Neuromodulation of cognitive-behavioral control

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Chapter Two

Color vision predicts processing modes of goal activation during action cascading

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Abstract

One of the most important functions of cognitive control is action cascading: the ability to cope with multiple response options when confronted with various task goals. A recent study implicates a key role for dopamine (DA) in this process, suggesting higher D1 efficiency shifts the action cascading strategy toward a more serial processing mode, whereas higher D2 efficiency promotes a shift in the opposite direction by inducing a more parallel processing mode (Stock, Arning, Epplen, & Beste, 2014). Given that DA is found in high concentration in the retina and modulation of retinal DA release displays characteristics of D2-receptors (Peters, Schweibold, Przuntek, & Müller, 2000), color vision discrimination might serve as an index of D2 efficiency. We used color discrimination, assessed with the Lanthony Desaturated Panel D-15 test, to predict individual differences (N = 85) in a stop-change paradigm that provides a well-established measure of action cascading. In this task it is possible to calculate an individual slope value for each participant that estimates the degree of overlap in task goal activation. When the stopping process of a previous task goal has not finished at the time the change process towards a new task goal is initiated (parallel processing), the slope value becomes steeper. In case of less overlap (more serial processing), the slope value becomes flatter. As expected, participants showing better color vision were more prone to activate goals in a parallel manner as indicated by a steeper slope. Our findings suggest that color vision might represent a predictor of D2 efficiency and the predisposed processing mode of goal activation during action cascading.

Introduction

One of the most important functions of cognitive control is action cascading, that is the ability to cope with multiple response options when confronted with various task goals. In such a situation, successful action control would require efficient activation of and switching between different task goals in order to properly organize behavior. This can be achieved via distinct strategies that are thought to lie on a continuum; on the one end is a more serial processing mode in which the next task goal is activated only when the previous task goal has finished, and on the other end is a more parallel processing mode in which the next task goal is activated when the previous task goal is still active (Mückschel, Stock, & Beste, 2014; Verbruggen, Schneider, & Logan, 2008).

Neurobiological models of action selection indicate dopamine (DA) plays a key role in action cascading and individual differences in DA function might predict the preferred (i.e., serial vs parallel) action cascading strategy. One particularly prominent model is the dual-state theory, which proposes that different DA receptors in the prefrontal cortex (PFC) exert opposite effects on activity states and cognition (Durstewitz & Seamans, 2008). This model, which is supported by a wealth of behavioral and electrophysiological data, suggests the dynamics of PFC activity lie on a continuum ranging from (i) a D1-dominated state that inhibits spontaneous but enhances task-related neural firing, thereby favoring robust online maintenance of representations, to (ii) a D2-dominated state that facilitates spontaneous neural firing and shifting between activity patterns, thereby allowing fast switching between representations. The dual-state theory has been successfully applied to action cascading performance, supporting the idea that different DA receptors shift the action cascading strategy into different directions: individuals with a genetic predisposition towards higher D1 efficiency demonstrated a more serial, step-by-step processing mode, whereas higher D2 efficiency predicted a more parallel, overlapping processing mode (Stock et al., 2014). Taken together, these findings suggest an individual with higher D1 efficiency is predisposed to a more serial action cascading strategy due to a stable but potentially rigid PFC processing state, whereas an individual with higher D2

efficiency is predisposed to a more parallel strategy due to a flexible but interference-prone PFC state.

