF10.0 = 58.89) indicated very strong evidence for the likelihood of the data under H1. Post hoc comparisons showed very strong evidence for the effect of no-cue trials on target-evoked pupil sizes in comparison to other trial types (Supplementary material, Table 5).

3.2.3. Relationship between pupillary indices of alerting and orienting effects

Similar to behavioral results, bivariate Pearson correlation analysis did not show a significant relationship between estimates of alertness and orienting effects, neither when total scores were used, nor with indices estimated in each SOA condition, all p values > 0.05, all BF10 factors < 0.5. However, we found a negative correlation (r = -0.24, p = .05, BF10 = 1.03) between total alertness and orienting scores in SOA1300. We also explored the relationship between behavioral and pupillary indices of alerting and orienting and found a negative correlation between total scores of behavioral and pupillary alertness (r = -0.30, p = .01, BF10 = 3.92) (all correlations are presented in Supplementary material, Table 6).

3.3. Individual difference analyses

3.3.1. Individual difference analysis with behavioral indices of alertness and orienting

Total RT (as an index for overall task performance) did not correlate significantly with total alertness scores, or with alertness scores in SOA800, but it did with alertness scores in SOA1300 significantly (r = 0.28). Total RT also correlated positively with total orienting scores (r = 0.37), and with orienting scores in SOA800 (r = 0.38), but not in SOA1300.1 Except for a positive relation between WMC and orienting scores in SOA1300 (r = 0.26), the results did not indicate any significant relationship between indices of general cognitive abilities (i.e., g factor and WMC) and estimates of alertness and orienting effects. Neither had the age significant effects on alertness and orienting scores (see Supplementary material, Table 3).

3.3.2. Individual difference analysis with pupillary indices of alerting and orienting

Results showed only a negative correlation between total RT and total orienting estimates (r = -0.27, p = .02, BF10 = 1.78). None of the indices of general cognitive abilities (i.e., g factor and WMC) correlated significantly with estimates of alertness and orienting effects (all p values > 0.05, all BF10 factors < 0.4); nor had age a significant effect on alertness and orienting scores (Supplementary material, Table 6).

Finally, after checking for normality distribution of dependent variables, we ran multiple linear regression analysis to investigate if indices of general cognitive abilities (i.e., g factor and WMC), along with overall task performance (i.e., overall RT) could predict total estimates of alertness and orienting effects or estimates in each SOA condition. All regression models were non-significant (all p values > 0.3). We were not concerned about the effect of multicollinearity problem on results because the correlation between WMC and g factor (r = 0.37, p = .002) was below 0.7 (O’Brien et al., 2012) and the variance inflation factor (VIF) estimates were also below 3 (O’Brien, 2007).

4. Discussion

The purpose of the current study was to test two competing

1 To double-check these behavioral results, we merged the present data with another dataset (N = 40) from our lab that was collected using the same Posner paradigm (total N = 114). We replicated the present results. The total RT was, in fact, positively associated with all behavioral indices of alertness and orienting estimates, except for the alerting scores in SOA800.
accounts that have been proposed regarding the role of LC phasic activity in alerting and orienting attention. According to the dual mechanism account (Fernandez-Duque & Posner, 1997), the “alerting” network is modulated by the LC-NE system, whereas the “orienting” system is modulated by cholinergic signals (Petersen & Posner, 2012). However, the singular account, proposed by Corbetta and Shulman (2008), suggests that the LC phasic activity may be involved in the reorienting of attention as well through its functional relationship with the ventral attentional network. To examine these accounts, we used a self-developed version of the Posner cuing task, pupillometry as an index of LC activity and an individual difference approach. Based on a common assumption that the fluctuations of pupil diameter and the LCs level and pattern of activation are strongly correlated (Aston-Jones & Cohen, 2005; Granholm & Steinhauer, 2004; Joshi et al., 2016; Murphy et al., 2014; Varazzani et al., 2015; Yellin et al., 2015), we expected that pupillary changes would throw light on the roles of the above processes.

