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Note

Cannabis, cocaine, and visuomotor integration: Evidence for a role of dopamine D1 receptors in binding perception and action

Lorenza S. Colzato *, Bernhard Hommel

Leiden University, Institute for Psychological Research & Leiden Institute for Brain and Cognition, Leiden, The Netherlands

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Abstract

The primate cortex represents and produces events in a distributed way, which calls for a mechanism that integrates their features into coherent structures. Visuomotor integration seems to be driven by dopaminergic (DA) pathways but which subsystems are involved is currently unknown. The present study compared the impact of the recreational use of two drugs on visuomotor integration: cannabis, which primarily targets dopaminergic D1 receptors, and cocaine, which mainly targets D2 receptors. Our findings show that cannabis but not cocaine use affects the strength of the binding between task-relevant stimulus features and the accompanying response. In contrast, cocaine but not cannabis use eliminates the inhibition of return. The observed pattern suggests that visuomotor integration is driven by DA/D1, but not DA/D2 receptor systems.

Keywords: Binding problem; Visuomotor integration; DA/D1; Cannabis; Cocaine

The so-called binding problem derives from the question of how our brain is able to properly integrate the feature codes that belong to a given event (Treisman, 1996). There is increasing evidence that at least two neurotransmitter systems are involved in feature integration: the muscarinic–cholinergic system, which seems to be associated with perceptual binding (Colzato, Fagioli, Erasmus, & Hommel, 2005; Rodriguez, Kallenbach, Singer, & Munk, 2004), and the dopaminergic system, which seems to drive the integration of perceptual and action-related information (Schnitzler & Gross, 2005; Colzato, van Wouwe, & Hommel, 2007a,b). Colzato et al. (2007a) showed recently that the binding of visual and action features is increased by the presentation of positive-affect inducing pictures—which can be assumed to stimulate the dopaminergic system (Ashby, Isen, & Turken, 1999). Along these lines, Colzato et al. (2007b) observed a positive correlation between the strength of binding between visual and action features and spontaneous eyeblink rate—a marker of dopaminergic functioning (Blin, Masson, Azulay, Fondarai, & Serratrice, 1990).

1. Purpose of study

Although the available evidence consistently points to a role of DA in visuomotor binding, it remains unclear which DA subsystem is responsible. Indeed, positive affect and eyeblink rate are associated with both the DA/D1 and the DA/D2 receptor system (Ashby & Casale, 2003; Elsworth et al., 1991). Given that these two dopaminergic systems seem to be related to different and separable cognitive functions (DA/D1 is presumably involved in working memory: Sawaguchi & Goldman-Rakic, 1991; and DA/D2 in response inhibition and cognitive flexibility: Lee, Groman, London & Jentsch, 2007), it would be important to know which one is implicated in visuomotor binding.

The rationale underlying the present study was to compare the (long-term and not acute) impact of two drugs on visuomotor binding that differ with respect to the dopamine subsystem they affect. We used cannabis, which primarily impacts DA/D1 functioning, and cocaine, which mainly targets the DA/D2 system. Cannabinoid stimulates, through the cannabinoid CB1 receptor, the release of acetylcholine, norepinephrine, serotonine (Iversen, 2000) and in particular the firing of DA neurons (Diana, Melis, & Gessa, 1998; Gessa, Melis, Muntoni, & Diana, 1998) producing supranormal stimulation of DA/D1 receptors in the prefrontal cortex (PFC). In contrast, while the acute effect of cocaine is to increase

* Corresponding author at: Leiden University, Department of Psychology, Cognitive Psychology Unit, Postbus 9555, 2300 RB Leiden, The Netherlands.
E-mail address: colzato@fsw.leidenuniv.nl (L.S. Colzato).

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synaptic DA, serotonine, and noradrenaline levels by blocking the reuptake of these neurotransmitters (Meyer & Quenzer, 2005), the long-term use of cocaine is primarily to reduce the functioning of DA/D2 receptors in PFC (Volkow, Fowler, & Wang, 1999) and of DA release, inducing an hypodopaminergic state (Volkow, Fowler, Goldstein, & Wang, 2002). Given the relationship between DA/D1 functioning and working memory (Sawaguchi & Goldman-Rakic, 1991) and the connection between explicit binding processes and working memory (Sala & Courtney, 2007), we expected cannabis, but not cocaine to affect visuomotor binding.

