



Ocular signatures of proactive versus reactive cognitive control in young adults

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Abstract

During the execution of a cognitive task, the brain maintains contextual information to guide behavior and achieve desired goals. The AX-Continuous Performance Task is used to study proactive versus reactive cognitive control. Young adults tend to behave proactively in standard testing conditions. However, it remains unclear how interindividual variability (e.g., in cognitive and motivational factors) may drive people into more reactive or proactive control under the same task demands. We investigated the use of control strategies in a large population of healthy young adults. We computed the proactive behavioral index and consequently divided participants into proactive, reactive, and intermediate groups. We found that reactive participants were generally slower, presented lower context sensitivity, and larger response variability. Pupillary changes and blink rate index cognitive effort allocation. We measured, concomitantly to the task, the pupil size and frequency of blinks associated with the cue maintenance and response intervals. During the cue period, nonfrequent, nontarget cues led to increased pupil dilation and number of blinks in all participants. During the response interval, we found more errors and increased pupil dilation to the probe when all participants had to overcome a response bias generated by the frequent cue. Only reactive participants showed larger response-related pupil when they had to overcome a response bias related to the frequent probe. Contrary to expectations, groups did not differ in ocular measures in the cue period. In conclusion, interindividual differences in cognitive control between healthy adults can be mapped onto different patterns of effort allocation indexed by the pupil.

Keywords Pupillometry · Eye blinks · Cognitive control · AX-CPT

Introduction

To solve everyday tasks, we need to integrate our action plans with relevant contextual information. Recent psychological theories have proposed that both context and goal-related information are maintained and manipulated within working memory, but the efficiency with which this is achieved depends on each

individual's processing capacity and effort investment (Braver & Barch, 2006; Koechlin, Ody, & Kouneiher, 2003; Miller & Cohen, 2001). An influential account on cognitive control called the Dual Mechanisms of Control (DMC) framework proposes that people tend to employ one of two different strategies to deal with attention-demanding tasks: reactive or proactive control (Braver, 2012). Specifically, the theory states that during proactive control, an individual prepares a response based on context information that may be available before the time when one needs to respond. Such an endogenous preparation should minimize interference at the time of the decision, but it requires sustained maintenance of the context information within cognitive control networks. In contrast, during reactive control, an individual produces the response only as the task requires it; this control mode implies the fast retrieval of goal representations in order to produce correct responses, and it requires only transient activity in cognitive control networks.

A central assumption in the DMC framework is that variability in cognitive control is determined by the dynamic balance between proactive and reactive processes. Importantly,

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many factors, including variables that vary from time to time, or vary from person to person, can potentially contribute to the weighting of proactive versus reactive processes in a particular task. Individuals appear to flexibly adjust their behavior in more proactive or reactive strategies according to the external demands (e.g., with emphasis on speed or accuracy; Irlbacher, Kraft, Kehrner, and Brandt, 2014) and the characteristics of the task at hand. In addition, inter-individual factors like motivation, age, personality or cognitive traits, and pathology (e.g., psychosis) can influence the likelihood to deploy a proactive or reactive strategy in a particular context (Braver, 2012; Braver, Paxton, Locke, & Barch, 2009; Bugg, 2014; Burgess & Braver, 2010; Haarmann, Ashling, Davelaar, & Usher, 2005; Lorscheid & Reimer, 2008; Paxton, Barch, Racine, & Braver, 2007; Redick & Engle, 2011; Van Der Meer et al., 2010; Van Gerven, Hurks, Bovend'Eerd, & Adam, 2016). One general assumption is that young, healthy adults will behave proactively and that they can act as a control group and baseline comparison for populations that are thought to use a reactive control strategy. Nevertheless, one would expect that some young adults might switch strategy within the very same task or might vary control mode from trial to trial due to individual differences in cognitive capacity, motivation, arousal, or other aspects of environmental factors or internal physiological states (Braver, 2012; Unsworth & Robison, 2017). In particular, in a group of young, healthy individuals, the majority are expected to maintain a proactive control mode while working on a cognitive task, but some individuals may use a reactive control mode in a large number of trials.

In the present study, we investigated this question in a large sample ($N = 172$) who performed the AX-continuous performance task (AX-CPT), which allows for assessing proactive and reactive control through behavioral indexes. The task entails the identification of a specific pair of cue-probe letters (target pair: A followed by an X) presented sequentially. In some trials, the cue is predictive of the correct answer (e.g., the letter B as a cue always predicts the appearance of a nontarget letter), and the correct response therefore can be prepared before the presentation of the probe. In others (when an A cue is presented), the subsequent probe defines whether the pair constitutes a target or not (an X probe defines a target pair while a non-X defines a nontarget) and, only at this point, the correct answer can be chosen. However, because AX trials are more frequent than other trial types, participants tend to learn to expect an X whenever the A cue is presented. Some individuals tend therefore to commit AY errors and therefore they can be labeled as “proactive,” whereas individuals that tend to commit BX errors can be labeled as “reactive.”

While individuals performed the task, we recorded task-related pupil dilations and eye blinks. The measure of pupil diameter change is a well-established way within psychology of assessing how persons allocate cognitive resources or

mental effort while they perform an attentional task (Beatty, 1982; Beatty & Lucero-Wagoner, 2000; Kahneman & Beatty, 1966; Laeng, Sirois, & Gredebäck, 2012). Typically, a task that involves increases in cognitive effort induces trial-related dilations of the pupil (independently of luminance changes), providing a “window” into brain activity within specific systems of the brain (Eckstein, Guerra-Carrillo, Singley, & Bunge, 2017). In particular, pupil dilation has been associated with the neuromodulation of cortical activity by the main noradrenergic hub in the brain, the locus coeruleus (LC) as revealed by neurophysiological studies in monkeys (Joshi, Li, Kalwani, and Gold, 2016) and neuroimaging in humans (Alnæs, Sneve, Espeseth, Endestad, van de Pavert, & Laeng, 2014). Noradrenaline (also called norepinephrine [NE]) is the main neuromodulator of cognitive arousal, possibly by controlling the gain of neuronal responses to concurrent relevant stimuli or events (Foote, Freedman, & Oliver, 1975; Waterhouse & Woodward, 1980). Increased pupil dilation marks increased effort to typically more difficult or demanding conditions, and proactive control is related to an increase in cognitive effort right after cue presentation, as measured with pupillometry (Bijleveld, Custers, & Aarts, 2009; Chiew & Braver, 2013; Van Der Meer et al., 2010). In contrast, reactivity relates to an increased effort allocated to the probe (Braver et al., 2009; Brown et al., 1999; Chatham, Frank, & Munakata, 2009; Laeng, Ørbo, Holmlund, & Miozzo, 2011; Paxton et al., 2007). Eye blinks might constitute another ocular signature linked to cognitive processes, because they appear to provide an indirect measure of dopaminergic activity, another monoaminergic neuromodulator of brain activity that is also released during cognitive control (Colzato, van den Wildenberg, van Wouwe, Pannebakker, & Hommel, 2009; Eckstein et al., 2017; van Bochove, Van der Haegen, Notebaert, & Verguts, 2013). While spontaneous eye blinks have been firmly associated with tonic dopaminergic activity in the brain (Elsworth et al., 1991; Groman et al., 2014; Karson, 1983; Stern, Walrath, & Goldstein, 1984; Taylor et al., 1999), the relationship between task-related eye blinks and phasic dopaminergic bursts associated with gating is less studied (Bacher, Retz, Lindon, & Bell, 2017; Werchan, Collins, Frank, & Amso, 2015). This neuromodulator could facilitate the functionality of working memory and of motivated attention. A central prediction in the DMC framework is that the updating of context representation rests on a gating mechanism that will update the representation when the gating signal occurs. This gating mechanism is thought to be mediated by phasic dopaminergic activity (Badre & Nee, 2017; Braver & Cohen, 2000; Frank, Loughry, & O'Reilly, 2001; Rougier, Noelle, Braver, Cohen, & O'Reilly, 2005). A recent study found that task-related eye blink rate was associated with efficiency of working memory updating, which according to the authors reflected gating signals released by phasic dopaminergic activity (Rac-Lubashevsky, Slagter, & Kessler, 2017;