All in all, our results provided better support for the dual mechanism account than the singular account. Both behavioral and pupillary responses revealed the alerting effect; i.e., more accurate and faster responses to trials with neutral cues compared to no-cue trials, along with larger TEP responses in all cued trials than non-cued trials. Behavioral responses also revealed orienting effect; i.e., faster responses to validly, compared to invalidly, cued targets, as has also been seen in previous studies with this paradigm. However, we found no TEP differences between valid, invalid, and neutral conditions, suggesting that TEP effects were driven by the alerting effect of cue presentation. Both the behavioral and pupillary indices of alertness and orienting effects were uncorrelated, both when the total scores were used and when scores from each SOA condition were applied. If a noradrenergic mechanism was also involved in (re)orienting of attention, there should have been a positive correlation between pupillary indices of alerting and orienting effects.

Nevertheless, we found a negative correlation ($\rho = -0.24$) between total alertness and orienting scores in SOA1300. That is, a higher level
of overall alertness and signal sensitivity was accompanied by smaller differences in pupil size between invalid and valid trials (i.e., smaller orienting effect) only when the SOA was longer (i.e., when the task was more demanding as indexed by larger TEP sizes). This finding may indicate a ‘situational’ interaction between these underlying mechanisms, as also proposed by Fan et al. (2002), who, using an ANT paradigm, found a reduced flanker interference effect on RTs only when an alerting cue with no spatial information was presented, relative to no cue and spatial-cue conditions. We also found a negative relation between the total behavioral alertness scores and both total pupillary alertness scores ($r = -0.30$), and pupillary alertness scores from SOA1300 ($r = -0.28$), indicating that the smaller alerting effect on pupil responses was associated with larger alerting effect (cost) on behavioral responses (RT).

### 4.1. Behavioral responses revealed both alerting and orienting effects

In accordance with the literature (Chen, Weidner, Vossel, Weiss, & Fink, 2012; Gabay et al., 2011; Geva et al., 2013; Fernandez-Duque & Posner, 1997; McDonald, Bennett, Chambers, & Castiello, 1999), our behavioral results provided evidence for cueing effects on both alerting and orienting. That is, accuracy in neutral trials was slightly better than accuracy in no-cue trials, which points to an alertness effect. Accuracy was also higher in the valid trials than all other trial types, which reveals a behavioral advantage of both alertness and orienting of attention because valid cues both trigger an alert modus and are spatially and temporally valid signals.

Similarly, RTs were faster in both valid (i.e., orienting effect) and neutral trials (i.e., alertness effect) than RT in invalid and no-cue trial types in SOA1300ms. Since there was no negative correlation between accuracy and RT in any of the trial types and SOA conditions, slower RTs in the invalid and no-cue trials cannot be explained by a speed-accuracy trade-off relationship, and they rather indicate the effect of alerting and orienting. However, in the SOA800 condition, we found only the orienting effect on RTs.

In fact, similar to findings from some other studies (e.g., Fernandez-Duque & Posner, 1997; Shin, Marrett, & Lambert, 2011), RTs in all cued trials were faster in longer SOA (1300 ms) than in shorter SOA (800 ms), suggesting that the performance benefited more from triggering an alert modus when the time interval between cue and target increased. Hayward and Ristic (2013) also found that when the probability of target presentation across trials was high (94%), mean RT in longer SOA (i.e., 931 ms) was faster than in shorter SOA (i.e., 106 ms). However, they also found faster RT in un-cued trials. In fact, finding better performance in longer SOA was opposite to our expectation, because we reasoned that longer covert attention to a cued place delays the reorienting and disengagement of attention, especially in older subjects (Greenwood et al., 1993; Langley et al., 2011; Olk & Kingstone, 2015). However, when we controlled for the effect of age, only the main effect of SOA was significant, which again indicated a better performance in longer SOA. As also explained in the next section, the better performance in all cued trials in SOA1300 was accompanied with larger TEP sizes in SOA1300, which may refer to a higher level of alertness and task engagement or higher mental effort in long SOA condition to keep the signal related information in mind (Aston-Jones & Cohen, 2005; Kahneman, 1973).