In the present study we investigated whether individual differences in DA function could indeed predict the processing mode of goal activation in action cascading, using color vision (CV) discrimination as an indirect but low-cost and non-invasive marker of DA function. The retina is rich in DA and dysregulated retinal DA function is associated with impaired CV (Brandies & Yehuda, 2008). This is illustrated by populations thought to suffer from dysregulated DA function and who demonstrate impaired CV, such as patients with Parkinson's disease (Büttner et al., 1995; Büttner, Patzold, Kuhn, Müller, & Przuntek, 1994; Kertegle et al., 2010; Müller, Kuhn, Büttner, & Przuntek, 1997; Oh et al., 2011; Pieri, Diederich, Raman, & Goetz, 2000; Price, Feldman, Adelberg, & Kayne, 1992), attention-deficit/hyperactivity disorder (Banaschewski et al., 2006; Soyeon Kim et al., 2014; Roessner et al., 2008), Gilles de la Tourette syndrome (Melun, Morin, Muise, & DesRosiers, 2001), cocaine users (Desai, Roy, Roy, Brown, & Smelson, 1997; Hulka, Wagner, Preller, Jenni, & Quednow, 2013), and in normal aging (Jackson & Owsley, 2003; Melun et al., 2001). One study so far has demonstrated CV can predict DA-related cognitive performance. Specifically, CV in healthy young adults predicted individual differences in the cognitive control of response conflict, with better CV predicting reduced response conflict in an auditory Simon task (Colzato, Sellaro, Hulka, Quednow, & Hommel, 2014).

Although the exact nature of the link between CV and DA-related performance is unclear, the modulation of DA release in the retina displays characteristics of D2 receptors (Peters et al., 2000), raising the possibility that CV can predict individual differences in performance related to D2 efficiency. Consistent with this idea, administration of D2-like receptor antagonists leads to impaired retinal function (Fornaro, Calabria, Corallo, & Picotti, 2002) as observed in schizophrenia (Shuwairi, Cronin-Golomb, McCarley, & O'Donnell, 2002). Additionally, cocaine treatment decreases D2 receptor function (Madhavan, Argilli, Bonci, & Whistler, 2013), leading to increased cocaine craving (Volkow et al., 2006) which in turn is associated with CV

impairment (Roy, Roy, Smelson, Brown, & Weinberger, 1997; Roy, Smelson, & Roy, 1996). Although these findings may point towards a particular role of D2 receptors in CV, it should be acknowledged that D1 receptors likely also play a role (Brandies & Yehuda, 2008) and to date it has been difficult to disentangle the exact contributions of D1 and D2 receptors. However, the aforementioned study relating action cascading performance to gene polymorphisms indicated that D1 and D2 exert opposite effects on the processing mode of goal activation (Stock et al., 2014). Hence, the present study can provide further insight into the role of D1 and D2 receptors in CV by comparing the relationship between CV and action cascading to the previous findings on action cascading and gene polymorphisms. Specifically, assuming CV indeed indicates D2 function and given that increased D2 efficiency is associated with a more parallel processing mode in action cascading (Stock et al., 2014), we would expect individuals with better CV to demonstrate a more parallel action cascading strategy. In contrast, if CV were to primarily reflect D1 receptor function then we would expect better CV to predict a more serial strategy. Because previous studies indicate DA function might be particularly related to CV in the blue-yellow domain (Banaschewski et al., 2006; Colzato, Sellaro, et al., 2014; Desai et al., 1997; Hulka et al., 2013; Melun et al., 2001; Roessner et al., 2008), we also investigated whether blue-yellow CV in particular predicts the action cascading strategy.

To assess action cascading performance we used the stop-change paradigm (Verbruggen et al., 2008), an established diagnostic measure of action cascading. In this task participants need to respond as fast as possible to a GO stimulus, but in some trials a STOP signal, presented after a variable delay, indicates the need to withhold this response. A subsequent CHANGE signal indicates the new response rule that must be used to respond to the GO stimulus. In this task it is possible to calculate an individual slope value for each participant that estimates the degree of overlap in activation of the STOP and CHANGE goal. When the STOP process has finished at the time the CHANGE process is initiated, the slope value becomes flat and indicates more serial processing. In contrast, when the STOP process has not yet finished at

the time the CHANGE process is initiated, the slope value becomes steeper and indicates more parallel processing. In line with our expectations, we predicted participants with better CV to be prone to activating goals in a parallel manner and thus demonstrate a steeper slope.