As behavioral marker for feature-integration processes we adopted a variant of the task developed by Hommel (1998), which measures both visual–visual and visuomotor binding. Performance in such a task reveals interesting interactions between repetition effects: it is impaired in partial-repetition trials, that is, if one stimulus feature or the response is repeated while the other is not. These partial-repetition costs suggest that the stimulus and response features of S1 and R1 are still bound when facing response features of R2, so that repeating a given feature (response location) will retrieve the binding that the code of that feature has become a part of (Hommel, 1998). This creates conflict between the retrieved codes and those activated by the current R2, thus delaying reaction time and increasing error rates. Crucial for our purposes is that these partial-repetition costs can be taken to indicate visual–visual (e.g., integration of orientation and location stimulus feature) and visuomotor (e.g., integration of orientation stimulus feature and response feature) binding (Hommel, 2004).

Given the previous observation that dopaminergic drugs selectively impact bindings between task-relevant stimulus and response features (Colzato et al., 2007a,b), which presumably reflects the important role of dopamine in executive functioning (Braver & Cohen, 2000), we expected that a hypothetical effect of cannabis would be particularly (or only) visible in the integration of the task-relevant stimulus and response features (orientation and response location in our case). With regard to cocaine, we expected no impact on visuomotor binding but a replication of our previous observation that long-term use of this drug eliminates the otherwise robust inhibition of return (IOR) effect (Colzato & Hommel, 2007)—the finding that people respond slower to stimuli appearing at a just-attended location (Posner & Cohen, 1984).

2. Methods

2.1. Participants Experiment 1 (cannabis study)

Twenty-four young healthy adults served in partial fulfillment of course credit or for a financial reward, and they constituted the two groups: cannabis users and drug-naive controls. Informed consent was obtained from all participants after the nature and possible consequences of the study were explained to them; the protocol was approved by the local ethical committee (Leiden University Institute for Psychological Research). Participants in the two groups were matched for race (100% Caucasian), age, sex and IQ (measured by Raven's Standard Progressive Matrices [SPM]). Demographic and drug use statistic are provided in Table 1.

Subjects were selected with the Mini International Neuropsychiatric Interview (M.I.N.I.; Lecrubier et al., 1997), a brief diagnostic tool that screens for several psychiatric disorders including, among others, depression, mania, obsessive–compulsive disorder. We made sure that the users met the following criteria: (1) subjects were "cannabis only" users; (2) a weekly consumption of cannabis (4–14 joints) for a minimum of 2 years; (3) no Axis 1 psychiatric disorder (DSM-IV); (4) no clinically significant medical disease; (5) no use of medication. Non-user controls met the same criteria except that they reported no history of past or current cannabis use. Participants were asked to refrain from taking drugs for 2 days and from all caffeine containing foods and beverages for 12 h prior to the experimental sessions, not to consume alcohol on the night before the experimental session and have a normal night rest. Subjects' compliance was encouraged by taking a saliva sample (not further analyzed) at the beginning of the session. All reported having normal or corrected-to-normal vision, and were not familiar with the purpose of the experiment. One cannabis user was excluded because it turned out that he did not comply with the instructions given by the experimental protocol consuming cannabis the night before the experiment.

Table 1
Demographic characteristics and self-reported use of cannabis

Sample	Cannabis-free controls	Cannabis users	Significant
N (M:F)	12 (10:2)	12 (10:2)	ns
Age (years)	21.8 (3.2)	22.6 (3.9)	ns
Raven IQ	120.7 (3.4)	125.1 (3.6)	ns
Lifetime exposure (joints)		3610 (2768)	
Weekly joints		8.4 (3.4)	
Age of onset		15.3 (0.9)	
Years of cannabis consumption		7.36 (4.4)	

ns, non-significant difference; Raven IQ, IQ measured by means of the Raven progressive matrices.
*$p < 0.05$.
**$p < 0.01$.