Lack of significant main effect of Trial Type on behavioral responses after controlling for the effect of age indicates that the cue effects on behavioral performance were considerably age-dependent. In fact, age correlated negatively with accuracy in neutral trials, indicating that older people may benefit less from temporally warning signals, and it correlated positively with RT in all trial types, indicating that elder participants performed the task slower, consistent with Langley et al. (2011). Greenwood et al. (1993) found that although elder subjects were always slower than younger participants, the relation between normal aging and RTs was not straightforward and RT costs and benefits appeared only in discrimination task (but not in detection task) when SOA was longer than 200 ms and cue was presented centrally (i.e., when the attentional shift is proposed to be voluntary and effortful; Jonides, 1981; Posner, 1980).

### 4.2. Pupillary responses revealed only an alerting effect

Consistent with the dual mechanism hypothesis (Fernandez-Duque & Posner, 1997; Petersen & Posner, 2012), both cue- and target-evoked pupillary responses were larger in cued trials than in no-cue trials, without any significant difference in mean TEP sizes between cued trial types (i.e., orienting effect on pupillary responses was not present). To our knowledge, this is the first evidence from pupillometry studies that provides supports for an exclusive alerting effect on pupillary responses triggered by presenting a warning signal that is spatially or temporally informative, perhaps modulated by a phasic increase in the LC-NE firings (Aston-Jones, Rajkowski, Kubiak, & Alexinsky, 1994; Aston-Jones & Cohen, 2005; Joshi et al., 2016; Geva et al., 2013; Murphy et al., 2014; Petersen & Posner, 2012; Rajkowski et al., 1994). We surmise that increased LC activity might trigger a change in alertness and the top-down dorsal network, and induces selective visuospatial attention (after spatial cues), or an explorative modus (after neutral cues), which operates globally to facilitates speeded target detection and prepare the individual for responding to the coming target fast and accurately (Aston-Jones & Cohen, 2005; Corbetta et al., 2008; Petersen & Posner, 2012; Thiele & Bellegrove, 2018). Noteworthy that increases in both cue- and target-evoked pupillary responses began to develop within around 300–400 ms after the cue and target presentation, which is in accordance with previous findings showing an association between LC spiking activity and pupil dilation (Joshi et al., 2016; Reimer et al., 2016).

As shown in Fig. 2, target-evoked TEP responses were larger in cued trials, but target presentation was indeed associated with pupil dilation in all trials and sustained after executing the behavioral performance (peak dilation occurred around 1100 ms after target presentation, i.e., around 550 ms after response execution, consistent with findings in Geva et al., 2013). Several hypotheses are proposed to explain the role of LC phasic activity in response to targets and the regulation of behavioral states (Aston-Jones & Cohen, 2005; Bouret & Sara, 2005; Corbetta et al., 2008; Hofmeister & Sterpenich, 2015; Yu & Dayan, 2005). Some of them are plausible to explain the current dataset. For example, according to adaptive gain theory (Aston-Jones & Cohen, 2005; Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010), the phasic activity of LC is involved in behavioral exploitation, task engagement, and optimizing behavioral performance by modulating the neural gain of involved brain areas. Consistently, larger pupil responses in all cued trials, relative to no-cue trials, can indicate exploiting the cue-related spatial and/or temporal information. Bouret and Sara (2005) proposed also that the phasic LC firings induce a “network reset” to reconfigure the cortical networks involved in processing the events that are just detected. Finally, Corbetta et al. (2008) suggested that the LC phasic activity is also involved in the re-orientation of attention by modulating the functional activity of ventral attentional networks after the detection of invalidly cued targets. However, the current measures do not provide supporting evidence for such a role, since the pupil responses in invalid trials did not differ from TEP sizes in the valid trials. Taken together with faster RT in cued trials, these results support the dual mechanism account better than a singular, by indicating a facilitatory effect of a noradrenergic mechanism activated by any alerting signal.

We found only two other pupillometry studies with the Posner’s cueing paradigm to compare for the consistency between the results. Gabay et al. (2011) used an exogenous cueing paradigm with only valid and invalid cues that were non-predictive, and they did not investigate (report) orienting effect with the pupillary responses. Dragone et al. (2018) used two versions of an endogenous Posner paradigm with predictive and non-predictive cues. The pupillary orientation (validity)
effect, defined as the difference between invalid and valid trials was found only in the non-predictive condition, but not in the predictive condition, which was like in our experiment. Therefore, similarly to our results, Dragone and colleagues did not find a difference in target-evoked pupil responses between invalid and valid trials.

