Investigating the human locus coeruleus-norepinephrine system in vivo : discussions on the anatomy, involvement in cognition and clinical applications

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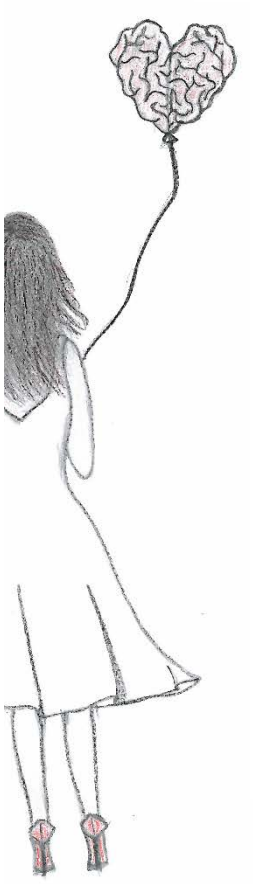
Chapter 4

The accessory stimulus effect is mediated by phasic arousal: a pupillometry study



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Abstract

People usually respond faster to a visual stimulus when it is immediately preceded by a task-irrelevant, auditory accessory stimulus (AS). This AS effect occurs even in choice reaction time tasks, despite the fact that the AS carries no information about the correct response. Researchers often assume that the AS effect is mediated by a phasic arousal burst evoked by the AS, but direct evidence for that assumption is lacking. We conducted a pupillometry study to directly test the phasic arousal hypothesis. Participants carried out a demanding choice reaction time task with accessory stimuli occurring on 25% of the trials. Pupil diameter, a common index of arousal, was measured throughout the task. Standard analyses of task performance and pupil diameter showed that participants exhibited the typical AS effect, and that accessory stimuli evoked a reliable early pupil dilation on top of the more protracted dilation associated with the imperative stimulus. Moreover, regression analyses at the single-trial level showed that variation in reaction times on AS trials were selectively associated with pupil dilation during the early time window within which the AS had an effect, such that particularly large AS-evoked dilations were associated with especially fast responses. These results provide the first evidence that the AS effect is mediated by AS-evoked phasic arousal.

Introduction

It has been shown that people respond faster in reaction time (RT) tasks when a visual imperative stimulus is immediately preceded by a task-irrelevant *accessory stimulus* (AS) presented in a different (e.g., auditory) perceptual modality, compared to when the imperative stimulus is presented alone. This AS effect occurs even in choice RT tasks, despite the fact that the AS carries no information about the correct response (Bernstein, Clark, & Edelstein, 1969; Hackley & Valle-Inclan, 1998; Posner et al., 1973; Sanders, 1975) Furthermore, an AS tends to speed up reactions without a concomitant reduction in accuracy, suggesting that the AS effect does not reflect a speed-accuracy-trade-off (Brown, van Steenbergen, Kedar, & Nieuwenhuis, 2014; Hackley & Valle-Inclán, 1999; Jepma, Wagenmakers, Band, & Nieuwenhuis, 2009; but see Posner at al., 1973).

Although the information processing stage(s) that benefit from the AS remain debated (Brown, Tona, et al., 2015; Hackley & Valle-Inclán, 1999; Jepma et al., 2009; Sanders, 1980), there seems to be a consensus that the AS effect is caused by a brief surge of arousal (i.e., phasic arousal; Bertelson & Tisseyre, 1969; Lawrence & Klein, 2013; Posner et al., 1973; Sanders, 1980). Indeed, both pioneering and more recent studies have used the terms "immediate arousal effect (Hackley & Valle-Inclán, 1999; Kiesel & Miller, 2007; Sanders, 1975) and "automatic alertness/arousal" (Posner et al., 1973) to refer to the AS effect. Despite the common inference that the AS effect is mediated by a phasic arousal response, there is only some indirect evidence to support this idea. The AS effect is stronger for auditory than for visual accessory stimuli (Bertelson & Tisseyre, 1969), and scales with the intensity of auditory accessory stimuli (Bernstein, Chu, Briggs, & Schurman, 1973; Stahl & Rammsayer, 2005). Furthermore, the AS effect is larger under conditions of temporal uncertainty, presumably characterized by relatively low arousal and thus offering more room for a phasic arousal effect (Hackley et al., 2009; Sanders, 1980). The time course of the AS effect, indexed by the effect of the stimulus onset asynchrony between AS and imperative stimulus, has also been argued to be consistent with a phasic arousal effect (Bertelson & Tisseyre, 1969).