Tharp & Pickering, 2011). Also, dorso-lateral prefrontal cortex (dlPFC) is causally involved in representing the currently relevant context (Nee & Brown, 2012), and the dopaminergic system is involved in gating an update signal to the dlPFC (D'Ardenne et al., 2012). In particular, phasic activation of the ventral tegmental area/substantia nigra (VTA/SN) was temporally associated with dlPFC activity but only in conditions in which context updating was required.

Both of the above neuromodulatory systems are highly interconnected, but there is scarce evidence of whether their specific roles can be related to individual differences in ocular signatures. Specific patterns of pupil dilation (Chatham et al., 2009; Chiew & Braver, 2013, 2014) and blinks (Warscher et al. 2015) have been related to the different events of the AX-CPT. By measuring task-evoked pupil dilation and eye blinks in this task, we intended to disentangle how people with different behavioral profiles dynamically allocate effort in a trial-specific way. In particular, we reasoned that pupil changes and eye blinks during the delay period of the AX-CPT (between the presentation of the cue and the probe), as well as after the presentation of the probe, would be most meaningful measures of control. That is, during the *delay* period, contextual information should be maintained, as previous studies using physiological measurements suggested different patterns of neural processing for the different cue types (valid -A-, invalid -B-; e.g., Chiew and Braver (2013, 2014)). During the *probe* period, the evoked pupil signal should reflect cognitive effort invested to process the probe and/or compute the response. We expected that proactive participants would evoke larger pupil dilation when a specific response could be prepared immediately following the cue (that is, during the delay period of B trials), while reactive participants would evoke larger signals at the moment of the probe, in particular during B trials (Chatham et al., 2009). Finally, we expected that if eye blinks reflected update signals under the different control strategies, blink rates would be greater in proactive people during the cue in B trials, reflecting context processing by the ventral tegmental area (D'Ardenne et al., 2012), whereas blink rates should be more frequent in reactive people during the probe period.

Methods

Participants

A total of 183 participants volunteered for one of a series of AX-CPT experiments, the data from which were pooled together for this report. All participants had normal or corrected-to-normal vision. All participants received a remuneration of 100 Norwegian kroner (NOK) per hour. Eleven participants were excluded from the analysis, because they had performed nonstandard versions of the task as part of other projects,

leaving 172 participants (mean age: 27; SD: 7 years; age range: 18–46 years; female: N = 85; male: N = 87). The study was conducted according to institutional guidelines and approved by the local ethics committee.

Task paradigm

The paradigm employed was the AX continuous performance task (AX-CPT; Rosvold, Mirsky, Sarason, Bransome Jr, & Beck, 1956). During each trial, participants were presented the cue stimulus for 500 ms and, after a 2,500-ms fixation period, the probe stimulus was presented for 500 ms (Fig. 1). After a fixation interval of 2,700 ms, a feedback was presented for 500 ms, and between trials, participants fixated on a cross (intertrial interval: 700 ms). The participant's task consisted of detecting the occurrence of a certain cue-probe pair (the target pair AX). Participants had to respond after a target pair by pressing a key with the index finger of the left hand. For all other combination of cues and probes (nontarget pairs), they had to respond by pressing a key with the index finger of the opposite hand (hand side was counterbalanced). Some of the participants performed different variants of the task, and these were further employed for other research purposes; therefore, some of the parameters employed (stimulus type and number of trials) varied across participants. In total, 133 individuals performed the letters version of the AX-CPT, where the target cue was a letter "A" and a target probe was a letter "X." Any other combination of letters constituted a nontarget pair. Also, 111 participants completed 200 trials of the task, whereas the rest (22 participants) performed 300 trials. In addition, 50 participants performed the dots version of the AX-CPT, where the stimuli consisted of three-dots patterns instead of letters (Figure S1). One of the patterns played the same role as A and another as X in the classic version. The dots version has been shown to yield behavioral and physiological results that are comparable to the AX version (Lopez-Garcia et al., 2016). The dots version included 200 trials. In both letters and dots versions, the proportion of AX, AY, BX, and BY trials was 0.64, 0.12, 0.12, and 0.12, respectively, and they appeared in semirandom order. Across all versions of the paradigm used in this study, the cue, probe, and fixation cross stimuli were blue (RGB: 39, 100, 255) and the background was grey (RGB: 127, 127, 127). These colors were selected to obtain homogeneous luminance across stimuli on screen in order to minimize confounding pupil dilations due to changes in mean luminance during stimulus presentation (Kang, Huffer, & Wheatley, 2014). Thus, the letters and dots version of the AX-CPT employed in the present study were identical except for the stimuli used.

The AX-CPT includes four types of trials: AX target trials ("A" cue followed by "X" probe), AY trials ("A" cues followed by a letter other than "X"), BX trials (a letter other

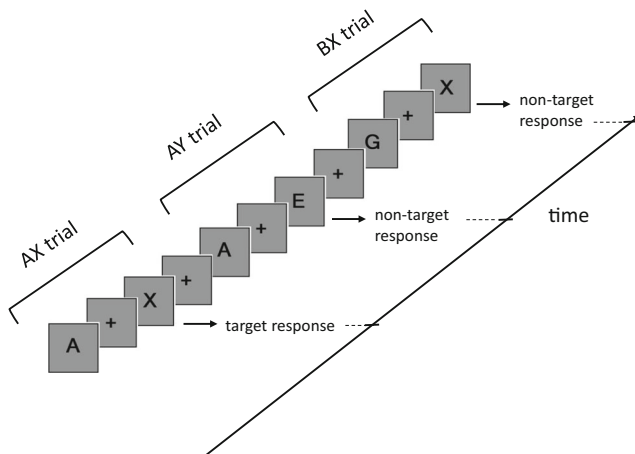


Fig. 1 Scheme of three trials of the AX-CPT

than “A” is followed by an “X”), and BY trials (both cue and probe are letters other than “A” and “X,” respectively).