The presence of a validity effect in the non-predictive condition may indicate that the effect of reorienting on the pupil responses can be state-specific, and appear only if the spatial signals are not highly expected to be valid. Without catch trials (N = 96), in which no target was presented after cues, in the non-predictive condition, 33% of all trials (50% of spatially cued trials) were valid. In contrast, in the predictive condition, 53% of all trials (80% of spatially cued trials) were valid, which is similar to our experiment, in which the cues were always valid in 60% of total trials (i.e., around 82% of spatially cued trials). Therefore, the uncertainty around the informative value of spatial cues was high in the non-predictive condition due to the validity ratio of spatial cues and the usage of directional catch trials. This interpretation seems related to the "expected uncertainty" theory (Yu & Dayan, 2005), which proposes that the norepinephrine (NE) signals report on unexpected uncertainties whereas the acetylcholine (ACH) signals report on expected uncertainties that are inherent in the task (for example, when cues are invalid with a stable ratio of 20% of spatially cued trials). Although an invalid cue is not an "unexpected" event in the non-predictive condition, the uncertainty around the informative value of spatial cues is high. In fact, in the majority of trials, the cue is either invalid or not followed by a target. Further studies are needed to investigate the underlying mechanism of pupillary responses in covert orienting in non-predictive conditions.

In the predictive condition, on the other hand, Dragone and colleagues found larger cue- and target-evoked pupil dilations in the directionally (spatially cued) vs. non-directional (neutral) trials. We did not find a difference in TEP sizes between valid or invalid trials and neutral trials. But this directional effect is different from the (validity) reorienting cost, and its effect on pupillary responses, which is the question of interest in the current study. However, to investigate whether we find this directional effect on cue- and target evoked responses, we combined mean TEP sizes in the valid and invalid trials to obtain mean directional TEP sizes and compared it with TEP sizes in neutral trials. For cue-evoked pupil responses, we found a main effect of SOA, \( F(1, 71) = 27.57, p = .001, \eta_p^2 = 0.28 \), and an interaction between SOA and Cue type (directional vs. non-directional), \( F(1, 71) = 4.01, p = .05, \eta_p^2 = 0.05 \). Post-hoc analyses indicated that TEP sizes in both directional and neutral trials in SOA1300 were larger than directional and neutral TEP sizes in SOA800 (all \( p \) values < 0.01). For target-evoked pupil responses, only the main effect of SOA was significant, \( F(1, 71) = 99.23, p = .001, \eta_p^2 = 0.58 \).

This discrepancy may be due to several differences in the experimental design between the present and Dragone et al. study that together might have induced higher arousal (alertness) level in directional compared to non-directional trials. That is, rather than being related to an orienting effect, the larger pupil sizes in directional trials may be related to a larger alertness effect due to several factors. For example, instead of SOA duration, the duration of the cue presentation was manipulated in Dragone et al. study. Longer cue presentations (from 900 to 1200 ms), compared to that in our study (100 ms), may have induced a higher arousal level in directional trials that, compared to non-directional trials, are both spatially and temporally informative. This may happen for several reasons. First, because there were also catch trials, in which the neutral signals were not followed by a target, which reduces the temporally informative value of and consequently the alerting effect induced by neutral cues. Second, because there were four cue duration conditions in their study, compared to two SOA conditions in our study. In other words, after neutral cues, the target might appear after 900, 1000, 1100, or 1200 ms or does not appear at all. This might again have had an influence on the alerting value of neutral signals. Third, because the number of trials (576 experimental + 72 training trials) was also as twice large as ours (300) which could induce a strong learning effect about the relative informative value of directional vs. non-directional cues. Finally, in the present study, there were also no-cue trials, and compared to these trials, the neutral and spatial cues were always temporally informative that a target will appear either in 800 or 1300 ms, inducing similar alertness level in directional and non-directional trials.