Methods

Participants

Eighty-five undergraduate students from Leiden University (71 females, 14 males, mean age 20.00 years, standard deviation 2.09) were recruited to participate in this study for partial course credit. Participants were screened individually using the Mini International Neuropsychiatric Interview (MINI), a short, structured interview of approximately 15 min that screens for several psychiatric disorders and drug use (Sheehan et al., 1998) and is typically used in clinical and cognitive research (Colzato, de Bruijn, & Hommel, 2012; Colzato, van den Wildenberg, & Hommel, 2013). Participants were included if they met the following criteria: (i) between 18 and 30 years; (ii) no personal or family history of neurological or psychiatric disorders; (iii) no history of substance abuse or dependence; (iv) no chronic or acute medication; (v) no known color blindness; and (vi) females were actively taking hormonal contraceptives.

Informed consent was obtained from all participants upon arrival in the lab. The study conformed to the ethical standards of the Declaration of Helsinki and the protocol was approved by the local ethical committee (Leiden University, Institute for Psychological Research).

Lanthony Desatured Panel D-15 Test

In order to test CV discrimination we used the Lanthony Desaturated Panel D-15 test. This test comprises a fixed reference cap and 15 changeable color caps that need to be ordered in sequence. The color caps are of low saturation (decreased chroma) and increased lightness. The test was carried out under a daylight fluorescent lamp with an illumination of 1400 lx. Participants did not have a time limit but typically took at most 5 min to complete the test.

Quantitative scoring was based on the color scoring method proposed by Geller (2001) and resulted in a total color distance score (TCDS). A perfect TCDS score of 56.41 indicates all caps are arranged in the correct order and higher scores indicate CV impairment.

Qualitative scoring was based on the method outlined in (Hulka et al., 2013), which comprises plotting the individual participant's cup order on a template that describes a hue circle containing four reference axes. These axes are named protan, deutan, tritan and tetartan, and reflect the red, green, blue and yellow color domains respectively. Cap reversals that are parallel to one of the axes indicate an error in the respective color domain. Single cap inversions (e.g. 1-3-2-4-…) are classified as minor errors or normal confusion, whereas cap reversals spanning two or more caps are considered major errors. Two or more major errors indicate a CV disorder, which was classified based on Verriest's classification (Verriest, 1963): type I reflects CV impairment along the red-green axes; type II is a combined impairment of the red-green and blue-yellow axes; type III reflects impairment along the blue-yellow axes; type IV is diagnosed when no clear pattern can be determined.

Stop-Change Paradigm

The paradigm was adapted from Steenbergen, Sellaro, Stock, Beste, & Colzato, 2015 and Verbruggen et al., 2008, and was previously used to investigate the relation between D1 and D2 efficiency and action cascading (Stock et al., 2014). For an illustration of the task, see Figure 1.

The task consisted of a total of 864 trials divided in six equally sized blocks. Throughout each trial a white rectangle of 20 x 96 mm was presented on a black background. Within the rectangle were three horizontal reference lines (line thickness 1 mm, width 13 mm) that divided four vertically aligned circles (diameter 7 mm). At 250 ms after the onset of each trial one of the circles was filled white, thus becoming the GO target stimulus. In 67% of trials (the GO condition) participants needed to indicate whether the GO stimulus was located above or below the middle reference line, using a button press with the right middle finger to indicate "above" and the right index finger to indicate

"below". The GO stimulus was either response terminated or disappeared after 2500 ms had elapsed. If a response had not been given at 1000 ms after GO stimulus onset, the word "Quicker" was presented above the rectangle until the participants responded.

The remaining 33% of trials comprised the stop-change (SC) condition, which started with presentation of the GO stimulus but a STOP signal was also presented after a variable stop-signal delay (SSD). The STOP signal comprised the border of the rectangle turning red, which indicated to participants to try and withhold their right-handed response. Every STOP signal was followed by a CHANGE signal, which was a sine tone presented via headphones for 100 ms at 75 dB SPL and could be either high (1300 Hz), medium (900 Hz), or low (500 Hz) in pitch. This CHANGE signal indicated which of the three reference lines had to be used on the current trial to evaluate the GO stimulus' location (above vs below). The high, medium and low tones indicated the upper, middle and bottom reference lines respectively. All three lines were used with equal frequency. The CHANGE response had to be carried out with the left hand, using a button press with the left middle finger to indicate "above" and the left index finger to indicate "below". Crucially, in half of the SC trials the stimulus onset asynchrony (SOA) for the CHANGE signal was set to 300 ms (SCD300 condition), in the other half the STOP and CHANGE stimuli were presented simultaneously (i.e., SOA of 0 ms; SCD0 condition). If reaction time (RT) to the CHANGE signal was longer than 2000 ms, the word "Quicker" was presented above the rectangle.