We recently tested the phasic arousal hypothesis by examining the effect of clonidine, an α2–adrenergic agonist, on the AS effect (Brown, Tona, et al., 2015). Clonidine administration led to decreased blood pressure and increased simple reaction times, consistent with reduced arousal. Yet, we also observed that clonidine increased the size of the AS effect. Although at first glance this finding seems at odds with the phasic arousal hypothesis, an important distinction is that the primary effect of clonidine is to decrease tonic/baseline arousal levels (Arnsten, Steere, & Hunt, 1996; Samuels & Szabadi, 2008b), whereas the phasic noradrenaline-mediated arousal response may be preserved or even enhanced (Aston-Jones & Cohen, 2005). We concluded in this study that the clonidine-related reduction in general alertness provided greater scope for compensatory AS-induced performance improvements that were mediated by the phasic arousal response (Brown, Tona, et al., 2015). However, because this argument relies on several

assumptions about the effect of clonidine administration, a further, more direct test of the phasic arousal hypothesis is warranted.

Here, we exploited pupil dilation as a common index of phasic arousal (Beatty & Lucero-Wagoner, 2000), and examined its relationship with the AS effect. Participants carried out a four-choice Simon task with accessory stimuli occurring on 25% of the trials. Pupil diameter was measured throughout the task. Trials were separated by long and variable intervals to allow the pupil response to develop, and to minimize preparation for the next stimulus, thus increasing the impact of the AS (Hackley et al., 2009; Sanders, 1980). Finally, the AS was presented almost simultaneously with the imperative stimulus (30 ms prior to the stimulus; Hackley & Valle-Inclan, 1998; Jepma et al., 2009). This time period is too short for the AS to serve as a cue for the participant to start voluntary preparation. Indeed it has been shown that at stimulus onset asynchronies shorter than 200 ms, the endogenous effect of a preceding cue signal is minimal (Lawrence & Klein, 2013).

Our hypothesis was threefold: first, at the behavioral level, we expected that participants would exhibit the typical AS effect. Second, we expected that accessory stimuli would evoke a reliable transient pupil dilation on top of the dilation associated with the imperative stimulus. This would imply that the AS causes a phasic increase in arousal. Finally, we tested a critical prediction of the phasic arousal hypothesis, which capitalized on the trial-to-trial variability in the size of AS-evoked pupil dilation: RTs on AS trials should be negatively correlated with the size of the AS-evoked pupil dilation. That is, large-dilation trials, reflecting increased phasic arousal, should be associated with faster responses.

Method

Participants

Twenty-eight volunteers (19 women; aged: 19-27 years; mean age = 21 years) participated in a 1-hour experimental session and were given €6.50 or course credits in return. The study was approved by the local ethics committee and only healthy participants with no neurological or psychiatric history were included.

Task

Participants performed a four-choice Simon task implemented in E-Prime (Psychology Software tools, Sharpsburg). Their task was to identify an imperative stimulus and classify it by pressing one of four keys on a QWERTY keyboard (a, z, k, m). To induce the Simon effect, the four keys had a similar spatial configuration as the four screen locations where the stimuli could appear (Figure 1).