Procedure

Participants were seated in front of the monitor with their chin resting on a support to minimize head motion. The eye tracker registers head position, which allows computing the mapped pupil diameters in millimeters instead of pupil diameter in video pixels. The experiment was controlled by E-prime software (Psychology Software Tools, Pittsburg, PA). Responses were given on a response box (Psychology Software Tools) connected to the stimulus computer. Participants gazed at a central spot signaled by the fixation cross. An SMI Eyetracker (SensoMotoric Instruments (SMI), Teltow, Germany) collected pupil data with a sampling rate of 60 Hz. Calibration and validation of gaze direction were conducted once, right before the experiment. Each pupil size sample was assigned a value of 1 if a blink was registered and a 0 if no blink was registered by the eye-tracker built-in detector. The time courses of the pupil diameter measured in millimeters were exported for preprocessing and baseline-corrected to obtain the main dependent variable of pupil change. Pupillometry data were preprocessed by using R (github.com/thohag/pupilParse) and visualized using pupilPlot (github.com/thohag/pupilPlot). For pupil-dilation analysis, blinks were corrected using linear interpolation. Only correct trials were further analyzed while incorrect trials were discarded.

Data analysis: behavior

Statistical analyses of behavioral data were performed in IBM SPSS Statistics 22.0. The proactive behavioral index (PBI) was computed for each participant by relating AY and BX

error rates, as in previous publications (Braver et al., 2009) and according to the following formula:

$$PI = \frac{E_{AY} - E_{BX}}{E_{AY} + E_{BX}}$$

Where E, the error rate for each condition, is computed using the following formula which avoids complications when the number of errors is small or zero:

$$E = \frac{\text{number of errors} + 0.5}{\text{number of trials} + 1}$$

The PBI varies between -1 and $+1$: the closer the score is to $+1$, the more proactive-like is the strategy of the participant; the closer the score is to -1 , the more reactive-like is the strategy. A score of 0 means equal amount of AY and BX errors. Participants were classified according to their PBI into three groups: PBI < 0 (reactive-like behavior - REACT), PBI = 0 (intermediate behavior - INT) and PBI > 0 (proactive-like behavior - PROACT). This classification allowed us to compare both the behavioral and physiological signatures of each strategy. The number of participants in each group was 25 for REACT, 42 for INT, and 105 for PROACT, and the mean PBI of each group was: PROACT, 0.80 ± 0.02 ; INT, 0 ; REACT: -0.72 ± 0.06 .

To study variability of behavior within each group, the reaction time (RT) standard deviation (SD) and the RT coefficient of variation (CV),

$$CV = \frac{SD}{\text{mean}} * 100$$

were calculated per participant considering all the trials.

CV, RT SD, and RT were analyzed by using repeated measures ANOVAs with Group (REACT, INT and PROACT) as between-subject factor and Trial Type (AX, AY, BX, and BY) as within-subjects factor and the Greenhouse-Geisser correction for sphericity was applied. For accuracy, nonparametric tests were employed because accuracy followed a nonnormal, right-skewed distribution (Kolmogorov-Smirnov test, $p < 0.001$). The main effect of accuracy in the different trial types was tested with a Friedman’s test. The main effect of accuracy across groups was tested with Kruskal-Wallis tests for independent samples and post-hoc Mann-Whitney U tests were performed subsequently. A Wilcoxon test for paired samples compared accuracy between conditions.

To study possible confounds with respect to task stimuli (i.e., letters vs. dots), we compared the total accuracy and the accuracy in the different conditions between task versions with the Kruskal-Wallis test for independent samples. For the RT, we included task version as a between-subjects factor. In addition, we studied the frequency of proactive, reactive and intermediate participants across task versions with a chi-square test.

The context- d' was calculated for each participant. This measure is derived from the d' of signal detection theory and indicates sensitivity to distinguish the different types of probes (target X in AX trials vs. nontarget X in BX trials) (Stanislaw & Todorov, 1999). Larger values of context- d' indicate greater sensitivity. Context- d' was calculated based on AX hit rates and BX false-alarms and compared across groups with independent samples Mann-Whitney tests, because it followed a nonnormal distribution (Kolmogorov-Smirnov test, $p < 0.001$). Finally, age was compared between groups with independent samples t tests.

Data analysis: ocular measures

Evoked pupil responses were analyzed as follows: we calculated the mean of each trial's pupil size (time-locked to the presentation of the cue), and then we subtracted from it the pupil size of a 700 ms pre-cue interval (baseline). We were interested in the delay and the probe periods to analyze pupil differences in the different groups. For the analysis of the delay, we defined a time windows of 500 ms covering the interval of largest difference between A and B cues (i.e., 2,000–2,500 ms; Fig. 3). For the probe interval, we defined consecutive 100-ms windows in the interval 1,000–2,000 ms after the probe. This window spans the interval when the pupil peaks, where maximal differences are reached between conditions (Fig. 3). After calculating the mean pupil change across the time window for each condition and group, repeated measures ANOVAs were performed with Group as between-subject factor and Trial Type as within-subject factor. Post-hoc t tests were performed after significant effects applying Bonferroni correction for multiple comparisons.

Pupil dilation latency at the probe period was measured as the time point at which the pupil reached its peak after the onset of the probe. Because there is no clear peak in the cue/delay interval, no latency measure was computed there.

Blinks occurrences were measured in two intervals: during the delay after the presentation of the cue (1,000–2,500 ms) and after the presentation of the probe (4,500–5,000 ms). Total blinks per condition, interval and individual were normalized by the total number of blinks per individual (Siegle, Ichikawa, & Steinhauer, 2008) and per number of trials within the condition. The variables containing the number of blinks were nonnormally distributed and therefore nonparametric tests were used. Group effects were obtained with the Kruskal Wallis test and U tests for independent samples were employed for post-hoc comparisons. Blink latency at the delay (probe) period was measured as the time point at which a blink started after the onset of the cue (probe), respectively. For all ocular analyses (pupil change and blinks), only correct trials were considered.

Results

Characterization of task variants and proactivity groups

First, we compared the accuracy in the two AX-CPT versions (letters and dots) to investigate whether the tasks are comparable at the behavioral level (Table 1). Participants performing the dots version presented overall lower accuracy than the letter version ($Z = 3.02$, $p = 0.002$) and lower accuracy in AY trials (letters: 0.92 ± 0.08 , dots: 0.89 ± 0.07). When looking at the reaction times (RT), we found slower RT in the dots version (main effect of task version: $F(1,170) = 9.49$, $p = 0.002$) and no interaction between trial type and task version. The participants that performed the dots version showed the general finding of slower RT in AY with respect to the other trial types and, therefore, a similar behavior than the participants that performed the letters version. Then, we compared the frequency of proactive, intermediate and reactive participants across task versions and found no significant differences ($\chi^2 = 4.27$, $p = 0.118$; Table 1). Furthermore, the PBI did not significantly differ between the groups ($p = 0.745$). In conclusion, the dots version was more difficult than the letters version as showed by reduced accuracy and longer RT. However, it did not affect the proportion of participants showing proactive (PROACT), intermediate (INT) or reactive (REACT) behavior, and therefore it seemed plausible to pool the data. In the following, we report the results for the whole sample, including task version as a covariate.