2.2. Participants Experiment 2 (cocaine study)

Twenty-four young healthy adults served in partial fulfillment of course credit or for a financial reward, and they constituted the two groups: recreational users of cocaine and cocaine-free controls. We matched and selected the subjects using the same diagnostic tool (by means of the M.I.N.I.) and criteria as in Experiment 1, except that we selected users if they consumed cocaine on a monthly basis (1–4 g)[1] by snorting route for a minimum of 2 years. Again, the cocaine-free controls met the same criteria except that they reported no history of past or current cocaine use. Given the high relation between cocaine and alcohol (used in order to increase the euphoria associated with cocaine use) we matched the two groups also for alcohol consumption (McCance-Katz, Kosten, & Jatlow, 1998).

Demographic and drug use statistics are provided in Table 2. Two cocaine users were excluded because it turned out that they did not comply with the instructions given by the experimental protocol consuming cocaine the night before the experiment.

[1] While chronic users consume at least 1 g daily (30 g monthly), our subjects consumed less than 10% of this amount (an average of 2.29 g per month)—not much but enough to impair inhibitory control (Colzato & Hommel, 2007). For reasons unrelated to the current study, we tested whether recreational users were more extrovert than cocaine-free controls by using the Eysenck Personality Questionnaire Revised Short Scale (EPQ-RSS) (Eysenck & Eysenck, 1991)—a test that measures four major dimensions of abnormal and normal personality: Psychoticism (P), Extraversion (E), Neuroticism (N), and Social Approval (S). Even though recreational cocaine users tended to be more extrovert than controls, this difference failed to even approach conventional levels of significance, $F(1,11) = 1.25$, $p = .28$, as did the differences on the other three personality dimensions, $F < 1$.

Table 2
Demographic characteristics and self-reported use of cocaine

Sample	Cocaine-free controls	Cocaine users	Significant
N (M:F)	12 (10:2)	12 (10:2)	ns
Age (years)	26.7 (6.6)	29.3 (5.0)	ns
Raven IQ	118.5 (3.9)	112.5 (5.0)	ns
Monthly drinks	48.4 (63.9)	88.0 (80.7)	ns
Monthly cigarettes	76.7 (259.3)	386.7 (201.1)	**
Highest regular frequency (times per month)		3.2 (2.7)	
Highest amount in a 12-h period (peak; grams)		1.25 (0.75)	
Monthly grams		2.29 (1.12)	
Monthly money cocaine (€)		114.5 (55.8)	

ns, non-significant difference; Raven IQ, IQ measured by means of the Raven progressive matrices; monthly drinks, monthly number of standard alcoholic drinks; monthly cigarettes, monthly number of cigarettes smoked per day.
*$p < 0.05$.
**$p < 0.01$.

2.3. Apparatus and stimuli

The experiment was controlled by a Targa Pentium III computer, attached to a Targa TM 1769-A 17 in. monitor. Participants faced three grey square outlines, vertically arranged, as illustrated in Fig. 1. From viewing distance of about 60 cm, each of these frames measured 2.6° × 3.1°. A vertical line (0.1° × 0.6°) and a horizontal line (0.3° × 0.1°) served as S1 and S2 alternatives, which were presented in red or green in the top or bottom frame. Response cues were presented in the middle frame (see Fig. 1), with rows of three left- or right-pointing arrows indicating a left and right key press, respectively. Responses to S1 and to S2 were made by pressing the left or right shift key of the computer keyboard with the corresponding index finger.

The actual experiment consisted of a 50-min session in which subjects completed a version of the task adopted from Hommel (1998), see Fig. 1. Participants faced three grey, vertically arranged boxes in the middle of a monitor and carried out two responses per trial. R1 was a delayed simple reaction with the left or right key, as indicated by a 100%-valid response cue (left- or right-pointing arrow in the middle box) that preceded the trigger stimulus S1 by 3000 ms. S1 varied randomly in orientation (a thin vertical or horizontal line), color (red or green), and location (top or bottom box). R1 was to be carried out as soon as S1 appeared, independent of its orientation, color, or location; i.e., subjects were encouraged to respond to the mere onset of S1. R2 was a binary-choice reaction to the orientation of S2 (vertical or horizontal orientation), which also appeared in red or green, and in the top or bottom box, 1000 ms after S1 onset. Responses to S1 and to S2 were made by pressing the left or right shift key of the computer keyboard with the corresponding index finger. Each session was composed of a factorial combination of the two possible orientations, colors, and locations of S2, the repetition versus alternation of orientation, color, location, and the response, and three replications per condition (=384 trials).