After each SC trial, the SSD was adapted using a staircase algorithm to yield an approximate 50% of successfully inhibited GO responses (Logan & Cowan, 1984). The SSD was initially set to 250 ms and after an entirely correct SC trial (successful inhibition of the initial GO response before the CHANGE signal and subsequent correct left-handed response), the SSD was lowered by 50 ms. If these criteria were not met, the SSD was increased by 50 ms. This was constrained such that the SSD never became lower than 50 or higher than 1000 ms. This procedure allows an accurate estimate of the stop-signal reaction time (SSRT), an index of the duration of the covert response inhibition process

(Logan & Cowan, 1984). After each trial, a fixation cross was presented in the middle of the screen for the duration of the inter-trial interval (ITI; fixed duration 900 ms). All conditions were presented in a random order and participants were instructed to respond as fast and accurate as possible.

To estimate the degree of overlap between activation of the STOP goal and the CHANGE goal, we calculated an individual slope value for each participant (Stock et al., 2014; Verbruggen et al., 2008). This measure reflects the difference in RT between the SCD0 and SCD300 condition divided by the difference in SOA (i.e., -300). Following the line of argumentation in (Stock et al., 2014), RT is expected to be higher in the SCD0 condition, resulting in a typically negative slope that becomes steeper as the difference in RT increases. In brief, assuming that participants are able to resolve the stopping process at least partly during the SCD in the SCD300 condition, this promotes a more serial processing mode of the STOP and CHANGE goals. On the other hand, in the SCD0 condition participants have the option of either processing these goals serially or in parallel. If processed in parallel, there is a risk of interference between the two task goals that results in increased RT in the SCD0 relative to the SCD300 condition and thus leads to a steeper slope (for further elaboration, see Stock et al., 2014; Verbruggen et al., 2008).

Procedure

Participants arrived in the lab to be tested individually. After informed consent was obtained they completed the D-15 test to measure CV, which took on average 5 min. Participants then practiced the stop-change before completing the real task in approximately 45 min. Subsequently they were debriefed, rewarded with partial course credit and thanked for their participation.