AX-CPT performance

The analysis of error rates showed that, as expected, participants made significantly more errors in AY than all other conditions (Friedman test: $\chi^2 = 126.96$, $p < 0.001$; post-hoc Wilcoxon test, $p < 0.001$; Table 2) and in BX than AX ($p < 0.001$). Next, we compared total accuracy between proactive, reactive, and intermediate participants. Independent samples U tests between groups showed that INT participants were more accurate than REACT ($Z = 3.30$, $p < 0.001$), and PROACT participants ($Z = 5.01$, $p < 0.001$; Fig. 2a). We then compared the distribution of context- d' across groups (Fig. 2b). Independent samples U tests showed a significantly smaller context- d' for REACT compared to PROACT ($Z = 5.67$, $p < 0.001$) and INT ($Z = 4.52$, $p < 0.001$), with no difference between PROACT and INT ($Z = 0.87$).

We then examined the RT (Fig. 2c). We found significant main effects of Trial Type ($F(1.93,325) = 43.84$, $p < 0.001$, e.s. 0.20) and Group ($F(2,168) = 12.90$, $p < 0.001$, e.s. 0.13). Post-hoc t tests showed that participants were significantly slower in AY compared with AX, BX, and BY trials ($p < 0.001$). PROACT participants were faster than REACT ($p < 0.001$).

Table 1 Accuracy, RT, and frequency of proactivity groups in letters and dots versions of the AX-CPT

	letters	dots
Mean Accuracy (SD)	0.96 (0.03)	0.94 (0.06)
Mean rt (SD)	442 (113)	506 (0.06)
% Proactive	58	68
% Intermediate	29	14
% Reactive	13	18

and INT ($p = 0.001$). Furthermore, PROACT participants were significantly faster than REACT in all trial types and faster than INT in all trial types except AY (interaction of group \times condition: $F(3.87,325) = 3.96$, $p = 0.004$, e.s. = 0.045). In addition, PROACT, but not REACT or INT, was faster in B- trials (BX, BY) with respect to AX trials ($p < 0.001$).

We next inspected the characteristics of the proactivity groups with respect to variability in behavior. For this purpose, we measured the coefficient of variation (CV) and standard deviation (SD) of the reaction times. The conditions presented differences in CV: AY showed the lowest values and BX the largest (main effect of condition: $F(1.80,303.19) = 6.34$, $p = 0.003$, e.s. = 0.084). Reactive participants had larger RT CV in BX than the two other groups (Fig. 2d; interaction effect: $F(3.60,303.19) = 7.62$, $p < 0.001$, e.s. = 0.083; post-hoc t tests REACT vs. PROACT in BX: $p = 0.006$; REACT vs. INT: $p = 0.033$). The proactive group showed larger RT CV in AY than INT ($p = 0.011$). The conditions did not differ in the standard deviation of RT (main effect of condition: $F(2.76,464.78) = 2.40$, $p = 0.072$). However, REACT participants showed larger RT SD than PROACT (main effect of group: $F(2,168) = 5.61$, $p = 0.004$, e.s. = 0.063; post-hoc T tests REACT vs. PROACT: $p = 0.004$). Furthermore, PROACT

showed smaller RT SD in BX than REACT (interaction effect: $F(5.53,464.78) = 6.70$, $p < 0.001$, e.s. = 0.074; post-hoc t test: $p = 0.003$) and larger RT SD in AY than INT ($p = 0.008$). As an example illustration, Figure S4 shows the plot of RT at every trial in sample participants from each group. Together, the results suggest that the REACT group had larger behavioral trial-to-trial variability overall and particularly in BX trials and that in the PROACT group RT variability was comparable to the RT variability of the INT group, except for increased CV in AY trials.

The groups did not differ in age ($F(2,164) = 2.74$, $p = 0.067$). We performed other analyses to provide additional evidence for the qualitative differences between groups in terms of their strategy (RT correlations and conditionalized accuracy, [Supplementary material](#)).

Ocular measures

Pupil size

The pupil waveforms evoked during the different trial types were investigated (Fig. 3). Pupil size was significantly larger for B than for A cues during the delay period (main effect of trial type: $F(1,168) = 7.23$, $p = 0.008$, e.s. = 0.04). Contrary to what we hypothesized, no significant main effect of group or interaction were found.

Next, we looked at the probe period. After the presentation of the probe, AY trials showed increased pupil size with respect to the other trial types in all time windows ($p < 0.001$), consistent with the high conflict induced by this trial. We found a significant effect of group \times trial type interaction in the interval 1.6–1.8 sec after probe presentation (Fig. 4; 1.6–1.7 sec: $F(5.55, 464.01) = 2.22$, $p = 0.045$, e.s. = 0.026; 1.7–1.8 sec: $F(5.41, 451.73) = 2.38$, $p = 0.034$, e.s. = 0.028). In the REACT group, BX was significantly different than AX and BY (1.6–1.7 sec: $p = 0.003$ and $p < 0.001$; 1.7–1.8 sec: $p = 0.004$ and $p = 0.001$) but not different from AY (1.6–1.7 sec: $p = 0.035$; 1.7–1.8 sec: $p = 0.025$). In the PROACT and INT groups, AY was significantly different from the other conditions ($p < 0.001$), and there were no other significant differences between conditions. These results were confirmed by an independent, data-driven analysis where no predefined window was specified ([Supplementary material](#): Pupil waveform analysis). A complementary analysis of probe-related pupil dilation including the continuous PBI score as a covariate led to similar results ([Supplementary material](#): Pupil waveform analysis). No differences between groups survived the correction for multiple comparisons.

In the probe period, we found that pupil peaked later in AY with respect to all other conditions (Table 3; main effect of condition: $F(2,442) = 23.47$, $p < 0.001$). In addition, the

Table 2 Accuracy and RT per group and trial type

	AX	AY	BX	BY
Mean accuracy (SD)				
Total	0.98 (0.01)	0.91 (0.08)	0.96 (0.08)	0.97 (0.06)
Proactive	0.98 (0.01)	0.87 (0.08)	0.97 (0.03)	0.97 (0.04)
Intermediate	0.99 (0.01)	0.97 (0.03)	0.97 (0.03)	0.98 (0.02)
Reactive	0.98 (0.02)	0.97 (0.03)	0.86 (0.19)	0.94 (0.14)
Mean RT (SD)				
Total	438 (104)	583 (117)	409 (163)	412 (152)
Proactive	408 (73)	561 (109)	366 (114)	375 (120)
Intermediate	475 (121)	596 (108)	461 (184)	454 (175)
Reactive	502 (137)	652 (135)	505 (229)	495 (182)