The task consisted of 240 experimental trials that were presented in two blocks of 120 trials. No feedback on response accuracy was provided during the actual task. Half of the trials were congruent, meaning that the stimulus appeared in a location that matched the required response. The other half of the trials were incongruent, meaning that the stimulus

appeared in one of the other three locations. The AS – a loud tone (800 Hz, 77 dB, 150 ms), which started 30 ms prior to the onset of the imperative stimulus – was presented binaurally through headphones and accompanied two of the four possible stimuli in 50% of the trials on which those stimuli were presented. The trials in which these stimuli were accompanied by an AS will be referred to as "AS trials", whereas the trials in which these stimuli were not accompanied by an AS are referred to as "no-AS trials". The other two stimuli were never accompanied by an AS. Trials on which these stimuli were presented are referred to as "filler trials". The filler trials were included in the study design in order to reduce the overall proportion of AS trials and to minimize habituation to the AS. The two stimuli that were followed by an AS varied across participants in a counterbalanced fashion.

Each trial started with a fixation cross (occupying 0.2° of the visual angle), presented for 3600-4100 ms with a mean duration of 3850 ms, and surrounded by four placeholder frames (each of which occupied 28.3° of the visual angle; Figure 1). Next, the imperative stimulus, one of four adjusted Glagolitic characters (characters of an early Slavic/Cyrillic script developed in the 9th century AD by the Greek Byzantine monk Cyril; occupying on average 9.5° of the visual angle) appeared in one of the frames (Figure 1). The stimulus was presented for 1000ms, after which the next trial started.

Throughout the task, colors from the Teufel colors set were used to ensure isoluminance and avoid luminance-related changes in pupil size: the background was slate-blue (RGB code:166,160,198) and the stimuli, the placeholder frames and the fixation cross were salmon (217,152,158). Additionally, each of the four Glagolitic stimuli consisted of the same number of salmon pixels.

Participants were told that they would occasionally hear a loud tone that was not relevant to the task. They were encouraged to ignore the tone and complete the task by responding as quickly and accurately as possible. They were also instructed to blink as little as possible and keep their eyes on the fixation cross while performing the task. The stimuli were presented in close proximity to the cross, in such a way that the participants could detect and categorize their identity while maintaining fixation. All four possible stimulus positions had the same distance from the fixation cross (7.6°).

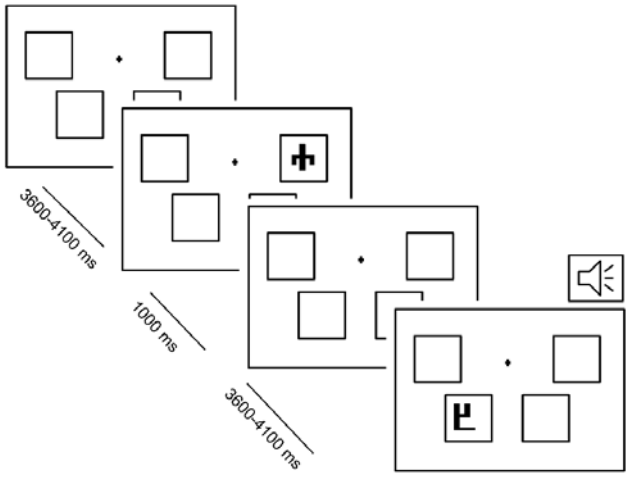

Figure 1. Overview of the trial procedure in the four-choice Simon task. The stimuli were isoluminant (see Method for actual colors). Accessory stimuli started 30 ms prior to the onset of the imperative stimulus, could accompany two of the four possible stimuli, and occurred on 25% of all trials.

Procedure

The study was conducted in a dimly-lit room. The session started with a block of trials that facilitated measurement of the pupil response to the AS in the absence of the visual stimuli. While the participant was looking at the fixation cross, the AS was presented at pseudorandom time points. Specifically, the temporal spacing of accessory stimuli was similar to that in the actual task: On seven out of the 28 'trials' an AS was presented (referred to below as "AS-only trials"); on the remaining 21 trials no AS was presented ("null trials"). No visual stimuli were presented, except for a fixation cross that remained on the screen, and participants were not required to respond to the AS in any way.

Next, to learn the stimulus-response mappings participants performed 80 practice trials in which the stimuli were presented in the center of the screen and feedback on response accuracy was presented after each trial. Following this practice block, participants performed an additional 16 practice trials with the Simon task described above. Finally, the 240 experimental trials were administered.