Altogether, the present results do not reveal any orienting or reorienting effect on the pupillary responses. Since the behavioral results in the present study are comparable with results from previous studies (Dragone et al., 2018; Gabay et al., 2011; Geva et al., 2013), it is doubtful that lack of (re)orienting effect on pupillary responses can be explained by low task difficulty level. However, more studies are needed to investigate whether or, in fact, when (in which states or in which individuals) pupillary responses (as an index of phasic LC activity) get involved in covert (re)orienting of attention in predictive conditions. It should also be examined whether the (re)orienting effect can be observed in the latency rather than in the magnitude of pupil responses. Using attention network task, Geva et al. (2013) investigated the effect of three alerting, orienting and executive networks on amplitude and latency of two distinct pupillary responses after target presentation; i.e., “an early peak (Pa) preceding the response, and a later higher peak (Pe) that occurs about 600 ms after the response.” Similarly to our results, they found an alerting effect on pupil dilations; i.e., Pa was larger (also initiated 300 ms faster) in double cue relative to no-cue trials. In the orienting network, the magnitude of Pa did not differ between spatially and centrally cued trials, which is consistent with the present results, also indicating no (re)orienting effect on the magnitude of pupil dilations. In fact, their definition of orienting effect (spatial vs. central trials) differed from the definition of (re)orienting effect in the present study (invalid vs. valid trials). But our directional analyses (spatial vs. neutral trials), which was similar to their orienting analysis, also showed consistent results. However, they found a significant difference in the latency of peak dilations; i.e., Pa peak appeared 200 ms earlier in spatially vs. centrally cued trials. We did not make any predictions about the latency of pupillary responses but a visual inspection of Fig. 4 does not indicate the presence of such an orienting effect on the latency of target-evoked responses in spatially cued trials. It is, however, important to consider several differences that exist between Geva et al. and the present study. For example, the ANT task is an exogenous cueing paradigm. In fact, the earlier Pa peak in spatial vs. central trials appeared after the gaze entrance to the target area of interest (AOI). Geva and colleagues proposed that this acceleration of the Pa component in spatial trials facilitates the covert orienting; i.e. modulating the orienting through an accelerated arousal mechanism. Another difference is that, in addition to alerting and orienting effects, the ANT involves the processing of the congruency effect. Thus, the orienting effects on the decreased peak latency in spatial vs. central cueing trials may also be contaminant with the processing of target-evoked congruency effects. It is, however, noteworthy that they found a separate congruency effect on the amplitude of Pe component that is consistent to our results from Mont-Carlo analyses (Supplementary materials, section 8) showing the difference in TEP sizes between invalid and valid trials 1000 ms after target onset (500-600 ms after response), which is probably related to conflict resolution processes.

Cue- and target-evoked pupillary responses were also larger in longer (1300 ms) than shorter (800 ms) SOA condition, which was again in line with Dragone et al. (2018) and with our expectations. Larger TEP sizes in longer SOA were also accompanied with better behavioral responses in all Trial Types except in no-cue trials. Similar to behavioral analyses, after controlling for the effect of age, only the main effect of SOA remained significant. The effect size of Trial Type conditions \( \eta_p^2 = 0.11 \) was not as large as the effect size of SOA manipulation \( \eta_p^2 = 0.61 \) on target-evoked responses. Moreover, since the effect size of Trial Type manipulations on the behavioral responses (RT;
4.3. In contrast to general cognitive abilities, individual differences in overall task performance were associated with alerting and orienting indices