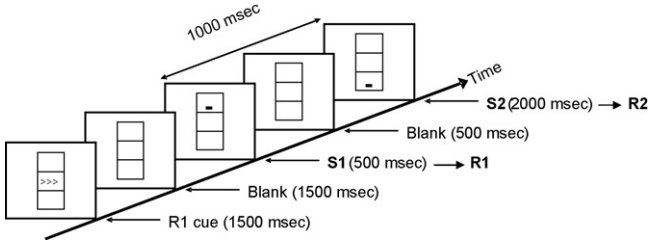

Fig. 1. Sequence of events in the present experiments (cf., Hommel, 1998). A response cue signalled a left or right key press (R1) that was to be delayed until presentation of S1, a red or green, vertical or horizontal line in a top or bottom box. S2 appeared 1 s later—another red or green, vertical or horizontal line in the top or bottom box. If, say, the response-cue arrow pointed to the right, subjects were to prepare a right key press, which they carried out as soon as S1 appeared—disregarding its orientation, color, or location. S2 orientation signalled R2, also a speeded left or right key press. R2 performance is commonly impaired in partial-repetition trials, that is, if one stimulus feature of the response is repeated, while the other feature is not (e.g., if S1 and S2 have the same orientation but are accompanied by different responses, or vice versa). This suggests that the co-occurrence of a feature–feature or feature–response conjunction is sufficient to create a temporary spontaneous binding of the respective codes, a kind of "event file" (Hommel, 1998). Repeating one feature seems to reactivate not only the corresponding code but also the just associated "fellow code", which creates a mismatch if the feature represented by that code was changed. This mismatch-induced conflict induces a time-consuming update or re-binding process, which impairs performance in partial-repetition trials.

2.4. Procedure and design

All participants were tested individually. During all sessions, participants provided a saliva sample (further not analyzed) and then completed the intelligence test and a behavioral task measuring visuomotor binding. Individual IQs were determined by means of a 30-min reasoning-based intelligence test (SPM). The SPM assesses the individual's ability to create perceptual relations and to reason by analogy independent of language and formal schooling; it is a standard, widely used test to measure Spearman's g factor and of fluid intelligence in particular (Raven, Court, & Raven, 1988). The behavioral task measuring visuomotor binding consisted of a 45-min session, see Fig. 1.

2.5. Statistical analysis

We adopted a significance level of $p < .05$. After excluding trials with missing (>1500 ms) or anticipatory responses (<200 ms), mean reaction times (RTs) and proportions of errors for R2 were analyzed. ANOVAs were run with group (cannabis users vs. cannabis-free controls in Experiment 1 and cocaine users vs. cocaine-free users in Experiment 2) as between-subject factor, the repetition versus alternation of response (R1 → R2), stimulus orientation, color, and location (S1 → S2) as within-subject factors.

3. Results

3.1. Experiment 1 (cannabis)

Table 3 provides an overview of the ANOVA outcomes for RTs and PEs obtained for R2.

Replicating earlier findings (Hommel, 1998), RTs revealed a significant main effect of location, which reflects IOR—the common observation that attending to an actually irrelevant stimulus impairs later responses to relevant stimuli appearing in the same location (Posner & Cohen, 1984). We obtained significant interactions between orientation and location, between response and orientation and response and location—repeating one but not the other (stimulus or response) feature slowed down responding. Group affected only the task-relevant binding of orientation and response, thus producing a three-way interaction. Fig. 2 suggests that the orientation-by-response interaction was reliable for both, cannabis users and cannabis-free controls group, respectively. However, it is also noticeable that the interaction is boosted in users, indicating that cannabis increased the impact of the task-relevant visuomotor binding on behavior.