Pupil recordings and pre-processing

Participants were seated at a distance of 60 cm from a 17-inch monitor on which stimuli were presented. Pupil diameter was recorded continuously at 60 Hz using a Tobii T120 eye tracker (Tobii Technology, Stockholm, Sweden).

We performed a trial-averaged and a single-trial analysis where pupil dilation was defined as the mean pupil diameter during a 300-500 ms period (early time window) or a 500-2500 ms period (late time window) following stimulus onset, relative to a 200-ms prestimulus baseline (see Results for rationale).

Pupil data were analyzed using custom-made macros in BrainVision Analyzer (BrainVision Analyzer 2.0, Brain Products GmbH). Linear interpolation was applied to artifacts such as blinks and missing data (during the interval between -200 and 2500 ms after stimulus onset). In a second phase, trials containing a large number of interpolated data points (i.e., less than 50% valid data points in the interval of interest) were excluded from the analysis (17.0% and 15.6% of the trials for the early and late time windows, respectively).

Data analysis

Data from three participants were excluded due to technical failure of the eye tracker or a high proportion of invalid eye-tracking data (>50% trials discarded). Data from three other participants were excluded due to low overall response accuracy rates (62.9%, 75.0%, 58.8%), which resulted in fewer than 20 trials in one or more cells of the design. For the remaining 22 participants, trials were excluded from the behavioral and pupil data analysis if the RT was longer than 1000 ms (6.2% of the trials).

Correct RT, accuracy and pupil dilation were analyzed using repeated-measures ANOVAs with AS presence (AS vs. no-AS) and congruency (congruent vs. incongruent trials) as within-subject factors. The AS-only trials were not included in any of the analyses. Greenhouse-Geisser correction was applied whenever the assumption of sphericity was violated. In these cases we report corrected *p* values and uncorrected degrees of freedom. Partial eta-squared values are reported as measures of effect size.

To investigate whether AS-related pupil dilation can predict RT on AS trials, we performed a within-subject, multiple-regression analysis on the single-trial RT data, separately for the early and for late window. More specifically, we fitted the following linear regression model:

$$RT = \beta_0 + \beta_1 * Congruency + \beta_2 * Pupil + \beta_3 * (Congruency * Pupil)$$

where *RT* indicates reaction times, *Congruency* is a binary indicator variable representing single-trial congruency (coded as 1 = congruent, 0 = incongruent), *Pupil* represents single-trial pupil dilation, and the final term represents the interaction between the *Congruency* and *Pupil* predictors.

This approach yielded β weights that indicated the extent to which each factor predicted the RTs. Standardized β coefficients were extracted for each term and participant and group-wise distributions for each term were subjected to one-sample *t* tests (two-tailed) to test whether they were significantly different than zero at the group level. A similar analysis was conducted for the no-AS trials.

Results

Behavior

Mean correct RTs and response accuracies for each cell of the study design are reported in Table 1. The behavioral results showed a standard congruency effect: RTs were shorter for congruent trials (674 ms) than for incongruent trials (725 ms), $F(1,21) = 98.6$, $p < .001$, $\eta^2_p = .824$, and response accuracy was higher for congruent trials (96.3%) than for incongruent trials (92.6%), $F(1,21) = 22.7$, $p < .001$, $\eta^2_p = .519$. Furthermore, we found a typical AS effect on RT: AS trials were associated with shorter RTs (686 ms) than no-AS trials (713 ms), $F(1,21) = 30.7$, $p < .001$, $\eta^2_p = .594$. There was no main effect of AS presence on accuracy, ($p = .83$), and no interaction between AS presence and congruency for either RTs ($p = .97$) or accuracy ($p = .92$).

Table 1. Mean correct reaction times and standard deviations for each task condition.