Finally, results from the individual difference analysis showed that neither alertness indices nor the orienting estimates were related to individual differences in indices of general cognitive abilities in our study (i.e., g factor and WMC). This is similar to findings from Ishigami et al. (2016) study with ANT-I task, in which orienting and alerting scores did not predict scores on neuropsychological measures. These neuropsychological measures were similar to those used in the present study to measure the g factor. The only exception was a positive relation between WMC and (behavioral) orienting scores in SOA1300. The association between WMC and orienting scores may indicate that the interval between cue and target onsets was longer, individuals with a higher level of WMC were more influenced by the perceptual representations of spatial cues in WM and they might have needed more time to disengage and reorient their focus of attention. This is consistent with previous reports regarding the relation between WMC and both attention control (Unsworth and Robinson) and attentional orienting (Kahneman, 1973), as indexed by pupil size, to reorient their attention and keep their optimal level of performance. This view is supported by our behavioral findings showing that the overall RT correlated positively with behavioral indices of orienting effect. That is, although high performers had larger pupil sizes compared to low performers in invalid relative to valid trials, they were behaviorally less influenced by orienting and their RT did not increase in invalid trials (relative to valid trials) as much as the RTs of low performers. This is similar to results from individual difference analysis in a study with the Stroop task (Laeng et al., 2011), in which individuals with smaller Stroop interference in RTs showed a larger pupillary Stroop effect. However, the mean pupil size of high performers was larger than low performers also in no-cue trials in SOA1300. This may suggest a higher level of arousal (in the absence of any alerting cue), rather than a higher general level of engagement in high performers. In fact, Sara and Bouret (2012) proposed a modulating role of LC in (re)orienting through arousal. Finally, as Corbetta et al. (2008) suggested, the noradrenergic mechanism may also be involved in the reorientation of attention, but the present results suggest that it may happen only in high task performers (as reflected in their larger pupil responses in invalid relative to valid trials). Further studies are needed to investigate these trait/situation-dependent involvements of LC in (re)orienting.

Our ability to benefit from visuospatial signals to attend selectively to the incoming goal-related information along with the ability to shift the focus of attention in response to events that occur in the less expected space, e.g., when signals misinform us, is critical. It is critical to optimally detect targets of interest (e.g., danger), to provide adaptive and/or professional behavioral responses in complex environments (Mann, Williams, Ward, & Janelle, 2007) and to avoid fatal accidents (Stott, 2013). The deficit in visuospatial attention affects the functional state of stroke patients (Kaplan & Hier, 1983), and impaired functioning in visuospatial attention has been reported in children with developmental coordination disorder (Tsai, Pan, Cheng, Hsu, & Chiu, 2009), in children with attention deficit hyperactivity disorder (McDonald et al., 1999), in patients with visual neglect (Bartolomeo, Thiebaut de Schotten, & Chica, 2012), parietal brain injury (Posner, Walker, Friedrich, & Rafal, 1984), mild traumatic brain injury (Halterman et al., 2006), dementia (Parasuwan, Greenwood, Haxby, & Grady, 1992), schizophrenia (Fernandez-Duque & Posner, 2001), autism (Wallnau, Sharp & Bryson, 1993), anorexia nervosa (Dalmasso et al., 2015) and in older people (Langley et al., 2011). The neural and neuromodulatory basis of visuospatial attentional networks has been largely studied to find effective interventions and medications to improve or recover this ability (Borodovitsyna et al., 2017; Corbetta, Kincade, Lewis, Snyder, & Sapi, 2005; Reynaud et al., 2019; Simons et al., 2016; Riestra & Barrett, 2013). However, further investigations are required to explore...
the influence of situational factors and the effect of individual differences in cognitive abilities on the involvement of underlying mechanisms or their interactions.

5. Limitations

Several limitations should be considered when interpreting these results. First of all, like any other physiological markers, pupil responses should be interpreted cautiously. For example, it is important to note that pupil responses can be modulated by other brain areas and neuromodulators than LC-NE (Joshi et al., 2016; Reimer et al., 2016; Wang & Munoz, 2015) and they should be considered mainly as “reporter variables” that are associated with specific mental processes and states (Beatty & Lucero-Wagoner, 2000) without playing a processing role for the measured cognitive task (but see: Laeng et al., 2018).