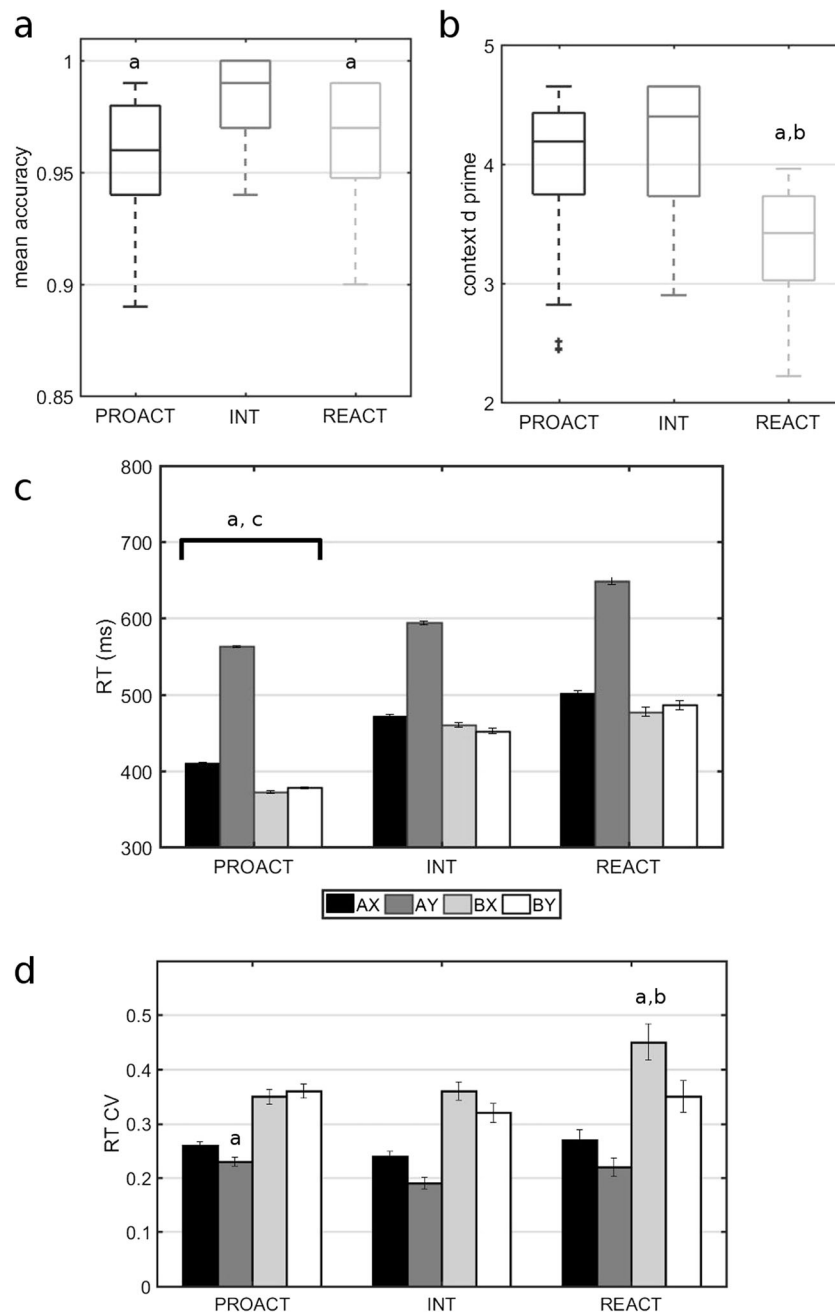


Fig. 2 Behavioral results. **a**) accuracy; **b**) context- d' ; **c**) mean reaction time (RT); **d**) coefficient of variation of RT. Subindexes: **a**: significantly different from INT group; **b**: significantly different from PROACT group; **c**: significantly different from REACT group

REACT group showed overall longer latencies (main effect of group: $F(2,442) = 3.39$, $p = 0.04$).

Blinks

The number of blinks during the delay period was significantly larger after B than A cues across groups (Fig. 5; Wilcoxon paired test, $Z = 5.18$, $p < 0.001$). We found no significant differences between groups for A or B cues. The number of blinks in the probe period

did not differ across conditions or groups. For a display of the proportion of blinks per condition and group, see Figure S7.

The latency to the first blink after the cue was shorter for A than B cues (Table 4; $T = 8.98$, $p < 0.001$), with no differences between groups. After the probe, the blink latency was longer for AY trials than other trials (main effect of condition: $F(2,414) = 21.68$, $p < 0.001$). No differences between groups were found in the probe period.

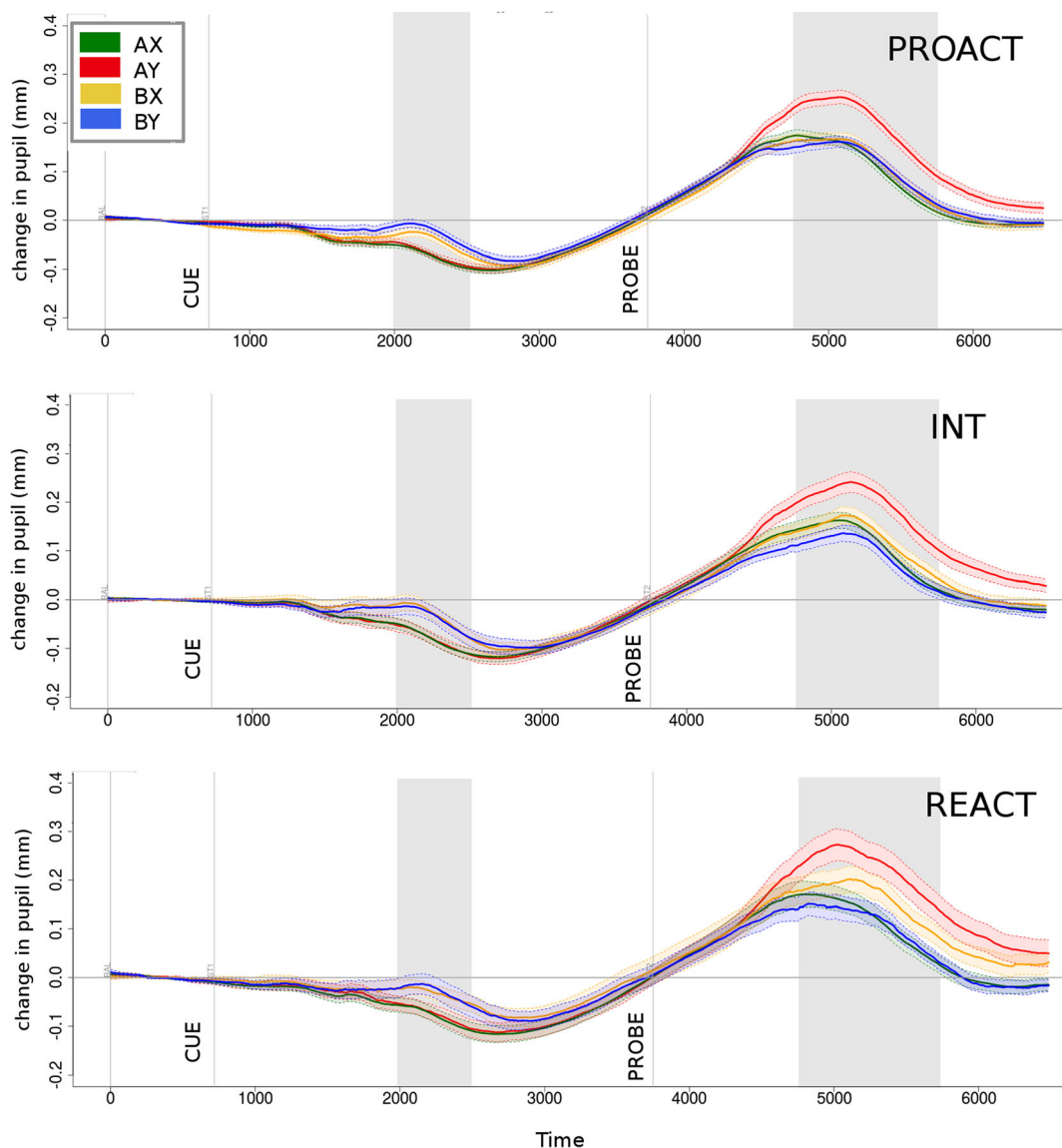


Fig. 3 Pupil change (mm) from baseline for the different trial types in PROACT (top), INT (middle), and REACT (bottom) groups

Discussion

In the present study, we investigated ocular signatures of proactive and reactive control. By having a large data sample and a task that allowed us to categorize the tendency of individuals for one or the other control strategy, we were able to reveal that a small group of healthy, young adults (~15%) behaved reactively. All participants allocated increased effort, as indexed by overall pupil dilations, and made more errors after a Y probe in the AY trials, consistent with the conflict associated to this trial. Notably, reactive participants also allocated effort to the X probe of BX trials. To the extent of our knowledge, this is the first study to reveal a pupillometric signature of the dynamics of reactive healthy adults in the AX-CPT task.