Table 3
Results of analysis of variance on mean reaction time of correct responses (RT) and percentage of errors (PE) for Experiment 1 (cannabis) and Experiment 2 (cocaine)

Effect	Experiment 1 (cannabis)							
	RT_{R2}				PE_{R2}			
	d.f.	MSE	*F*	PES	d.f.	MSE	*F*	PES
Color (C)	1.21	625.71	0.15	0.007	1.21	79.93	1.37	0.062
C × Group (G)	1.21	625.71	0.27	0.013	1.21	79.93	0.39	0.002
Location (L)	1.21	1405.27	5.24	0.200	1.21	31.03	0.00	0.000
L × G	1.21	1405.27	0.01	0.000	1.21	31.03	0.60	0.028
Shape (S)	1.21	1934.56	1.26	0.057	1.21	15.28	3.68	0.149
S × G	1.21	1934.56	0.39	0.018	1.21	15.28	0.56	0.026
Response (R)	1.21	1756.66	0.49	0.023	1.21	296.17	0.12	0.006
R × G	1.21	1756.66	0.48	0.023	1.21	296.17	0.00	0.000
C × L	1.21	590.37	3.36	0.138	1.21	18.65	2.23	0.096
C × L × G	1.21	590.37	0.01	0.000	1.21	18.65	0.11	0.005
S × L	1.21	419.92	31.31**	0.599	1.21	32.44	0.05	0.002
S × L × G	1.21	419.92	0.05	0.002	1.21	32.44	2.59	0.110
S × C	1.21	440.64	1.24	0.063	1.21	59.41	0.02	0.001
S × C × G	1.21	440.64	0.01	0.000	1.21	59.41	0.05	0.002
S × L × C	1.21	639.53	0.21	0.010	1.21	31.47	1.05	0.048
S × L × C × G	1.21	639.53	0.27	0.013	1.21	31.47	1.61	0.071
C × R	1.21	367.04	0.26	0.012	1.21	25.35	5.90**	0.219
C × R × G	1.21	367.04	0.01	0.000	1.21	25.35	0.13	0.006
L × R	1.21	611.16	34.03**	0.618	1.21	40.59	28.51**	0.576
L × R × G	1.21	611.16	2.42	0.103	1.21	40.59	1.05	0.048
S × R	1.21	1360.49	38.81**	0.649	1.21	76.08	35.29**	0.627
S × R × G	1.21	1360.49	4.85*	0.188	1.21	76.08	0.02	0.010
C × L × R	1.21	870.30	0.70	0.032	1.21	28.23	1.95	0.085
C × L × R × G	1.21	870.30	0.00	0.000	1.21	28.23	0.05	0.002
S × L × R	1.21	647.54	4.01	0.161	1.21	11.13	0.62	0.029
S × L × R × G	1.21	647.54	0.95	0.044	1.21	11.13	0.03	0.001
S × C × R	1.21	583.82	0.03	0.026	1.21	60.43	1.06	0.048
S × C × R × G	1.21	583.82	3.37	0.003	1.21	60.43	0.39	0.018
S × L × C × R	1.21	649.78	0.46	0.021	1.21	19.35	0.11	0.005
S × L × C × R × G	1.21	649.78	0.56	0.026	1.21	19.35	1.61	0.071
Effect	Experiment 2 (cocaine)							
	RT_{R2}				PE_{R2}			
	d.f.	MSE	*F*	PES	d.f.	MSE	*F*	PES
Color (C)	1.20	658.62	0.27	0.013	1.20	62.91	0.05	0.003
C × Group (G)	1.20	658.62	0.46	0.023	1.20	62.91	0.62	0.030
Location (L)	1.20	821.33	14.92**	0.427	1.20	43.03	2.43	0.108
L × G	1.20	821.33	5.25*	0.208	1.20	43.03	0.08	0.004
Shape (S)	1.20	1350.56	1.09	0.052	1.20	27.97	7.04	0.260
S × G	1.20	1350.56	0.02	0.001	1.20	27.97	2.69	0.119
Response (R)	1.20	974.41	0.67	0.033	1.20	37.95	3.06	0.133
R × G	1.20	974.41	0.06	0.003	1.20	37.95	0.01	0.000
C × L	1.20	501.11	0.07	0.003	1.20	39.28	2.06	0.093
C × L × G	1.20	501.11	0.67	0.033	1.20	39.28	0.43	0.021
S × L	1.20	1270.06	6.69	0.251	1.20	37.95	0.01	0.000
S × L × G	1.20	1270.06	0.35	0.017	1.20	37.95	0.03	0.001
S × C	1.20	804.31	4.90*	0.197	1.20	33.75	0.08	0.004
S × C × G	1.20	804.31	0.04	0.002	1.20	33.75	0.95	0.046
S × L × C	1.20	682.79	2.18	0.098	1.20	18.43	2.06	0.093
S × L × C × G	1.20	682.79	0.13	0.007	1.20	18.43	3.15	0.136
C × R	1.20	503.30	0.22	0.011	1.20	47.12	2.81	0.123
C × R × G	1.20	503.30	0.11	0.005	1.20	47.12	0.14	0.007
L × R	1.20	706.02	17.38	0.465	1.20	75.80	22.12**	0.525
L × R × G	1.20	706.02	4.33	0.178	1.20	75.80	0.37	0.018
S × R	1.20	1434.03	50.37**	0.716	1.20	272.47	24.62**	0.552
S × R × G	1.20	1434.03	0.15	0.008	1.20	272.47	1.89	0.086
C × L × R	1.20	347.06	0.05	0.003	1.20	17.48	0.04	0.002
C × L × R × G	1.20	347.06	2.52	0.112	1.20	17.48	2.41	0.107
S × L × R	1.20	453.47	0.20	0.010	1.20	46.50	2.93	0.128
S × L × R × G	1.20	453.47	2.91	0.127	1.20	46.50	1.84	0.084
S × C × R	1.20	401.25	1.07	0.051	1.20	27.93	0.03	0.001
S × C × R × G	1.20	401.25	0.10	0.005	1.20	27.93	1.95	0.089
S × L × C × R	1.20	535.84	0.39	0.019	1.20	34.07	0.50	0.024
S × L × C × R × G	1.20	535.84	1.27	0.060	1.20	34.07	2.93	0.220