It is also important to mention that the sample size is an important factor in individual difference investigations. Both behavioral and pupillary indices of alerting and orienting effects were only related to individuals’ level of Posner performance. But the non-significant relations with the measurements of general cognitive abilities may be accounted for by our limited sample size. However, the range, skewness, and kurtosis values of measurements in the present study were within the acceptable range for the normal distribution (i.e., −2 to +2; George & Mallery, 2010) and showed adequate variance in the dataset. Results from Bayesian analyses also showed anecdotal to substantial relations with the measurements of general cognitive abilities may be accounted for by our limited sample size. However, the range, skewness, and kurtosis values of measurements in the present study were within the acceptable range for the normal distribution (i.e., −2 to +2; George & Mallery, 2010) and showed adequate variance in the dataset. Results from Bayesian analyses also showed anecdotal to substantial evidence (BF₁₀ factors < 0.4) in favor of the null hypothesis. Still, these results should be taken with caution until they are replicated with other larger samples. This is especially important for correlational studies with well-established paradigms like the Posner cueing task that originally were developed for experimental research and their primary goal was to minimize the between-individuals differences in favor of increasing the within-subject effects. In particular, the difference scores, like alerting and orienting estimates, tend to be associated with poor reliability especially when the resulting effects are small (Hedge, Powell, & Summer, 2018). As presented in the Supplementary Material, Section 4, the reliability of our RT measurements are comparable and, in some cases, a little better than reliability results with Posner endogenous cueing paradigm in Hedge et al. (2018). However, the reliability estimates of alerting measurements were very low, although it was consistent with other studies (Ishigami et al., 2016). It could be argued that the low reliability of the alerting network is expected because it is related to “phasic alertness that involves a rapid change in mental state and physiological state following a presentation of a warning cue” (Posner, 1978) and that may change across trials” (Ishigami et al., 2016). However, since the reliability of pupillary alerting and orienting estimates were negative, we examined the relationships between Posner performance and general cognitive measurements with RT and TEP sizes in each trial type and SOA condition to avoid using difference scores. As shown in the Supplementary Table 7, in contrast to the general cognitive scores, the overall Posner performance was related to target-evoked pupil responses, especially in SOA1300. Thus, it is doubtful that the present individual differences results result from low reliability of measurements. But they require to be examined and replicated in future studies.

Moreover, we used only the LNS task to measure individuals’ WMC. To obtain a better estimate of WMC, a composite score can be estimated using different WM tasks in the future.

Another factor that should be taken into consideration is the length of our SOA conditions. We found consistently the effect of SOA manipulation on behavioral and pupillary results, on the relation between WM and orienting scores and on negative correlations between orienting and alertness effects. The main effect of SOA was, in fact, the only effect that survived controlling for the age effects. However, our SOA conditions, compared to other studies in the literature (Chica et al., 2014), were rather long, which may affect the orienting response. In fact, Fuentes and Campoy (2008), using the ANT paradigm, found that orienting was modulated by an alerting tone only in the shorter SOAs (i.e., SOA 100, 300, and 500 ms), but not at long 800 and 1200 ms SOAs. Since the ANT paradigm is not identical to the classic Posner paradigm, future studies should explore the effect of shorter SOAs on pupillary responses in the Posner cueing paradigm.

Finally, controlling for the eye movements can be important when SOA is longer than 200 ms because it gives enough time to move the eyes towards the cued location, and changes the state of covert attention to an overt orienting, which can influence the cueing effects (Wright & Ward, 2008). Our gaze deviation analyses showed that participants did follow the instruction. However, it is possible to control for eye movements in the future pupillometry studies by using an allocated area of interest (AOI) around the location of the cue (Karch, 2018). Then, feedbacks can be given if the participant looks away from this AOI. This procedure will limit the number of removed data due to large gaze deviations from the fixation point.

6. Conclusion

Using a Posner cueing paradigm, the present study provides the first evidence from pupillometry in favor of the dual mechanism hypothesis (Fernandez-Duque & Posner, 1997), which proposes that two separate noradrenergic and cholinergic mechanisms modulate, respectively, the alerting and orienting effects. Task-evoked pupil dilations, as an indirect index of activity in LC-NE system, revealed the effect of (1) increases in mental effort and task engagement, (2) triggering an alerting network that induced larger pupillary responses in all cued trials relative to non-cue trials, (3) individual differences in overall task performance, (4) age on both behavioral and pupillary measures of cued attention, and finally (5) a late (probably cholinergic modulated) orienting effect or executive network monitoring in invalid trials compared to valid ones (see results from Mont Carlo analysis in Supplementary materials).

CRediT authorship contribution statement

Samira Aminihajibashi: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. Thomas Hagen: Software, Data curation, Visualization, Writing - review & editing. Bruno Laeng: Supervision, Conceptualization, Methodology, Writing - review & editing, Thomas Espeseth: Supervision, Conceptualization, Methodology, Resources, Writing - review & editing, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bandc.2020.105597.

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