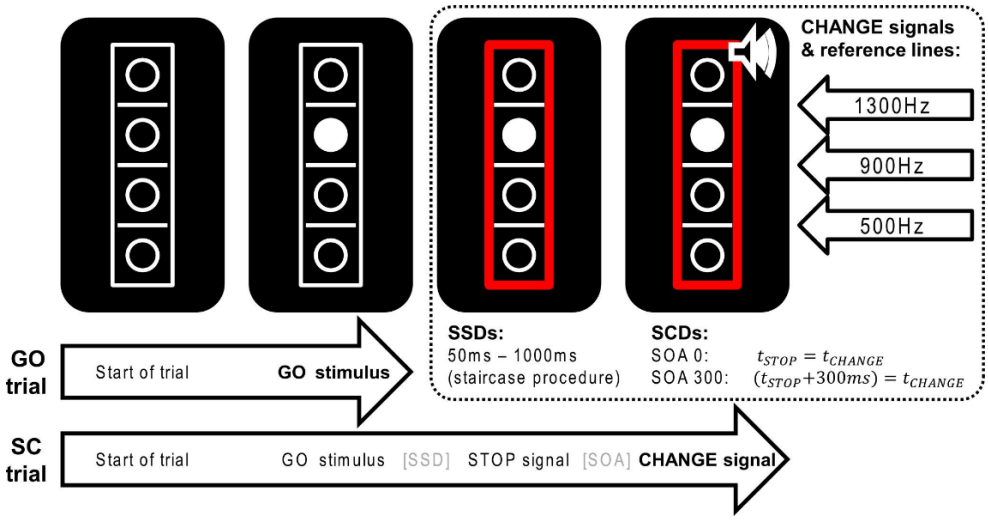

Figure 1. Schematic illustration of the stop-change (SC) paradigm. GO trials end after the first response to the GO stimulus, whereas SC trials end after the first response to the CHANGE signal. The stop-signal delay (SSD) was adjusted on a trial-by-trial basis using a staircase procedure. The stop-change delay (SCD) was set to either 0 or 300 ms, divided randomly and equally over all SC trials. As illustrated on the right, three tones of distinct pitch indicated the new reference line on SC trials. Figure adapted from Steenbergen, Sellaro, Stock, Beste, & Colzato, 2015.

Statistical analysis

For the behavioral data of the stop-change task, we first calculated individual mean RT separately for the three conditions (GO, SCD0, SCD300) and regardless of accuracy. Then for each condition we excluded trials with errors or RT above or below 2 standard deviations of the individual's mean RT in that condition. The SSRT was then calculated by subtracting the participant's mean SSD from the mean RT in the GO condition. Lastly, the individual slope was calculated by subtracting mean RT in the SCD300 from mean RT in the SCD0 condition and dividing the difference by -300. This results in a slope value that typically but not necessarily lies between 0 and -1, with lower values indicating more parallel processing.

To assess whether CV predicts a more serial or parallel processing mode of goal activation while accounting for a potentially skewed distribution of TCDS, we computed Spearman correlation coefficients between the TCDS and slope values. To determine whether impairment in the blue-yellow domain in particular predicts action cascading strategy, we investigated whether participants showing a specific blue-yellow disorder demonstrate a steeper slope than participants who did not show any CV disorder. For this comparison, a nonparametric one-tailed Mann-Whitney's U test was used to compensate for unbalanced sample sizes. To provide further insight in the relationship between CV and performance, we also computed Spearman correlation coefficients between TCDS, SSRT and mean RT in the GO, SCD0 and SCD300 conditions. A significance threshold of .05 was adopted for all statistical tests.

Results

For the quantitative analysis, TCDS (M = 76.50, SD = 12.28) was significantly positively correlated with the individual slope (M = -.62, SD = .23), $r_s(85)$ = .244, p = .025, see Figure 2. This indicates better CV (lower TCDS) is associated with a more parallel processing mode of goal activation (more negative, steeper slope). On the other hand, TCDS did not demonstrate significant Spearman correlations with mean RT in the GO (M = 629, SD = 202), SCD0 (M = 1138, SD = 295) or SCD300 (M = 952, SD = 310) condition or with SSRT (M = 280, SD = 65), all ps > .05. These null-findings suggest CV is not associated with a general change in response speed across conditions or a change in inhibitory control.

For the qualitative analysis, no participants demonstrated a type I disorder along the red-green domain, 1 demonstrated a type II disorder along the red-green and blue-yellow domain, 17 demonstrated a type III disorder along the blue-yellow domain, 4 demonstrated a type IV unclassified disorder, and 63 demonstrated only minor errors or 1 major error. No participants achieved a perfect score, i.e., all participants made at least a single minor or major error. Due to low sample sizes in the type II and IV disorder groups, we

only compared participants with a type III disorder along the blue-yellow axes with those who did not show any CV disorder. A nonparametric one-tailed Mann-Whitney's U test reveals no significant difference between the two groups in terms of slope, $U = 504$, $p = 0.356$, suggesting specific impairments in the blue-yellow domain do not explain the relationship between CV and the action cascading strategy.