The AX-CPT is a well-suited task for studying the dynamics of cognitive control. Given that AX trials are highly

frequent, the A cue becomes largely predictive of an X probe and, therefore, of a target response. Similarly, B cues are predictive of a nontarget response. Proactive control is associated with low error rates in B trials and high error rates in AY trials. On the other hand, reactive behavior is associated with more target responses at the X probe of BX trials, possibly because individuals do not maintain the B cue context information in working memory. Previous studies have consistently shown that young adults behave proactively (Braver et al., 2001; Haarmann et al., 2005; Paxton et al., 2007; Rush, Barch, & Braver, 2006; Staub, Doignon-Camus, Bacon, & Bonnefond, 2014; Van Gerven et al., 2016). Remarkably, by applying the proactive behavioral index to our large sample of young, healthy adults, we found a group that behaved reactively. These individuals showed also slow reaction times, lower context sensitivity, and higher behavioral variability. Slow

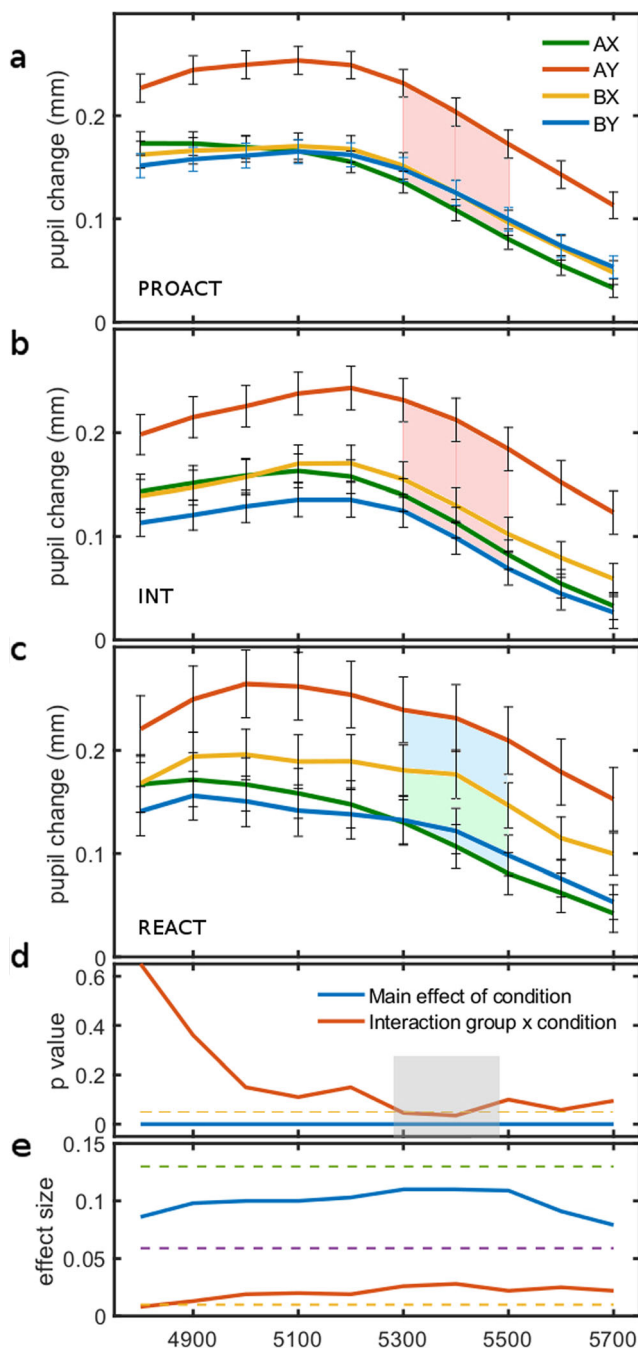


Fig. 4 a, b c: Pupil change from baseline in time intervals between 1 and 2 secs in the different groups. Shaded areas indicate significant difference in post-hoc tests in the interval of significant group by condition interaction (corrected for multiple comparisons): AY vs. AX, BX, and BY (red), AY vs. AX and BY (blue), and BX vs. AX and BY (green). **d**: *p* value for the indicated effects; grey shaded area indicates significant effects in the group by condition interaction, based on which the post-hoc tests were performed, dashed line corresponds to $p = 0.05$. **e**: Effect size for the main effect of condition and group by condition interaction, bottom, medium and top dashed lines for reference of small, medium, and large effect sizes

reaction times are consistent with the notion that reactive behavior implies a high-speed reactivation of information “on

Table 3. Latency of pupil peak in the probe period for the different trial types and groups

	Latency Pupil –Probe			
	AX	AY	BX	BY
Total	1188 (182)	1338 (204)	1196 (279)	1191 (258)
Proactive	1168 (183)	1315 (201)	1151 (286)	1174 (259)
Intermediate	1208 (180)	1372 (208)	1227 (240)	1192 (277)
Reactive	1238 (175)	1379 (207)	1336 (262)	1259 (212)

Mean (SD) of latency in ms

the fly” before taking the appropriate response. This is supported by the finding of an overall longer latency to peak of the pupil signal in the REACT group. This group showed also larger variability, possibly indicating the presence of more lapses of attention or less consistent use of strategy. In contrast, proactive participants showed short reaction times and high context sensitivity, displaying the most efficient behavior. In addition, we identified a group of people that showed equal amount of errors in AY and BX trials, therefore called “intermediate” group (INT). This group presented slower responses than PROACT group and higher accuracy than REACT group. One possibility is that these individuals are proactive participants that prioritized accuracy over speed and therefore do not show any trend in the proactive behavioral index, while they show the proactive pattern of slower AY responses and larger AY pupil dilation in relation to both reaction times and pupil responses. Overall, the results are consistent with a continuum in the way of performing within the population of healthy individuals, where some showed less consistent, more stimulus driven behavior while others showed a more consistent, goal driven behavior. We subsequently explored the signatures of these two modes of control.