	Congruent		Incongruent		Congruency	AS	Congruent	Incongruent
	AS	No-AS	AS	No- AS	effect	effect	filler	filler
RT (ms)	660	687	712	738	51	27	670	727
SD	63	73	68	76	24	23	55	54
Accuracy (%)	96.4	96.1	92.6	92.5	3.7	0.2	96.8	92.4
SD	3.8	3.8	3.5	5.3	3.6	4.1	3.4	5.6

Pupil diameter

Figure 2 shows the grand-average pupil waveforms for the task conditions of interest. Comparison of the waveforms suggests that the effects of AS presence and target congruency have distinct time courses. The difference between the AS and no-AS waveforms, and the time course of the AS-only waveform, suggest that the AS effect is particularly strong soon after onset of the imperative stimulus (300-500 ms). This AS-related effect on pupil diameter — larger dilation on AS than no-AS trials — is consistent with previous research showing increased pupil dilation after alerting stimuli (Geva, Zivan, Warsha, & Olchik, 2013). In contrast, the effect of congruency, driven by processing of the content of the imperative stimulus, only develops after this early time period and lasts much longer. To confirm this impression, we performed separate analyses for mean pupil size in an early time window (300-500 ms) and in a late time window (500-2500 ms). For the early time window, the results showed an effect of AS presence, $F(1,21) = 24.9$, $p < .001$, $\eta^2_p = .542$, but no effect of congruency, $F(1,21) = 0.6$, $p = .43$, $\eta^2_p = .030$. In contrast, for the late time window, there was no effect of AS presence, $F(1,21) = 0.8$, $p = .37$, $\eta^2_p = .039$, but consistent with previous research (van Steenbergen & Band, 2013) there was an effect of congruency, $F(1,21) = 4.7$, $p = .042$, $\eta^2_p = .182$. These results suggest that the pupil dilation related to the AS can be isolated from the pupil dilation related to the visual target (as indexed by the congruency effect).