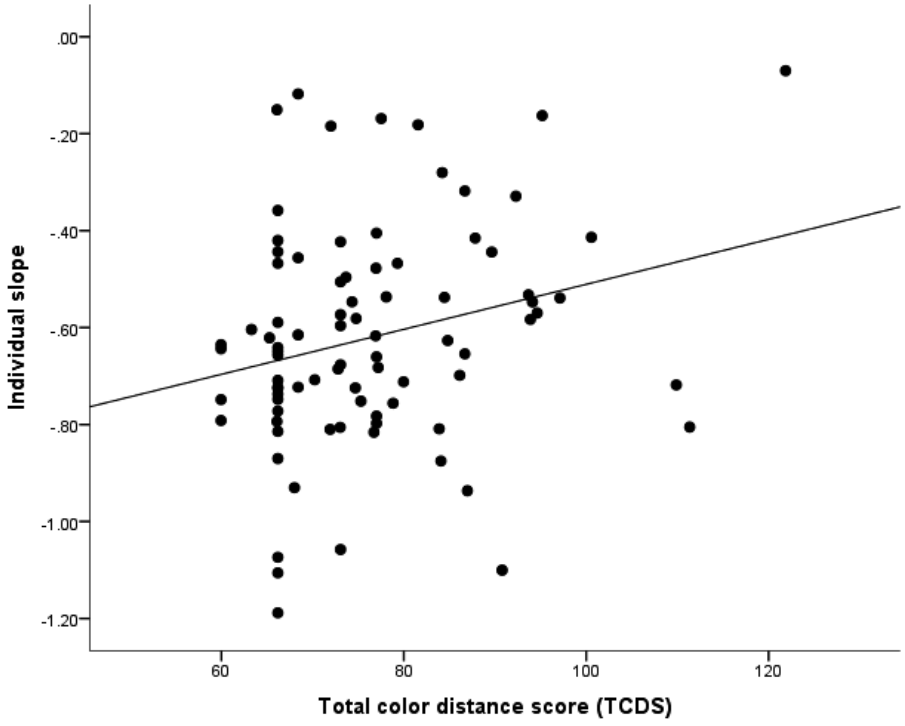

Figure 2. Scatter diagram of individual total color distance score (TCDS), with lower scores reflecting better performance, against the individual slope value from the stop-change paradigm, with lower scores indicating a more parallel processing mode.

Discussion

The present study investigated whether color discrimination can serve as an indirect marker of DA receptor function and therefore predict individual differences in the processing modes of goal activation in action cascading. So

far, little is known about the exact link between CV and DA, and it is likely that both D1 and D2 receptors contribute to visual function (Brandies & Yehuda, 2008). However, modulation of DA release in the retina resembles characteristics of D2 receptors (Peters et al., 2000), D2-like antagonists impair CV (Fornaro et al., 2002), and cocaine craving has been associated with both reduced D2 function (Volkow et al., 2006) and impaired CV (Roy et al., 1997, 1996). Although not conclusively, these findings support the hypothesis that CV might reflect D2 efficiency in particular. Given that increased D2 receptor efficiency has been shown to predispose individuals to a more parallel processing mode (Stock et al., 2014) and assuming CV reflects D2 function, we thus expected better CV to predict a more parallel action cascading strategy. Consistent with this hypothesis, individuals with lower TCDS (indicative of better color discrimination) were prone to activate goals in a parallel manner as indicated by a steeper slope value in the stop-change paradigm. This can be understood in light of the dual-state theory of PFC activation (Durstewitz & Seamans, 2008), which proposes increased D2 functioning (here indexed by CV) is associated with a more D2-dominated PFC activity state in which spontaneous firing is enhanced and representations are easily switched between. A downside of such a flexible activity state is that it may be particularly prone to interference when processing goals in parallel, resulting in delayed responses as compared to when goals are processed in a serial manner. Based on this reasoning, the present study provides converging evidence that CV is associated with D2 receptor efficiency, as indicated by a more parallel processing mode of goal activation.

Previous research has suggested CV in the blue-yellow domain is particularly indicative of DA function (Banaschewski et al., 2006; Colzato, Sellaro, et al., 2014; Desai et al., 1997; Hulka et al., 2013; Melun et al., 2001; Roessner et al., 2008), although this is not always the case (Barbato, Rinalduzzi, Laurenti, Ruggieri, & Accornero, 1994; Büttner et al., 1995; Shuwairi et al., 2002). However, our results do not indicate a relationship between specific blue-yellow impairment and stop-change performance. Although one might interpret non-specific CV impairment to reflect reduced