The pupillometry analysis during the delay period showed larger pupil changes to B cue than A cue. This result replicates other pupillometry studies (Chiew & Braver, 2013, 2014) and supposedly reflects the cognitive processing of the nontarget cue (B): the inhibition of the preparation of the target response, including inhibition of the predictive value of a possible X probe, and the preparation of B associated nontarget response beforehand. Another possibility is that the increased activity after B cues with respect to A cues reflects attentional processes related to the detections of infrequent stimuli (Aron, Robbins, & Poldrack, 2014). Contrary to our original hypothesis, we did not find differences in $B > A$ between groups during the delay period. In previous work, the manipulation of motivation (i.e. increased reward) was found to lead to proactive behavior and increased $B > A$ difference during the delay period (Chiew & Braver, 2013, 2014). One possibility is that increased $B > A$ in that studies was due to a general increase of excitability in the brain (suggested by an overall

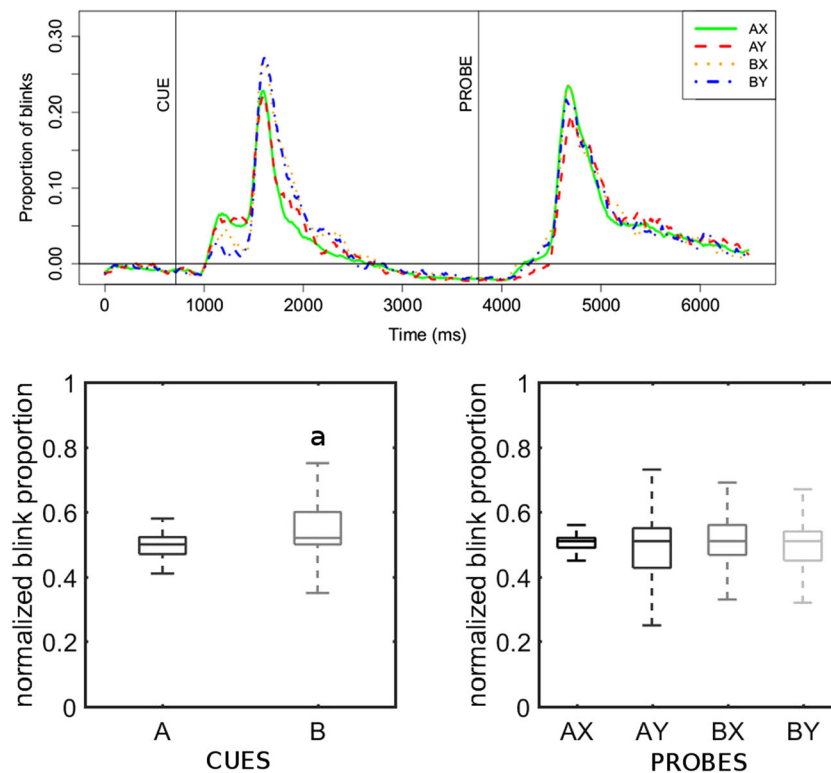


Fig. 5 Top: average blink waveforms per trial type (green: AX, red: AY, orange: BX, blue: BY). Bottom: proportion of blinks (normalized by total blinks per individual and trial number per condition) during cue (left) and probe (right) period. a: significant differences from A cues

increase in signal that spans to the probe period in the reward condition). A difference in $B > A$ was not found when comparing a proactive (8-year-old) to a reactive (3.5-year-old) population of children (Chatham et al., 2009) but an overall larger delay-related pupil size in proactive children. The results suggest that delay-related pupil change may not be a definite signature of proactive behavior in healthy adults performing the standard AX-CPT. In our study, reactive participants may have encoded the B cue correctly, but due to fluctuations in attention control or low memory capacity, they were not able to maintain this information (Unsworth & Robison, 2017).

During the probe period, Y probes of AY trials evoked the largest pupil response. A large AY effect may reflect the effort invested in inhibiting a frequent expected target response and choosing instead an infrequent unexpected non-target response. This inhibition may cause the long reaction times to

these trials. All groups showed the increased AY pupil response. While proactive and intermediate participants did not show differences in the probe-related pupil response between AX, BX, and BY trials, reactive participants showed a larger pupil response in BX relative to BY trials. This result agrees with the findings of Chatham et al. (2009) when comparing reactive vs. proactive children and may indicate the dynamic retrieval of the B cue in order to perform the correct nontarget response.

The lack of differences in pupil responses between groups during the cue period and the increased BX pupil in the probe period in reactive participants may be alternatively interpreted as follows: Reactive participants can encode the cue, but the X probe, which had high familiarity or higher binding to the A cue (van Wouwe, Band, & Ridderinkhof, 2009), reactivated the target response, which then had to be actively inhibited in reactive participants (Irlbacher et al., 2014). This reasoning leads to the conclusion that reactive participants suffer more interference from familiarity. This is consistent with results using behavioral models where a reactive manipulation was related to more “noise in the probe” (Lositsky, Wilson, Shvartsman, & Cohen, 2015). Thus, because AY trials imply a reactive response (in the sense that it acts as a No-Go trial), the mechanisms of errors underlying the AY and BX responses may express different aspects of reactive control. AY probe-related pupil signals may reflect inhibition of a prepared target response, and AY failures demonstrate strong

Table 4 Latency of blinks during the delay and probe periods for the different conditions

	Blink latency—cue/delay			
	A	B		
Total	786 (146)	855 (164)		
	Blink latency—probe			
	AX	AY	BX	BY
Total	1013 (481)	1113 (491)	1016 (471)	1020 (473)

Mean (SD) of latency in ms

proactive preparation of a target response, which arguably occurs more in proactive participants. In contrast, the BX probe-related pupil signal may reflect inhibition of a highly familiar stimulus-response association encoded in working memory, the potentially interfering value of which was not totally inhibited during the cue period. In both cases, pupil dilation appears to have been associated with inhibition of inappropriate motor responses.

Many studies have shown that interindividual variability within group may underlie differences in cognitive control. For instance, high working memory capacity (Heitz, Schrock, Payne, & Engle, 2008), high fluid intelligence (Burgess & Braver, 2010; Van Der Meer et al., 2010), high self-motivation (Savine, Beck, Edwards, Chiew, & Braver, 2010), or low anxiety (Krug & Carter, 2012) appear to play a role for the preference of proactive behavior. Other studies indicate that efficient responders, low-interference individuals, or high-capacity individuals are able to invest more effort, as measured by pupillometry (Heitz et al., 2008; Unsworth & Robison, 2017) or fMRI (Wolf, Walter, & Vasic, 2010). Because we did not collect either personality or neuropsychological measures of our sample, we can only speculate based on previous evidence that reactive participants might have had reduced working memory capacity or a higher threshold of self-motivation to implement proactive behavior. In a population of young, healthy adults, working memory capacity, personality traits, and self-motivation may underlie the differently preferred behaviors in a continuous manner. Future studies may help to shed light on this question.

The present study extends our knowledge on cognitive control and its physiological correlates. Previous work on pupillometry found that increased control, either proactive or reactive, was related to increased pupil change (Bijleveld et al., 2009; Satterthwaite et al., 2012; Siegle et al., 2008). Pupil changes have been shown to track locus coeruleus–norepinephrine (LC-NE) system activity (Alnæs et al., 2014; Joshi et al., 2016; Kihara, Takeuchi, Yoshimoto, Kondo, & Kawahara, 2015). This neuromodulatory system facilitates and enhances attentional processing (Aston-Jones and Cohen, 2005a, b; Berridge & Waterhouse, 2003; Corbetta, Patel, & Shulman, 2008; Sara & Bouret, 2012), and its phasic effect is fast enough to have effects on response selection after a cue that engages its activity (Aston-Jones, Foote, & Segal, 1985). Changes in LC activity correlated with changes in behavioral performance (Usher, Cohen, Servan-Schreiber, Rajkowski, & Aston-Jones, 1999). LC activity is partly driven by the anterior cingulate cortex (ACC) activity (Cohen, Botvinick, & Carter, 2000) through its direct connections (Rajkowski, Lu, Zhu, Cohen, & Aston-Jones, 2000). Activity in ACC and pre-SMA as measured by fMRI was observed on tasks requiring cognitive control (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004) and paralleled the results observed in pupillometry (Satterthwaite et al., 2012).