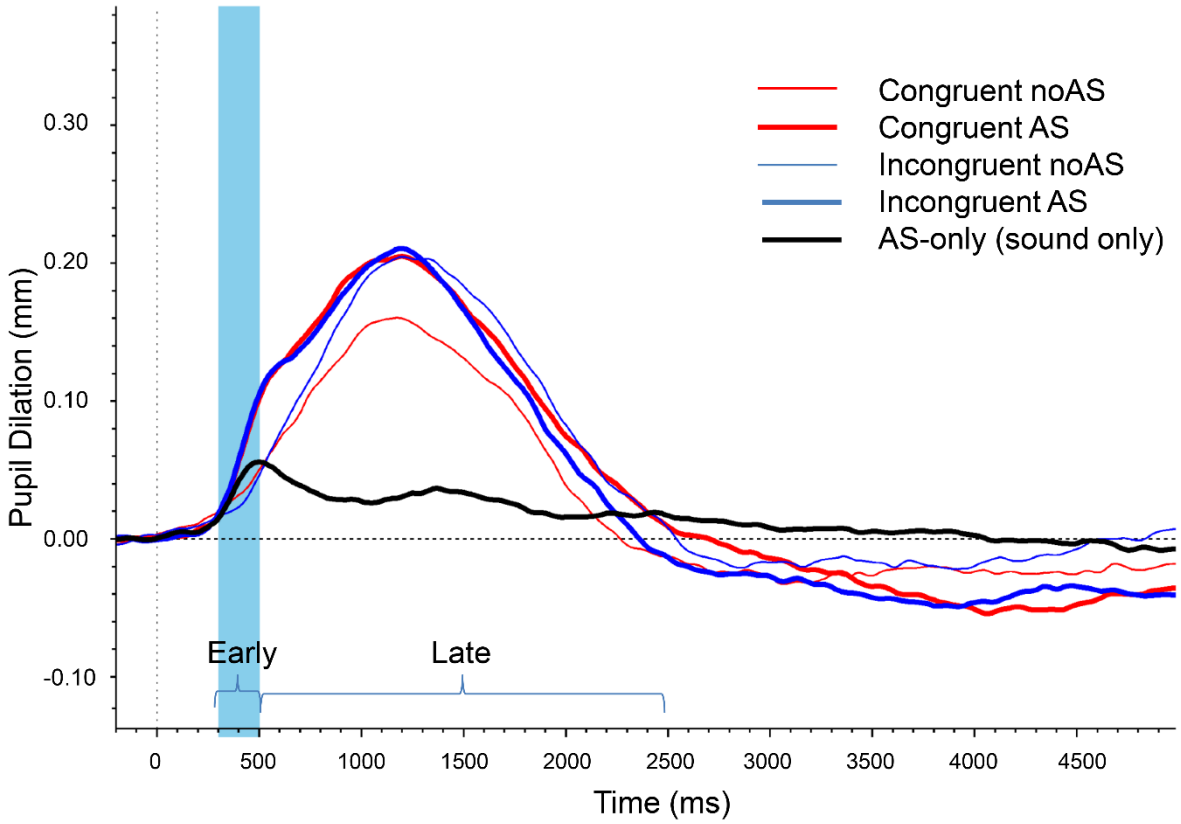

Figure 2. Effects of AS presence and congruency on grand-averaged pupil responses. Time 5 0 corresponds to the onset of the visual target stimulus. AS-only waveforms were obtained in a separate block.

Pupil-RT correlations

To investigate whether AS-related pupil dilation can predict RT on AS trials, we carried out a single-trial regression analysis (see Methods). For the early time window, congruency, $t(21) = 8.5$, $p < .001$, and pupil dilation, $t(21) = -2.9$, $p = .009$, were significant predictors of RT, while their interaction was not, $t(21) = 1.7$, $p = .11$. The significant negative relationship between pupil dilation and RT (Figure 3) supports the hypothesis that the AS effect on RT is mediated by a phasic arousal response. In contrast, for the late time window the only significant predictor was congruency, $t(21) = 7.3$, $p < .001$. The contributions of pupil dilation, $t(21) = 1.0$, $p = .33$, and the interaction between pupil dilation and congruency, $t(21) = 1.0$, $p = .35$, were not significant. However, it is important to note that, although not statistically significant, the relationship between RT and pupil dilation during the late time window was positive in direction, which contrasts with the negative relationship for the earlier measurement window. This corroborates the notion that the significant pupil-RT relationship for the early time window is driven by AS-evoked pupil dilation, not by pupil dilation associated with processing of the visual target.

An equivalent analysis for the no-AS trials yielded no significant contribution to RT of pupil dilation during the early time window, $t(21) = -1.2$, $p = .23$, potentially suggesting that AS presentation was a prerequisite for observation of a reliable negative relationship

between early pupil dilation and RT. However, the direction of the relationship was the same on both AS and no-AS trials, and the relatively low trial counts at our disposal prevented the construction of more complex multi-factorial regression models that would facilitate an appropriate statistical test of any pupil by AS-presence interaction effect. In the Discussion we will consider the implications of this issue.