attentional performance rather than specific DA impairments (Bertrand et al., 2012), we argue an explanation of our data in these terms is unlikely. If CV performance in our sample indeed reflected only attentional performance then this impairment should have extended to general task performance, especially since the task is often experienced as very demanding. However, CV did not reliably predict RT in the three conditions (GO, SCD0, SCD300) separately, nor does this account explain why impaired CV would have predisposed individuals to activate goals in a more parallel rather than serial manner. Instead, it is important to note that only 17 out of 85 participants were classified as having a disorder in the blue-yellow domain. This suggests the present study has less than 50% power to detect an effect with a small to medium effect size, as might be expected based on the strength of the correlation between TCDS and the slope values. Hence it would be informative for future studies to revisit this issue with a sample that includes more individuals with a blue-yellow CV disorder. In this context, it is interesting to note that an age above 25 years was previously associated with a drop in CV performance, especially for the blue-yellow domain (National Research Council, 1981). Hence, it may be considered a strength of the present study that our sample barely meets this cut-off (mean age = 20.00 years, standard deviation = 2.09), suggesting age did not confound our results. Indeed, calculating a partial Pearson correlation between TCDS and slope value while controlling for age results in near identical results to those reported above ($r(85) = .249$, $p = .022$). Nevertheless, it would be interesting for future research to include a wider age range to see if the relationship between blue-yellow CV and action cascading is modulated by age.

As the present study is the first to indicate CV may predict performance related to D2-functioning in particular, it is important future studies seek to validate this link. For example, previous studies have found that spontaneous eye blink rate (EBR), another presumed marker of DA and possibly D2 function (Jongkees & Colzato, 2016), reliably predicts performance on the alternative uses task, a test of creativity that strongly depends on divergent thinking and the fast and flexible switching between representations (Akbari

Chermahini & Hommel, 2010, 2012). Similarly, EBR predicts performance on an attentional set-shifting paradigm in which enhanced flexibility promotes performance in one condition but the coinciding increased distractibility impairs performance in another condition (Dreisbach et al., 2005; Müller, Dreisbach, Brocke, et al., 2007; Tharp & Pickering, 2011). Given these results, it would be interesting to establish whether CV as predictor of a more D2-dominated PFC activity state is also associated with enhanced divergent thinking, cognitive flexibility and distractibility.

Moreover, our results indicate a large spread in action cascading performance in individuals with near-perfect CV, whereas this variation seems to decrease as CV worsens, see Figure 2. This may suggest the relationship between CV, action cascading, and presumably the predisposed PFC activity state, increases as CV is further impaired. This pattern would resemble the dedifferentiation hypothesis, put forward to explain the age-related increase in the correlation between performance on different cognitive tasks (Baltes, Cornelius, Spiro, Nesselroade, & Willis, 1980), or between sensory and cognitive functions (Baltes & Lindenberger, 1997). The hypothesis states this increased correlation may be the result of degradation of specialized neural structures due to a shared cause (e.g. loss of catecholamine function or white matter), leading these functions to share more variance in performance. The D2 system may be one factor in such dedifferentiation (cf. Papenberg, Lindenberger, & Bäckman, 2015), as this system is known to degrade with age and mediate related cognitive decline (Bäckman et al., 2000). In light of our results, we speculate CV as predictor of D2 function may predict dedifferentiation of cognitive functions even in healthy young adults. Hence, it would be interesting for future research to examine whether the correlation between performance on different cognitive tasks indeed increases as a function of CV.

Lastly, the present study has focused exclusively on color discrimination performance as a measure of visual function, but there are other conceivable measures such as visual acuity and motion discrimination that remain open to investigation. Given the widespread influence of DA on visual

function (Brandies & Yehuda, 2008), it would be interesting for future research to validate whether action cascading and other DA-driven processes are predicted only by color discrimination or instead relate to visual function in general.

To conclude, our results indicate CV discrimination in healthy humans is related to individual differences in DA function and D2 efficiency in particular. Better CV predicted a more parallel processing mode of goal activation, consistent with a more D2-dominated PFC activity state. As such, this study is a first step towards elucidating the link between CV, DA and cognitive-behavioral performance.