Previous fMRI studies on the AX-CPT showed that different dynamics in the same attentional areas supported both proactive and reactive control. Prefrontal cortex shifted from cue-related activity in proactive participants to probe-related activity in reactive participants during AX-CPT trials (Edwards, Barch, & Braver, 2010). Event-related potential (ERP) studies suggest that proactive control is related to sustained frontal modulation (Czernochowski, 2015; West & Schwarb, 2006) while reactive control may be related to a negative potential referred to as Ninc (Czernochowski, 2015). It would be interesting to observe a relation between phasic AY and reactive-BX probe-related pupil activity and the Ninc potential in a concurrent EEG-pupillometry setup. Our results suggest that norepinephrine system might play a role in the different computations underlying proactive and reactive strategies.

Task-evoked blinks have been related to phasic dopamine neuromodulatory activity and have been suggested to reflect dopaminergic modulation of cognitive control (Eckstein et al., 2017; van Bochove et al., 2013). Interestingly, we observed a larger number of blinks after B cues than A cues during the delay period. This result agrees with previous work that found $B > A$ effect in blink proportion, although it did not reach significance (Wascher, Heppner, Möckel, Kobald, & Getzmann, 2015). More blinks to B than A cues may reflect within-trial attention-shift towards the nontarget response (Nee and Brown, 2012). Some previous work suggested that DA phasic activity relates to “go” processes “that increase the selective updating of contextual features that are relevant for ongoing goal-directed behavior” (Westbrook & Braver, 2016). In the probe period, we found no differences between trial types, indicating that the different probes may have not imposed different demands on the updating of working memory (Rac-Lubashevsky et al., 2017). While the underlying processes for the pattern of blink rates within each condition may be complex, a clear finding of our analysis is an absence of differential modulation of task-evoked blinks for the different groups, suggesting that dopamine-related updating is not involved in the differences between the different types of behavior.

In the analysis of blink latencies, we found longer latencies after B cues in the delay period. This result agrees with the findings of Wascher et al. (2015). We found longer latencies after Y probes of AY trials in the probe period, similar to Wascher et al. (2015), who additionally report longer latencies after X probes of AX trials. One possible source for this difference is that the AX trials were much less frequent in their experiment (40%), which also caused a lower accuracy in AX trials. It is likely then that blinks are performed after an evaluation of a stimulus is completed, followed by a disinhibition phase (Bonneh, Adini, & Polat, 2016; Wascher et al., 2015). In the AX-CPT, blinks may reflect the intensity of processing after

the specific stimuli, which is larger for B and Y of AY probes. Given that we found no differences between groups, we conclude that dopamine plays a role in cognitive control, presumably involving gating processes, and that these processes may be similar across the proactivity tendencies.

Several points warrant discussion. First, faster responses in AY in REACT participants compared with PROACT would have been expected. That is, if they reacted to the probes, a Y would elicit a fast nontarget response, whereas to an X probe, the cue would need to be retrieved and in turn the response would be slow. We found a similar pattern of RTs in all groups for the different trial types, with only a generalized slowing in REACT participants. This finding is consistent with previous literature, where reactive groups also present the AY slowing (Chatham et al., 2009; Edwards et al., 2010; Lesh et al., 2013; Lositsky et al., 2015; Paxton et al., 2007) and suggests that AY and/or BX accuracy may be a better indicator of control mode. Second, a proactive behavioral index was calculated based on accuracy to categorize participants. Previous work has employed proactivity indexes based on accuracy, RTs or both (Braver et al., 2009). We put forward a number of reasons for the categorization based on accuracy PBI: first, the establishment of groups is more straightforward from an accuracy-based index, where negative values signal tendency to reactive behavior and positive values, to proactive behavior; second, accuracy and RTs are likely to reflect different neural processes, and therefore it is not straightforward to combine them; third, accuracy-based and RT-based PBIs are correlated (Pearson rho: 0.238, $p = 0.002$). The supplementary analysis using PBI as a continuous variable gave similar results than the group-based analysis, supporting the idea that the accuracy-based PBI reflects the continuum in strategy tendencies of control. Finally, the reliability of psychometric measures has limitations (Cooper, Gonthier, Barch, & Braver, 2017). We examined the consistency in the classification of individuals into proactivity groups and found it reasonably high. The pupil dilation measures have been shown to present high reliability in control participants (Farzin, Scaggs, Hervey, Berry-Kravis, & Hessel, 2011; Unsworth & Robison, 2017), even across intervals of several years (Alnæs et al., 2014). Less is known about the reliability of eye blink frequencies and latencies as indices of cognitive control processing, although the consistency between our results and those of a previous AX-CPT study (Wascher et al., 2015) suggests that eye blinks do provide reliable data in the present context.

In the present work, we employed the standard version of the AX-CPT. Several manipulations of the standard task have been employed in different studies, such as

variations in the proportion of the different trial types, or inclusion of a fifth trial type, such as the no-go AX trials (Braver et al., 2009) and “CX trials” (Richmond, Redick, & Braver, 2015), which among other effects induce more proactive or reactive control modes in participants relative to the standard version of the task. These manipulations may serve to investigate the question of whether the ocular signatures reported in this work also reflect within-subject dynamical changes in cognitive control strategies. If this is the case, the ocular signatures can be regarded as indicators of the brain mechanisms that underlie proactive or reactive behavior both in a state- and trait-related manner. This would have significant implications for the study of neuropsychiatric conditions where cognitive control is compromised.

Several researchers have proposed that individuals compare incoming stimuli with representations kept in working memory in an online manner (Zacks, Speer, Swallow, Braver, & Reynolds, 2007). In this way, they can rapidly adapt their behavior on the basis of this comparison when in the presence of conflict. Cognitive conflict is in general related to an increased pupil size (Laeng et al., 2011; Van Steenbergen & Band, 2013). In addition, proactive control sets the neural excitability to minimize conflict whenever it is possible. Proactive and reactive behaviors may rely on different neural substrates in the medial frontal cortex. It is known that the LC receives input from the ACC in the medial frontal cortex (Aston-Jones and Cohen, 2005a, b) and may act as a useful marker to study the dynamics of cognitive control with the AX-CPT in healthy and psychiatric populations.

In conclusion, all groups had more dilated pupils and higher blink rates for B than A cues and also more dilated pupils to probes in AY trials. However, we found distinctive ocular signatures for proactive and reactive subgroups within a sample of young healthy individuals. Reactive participants exhibited relatively increased dilations to BX trial probes, suggesting a probe-induced retrieval of the relevant context or inhibition of the response to a stimulus that is strongly associated with the target identity.

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