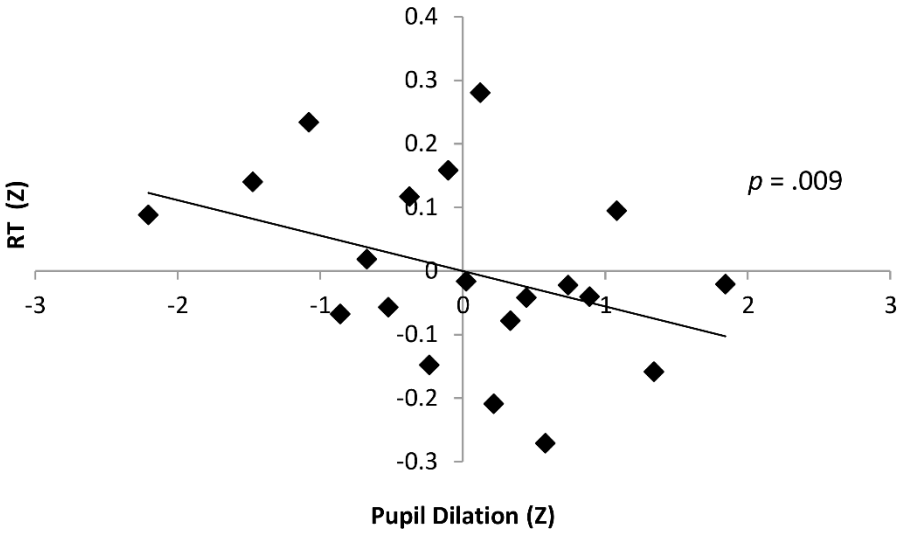

Figure 3. Scatter plot illustrating the negative relationship between ASrelated pupil dilation in the early window (300–500 ms) and correct RT on AS trials. Points reflect means of data that were z-scored for each participant separately, pooled across participants, and grouped into 20 five-percentile bins.

Control analysis: the AS effect does not reflect associative learning between AS and S-R pairs

Given that the AS in our task was associated with only 2 of the 4 stimulus-response (S-R) pairs, it is possible that participants implicitly learned this relationship. In this case, the AS effect on RT could reflect the fact that the presentation of the AS constrained the number of S-R pairs that could be presented, thus allowing participants to selectively prepare for these S-R pairs. To rule out this possibility, we performed the following control analysis: we divided the RT trials into four chronological bins (each of which contained 60 trials), and computed the AS effect for each of these bins. We reasoned that if the AS effect in our task reflects (in part) an experience-based associative-learning effect, then the AS effect should increase over time.

The mean AS effects in the four bins were 18, 30, 18 and 35 ms. A one-way repeated-measures ANOVA revealed that these values did not significantly differ from each other, $F(3,63) = 0.8$, $p = .50$, $\eta^2_p = .036$, suggesting that any associative learning between AS occurrence and S-R pairs did not substantially contribute to the AS effect. These results uphold our key conclusion that the AS effect reflects a genuine effect of increased phasic arousal.

Discussion

The AS effect is often assumed to be driven by a phasic arousal response to the AS. However, direct evidence for the phasic arousal hypothesis is lacking. In the current pupillometry study participants exhibited the typical behavioral AS effect, and the accessory stimuli evoked reliable pupil dilation on top of the dilation associated with the imperative stimulus. Importantly, and in line with the phasic arousal hypothesis, the RTs on AS trials were negatively correlated with the size of the AS-evoked pupil dilation: large-dilation trials, reflecting particularly strong phasic arousal evoked by the AS, were associated with particularly fast responses. A relationship that was opposite in direction, though not reliable, was observed between RT and the temporally extended pupil dilation evoked by the imperative stimulus, suggesting that our primary finding was specifically due to the AS. These results provide the first straightforward evidence that the AS effect is mediated by AS-evoked phasic arousal.

RTs on no-AS trials were also negatively correlated with pupil dilation in the interval from 300 to 500 ms after the stimulus, although this relationship did not approach statistical significance. Even if this finding reflects a genuine relationship that could be revealed with greater statistical power, we believe it would not pose a challenge for our central argument. Variability in the magnitude of early pupil dilation on no-AS trials might reflect spontaneous variability in baseline arousal or variability in the alerting effect caused by stimulus onset, before any higher-level processing of stimulus content has taken place. Such sources of arousal may influence RT in the same way as AS-evoked arousal does, but less strongly. The ensuing single-trial relationship between early pupil dilation and RT would further emphasize our argument that the AS effect on RT is driven by the robust difference in phasic arousal between AS trials and no-AS trials, as revealed by the trial-averaged early pupil dilation effect in Figure 2.

Although the information processing stage(s) that benefit from the AS have long been debated (Bernstein, Rose, & Ashe, 1970; Hackley & Valle-Inclán, 1999; Posner, 1978; Sanders, 1980), recent electrophysiological and computational modeling evidence suggests that the AS increases perceptual sensitivity and reduces the time needed for target encoding (Brown, Tona, et al., 2015; Jepma et al., 2009). In reaction-time tasks such as the Simon task employed presently, the earlier onset of the evidence accumulation process that results from faster stimulus encoding would translate to faster responses (Nieuwenhuis & de Kleijn, 2013; Seibold, Bausenhart, Rolke, & Ulrich, 2011). Moreover, in psychophysics tasks in which target stimuli are only briefly presented, it would ensure that evidence can accumulate to a higher level before the target is masked, resulting in higher response accuracy (Brown, Tona, et al., 2015; Nieuwenhuis & de Kleijn, 2013; Seifried, Ulrich, Bausenhart, Rolke, & Osman, 2010).

We consider two ways in which AS-related phasic arousal might cause this improvement in task performance through an effect on perceptual encoding. First, the AS may speed up perception through an arousal-evoked phase reset. Electrophysiological studies have shown that the momentary phase of neural oscillations at target onset is an important trial-

by-trial predictor of perceptual and attentional variability (Van Rullen, Busch, Drewes, & Dubois, 2011). Response errors, which are known to evoke a phasic arousal response (including pupil dilation; Hajcak, McDonald, & Simons, 2003; Murphy, van Moort, & Nieuwenhuis, 2016) lead to a phase reset of slow neural oscillations (van den Brink, Wynn, & Nieuwenhuis, 2014). Therefore, it seems possible that accessory stimuli improve performance by resetting oscillatory phase to an optimal value for processing of an immediately subsequent target (Diederich, Schomburg, & Colonius, 2012). Such an AS-evoked phase reset may be especially beneficial in tasks in which variability in interstimulus intervals prevents spontaneous entrainment of neural rhythms (cf. van den Brink et al., 2014), a notion consistent with the finding of larger AS effects when target onset is less predictable (Hackley et al., 2009; Sanders, 1980).

Second, the AS effect on behavior may be mediated by an arousal-related transient increase in neural gain. Increased arousal, including fluctuations in pupil size, is thought to be associated with global modulations in neural gain (Aston-Jones & Cohen, 2005; Clewett et al., 2016; Eldar, Cohen, & Niv, 2013; Vinck, Batista-Brito, Knoblich, & Cardin, 2015), a multiplicative change in the input-to-output function of a neuron (Servan-Schreiber, Printz, & Cohen, 1990). Thus, an AS may elicit a phasic increase in neural gain that, when occurring just before target onset, boosts neural responsivity and expedites the processing of that target, equivalent to a speeding up of perceptual encoding. Arousal-related changes in gain are likely to be regulated by neuromodulator systems such as the locus coeruleus-norepinephrine system. The brainstem nucleus locus coeruleus exhibits a rapid increase in activity in response to salient stimuli, including task-irrelevant intense auditory stimuli (Grant, Aston-Jones, & Redmond, 1988), and the consequent phasic increase in norepinephrine release increases neural gain. In recent research we have found that norepinephrine-mediated increases in gain enhance the precision of cortical perceptual representations (Frangos, Ellrich, & Komisaruk, 2014). Several researchers have proposed that the AS effect and related phasic alerting effects are mediated by phasic norepinephrine release (Fernandez-Duque & Posner, 1997; Hackley & Valle-Inclán, 1999, 2003). Although direct evidence is still lacking, the current findings provide indirect evidence for this hypothesis, given that recent studies have found correlations between LC activity and pupil diameter (Joshi et al., 2016; Murphy, O'Connell, et al., 2014; Varazzani et al., 2015).

It is worth noting that the two accounts discussed above are not mutually exclusive: Bursts of LC firing can reset the phase of ongoing low-frequency oscillations, thus influencing cortical excitability and sensory processing (Safaai, Neves, Eschenko, Logothetis, & Panzeri, 2015), while the phase of ongoing low-frequency oscillations can reflect fluctuations in neural gain (Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008).

To conclude, our study utilized pupillometry methods to provide important new evidence for the long-standing assumption that the AS effect is mediated by phasic arousal. A limitation of our findings is that they are correlational in nature and thus do not provide definitive evidence for the causal role of such phasic arousal. Future studies should

examine whether experimenter-controlled phasic arousal bursts (e.g., optogenetically induced in animals), of a size comparable to those evoked by accessory stimuli, facilitate task performance in a similar way.