MSE, mean square error; PET, partial eta squared.
* $p < .05$.
** $p < .01$.

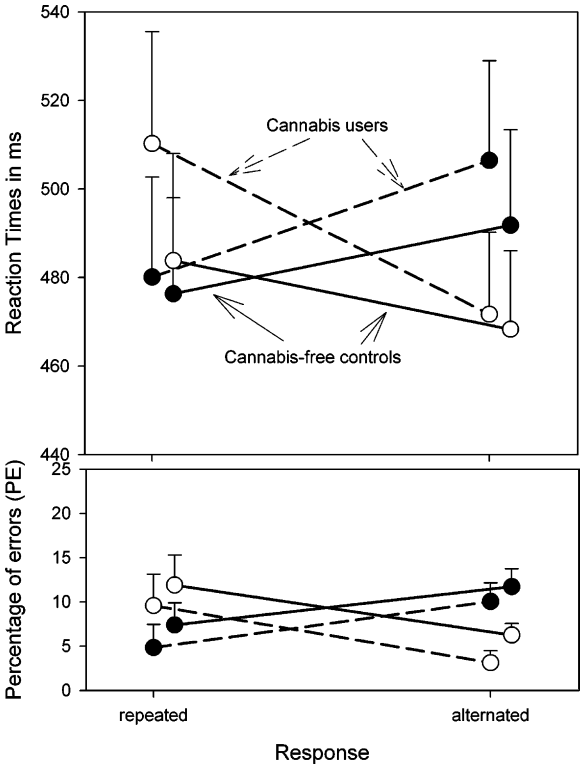

Fig. 2. Mean reaction times and error percentages for RT2 as a function of group (cannabis users = dotted line and cannabis-free controls = straight line), repetition vs. alternation of stimulus task-relevant feature and response. Vertical capped lines indicate standard error of the mean. Typical binding effects are indicated by patterns showing worse performance for filled circle on the left and unfilled circle on the right (one stimulus feature is repeated while the response alternates, or vice versa). Cannabis, compared to no use, increased the binding effect between orientation and response.

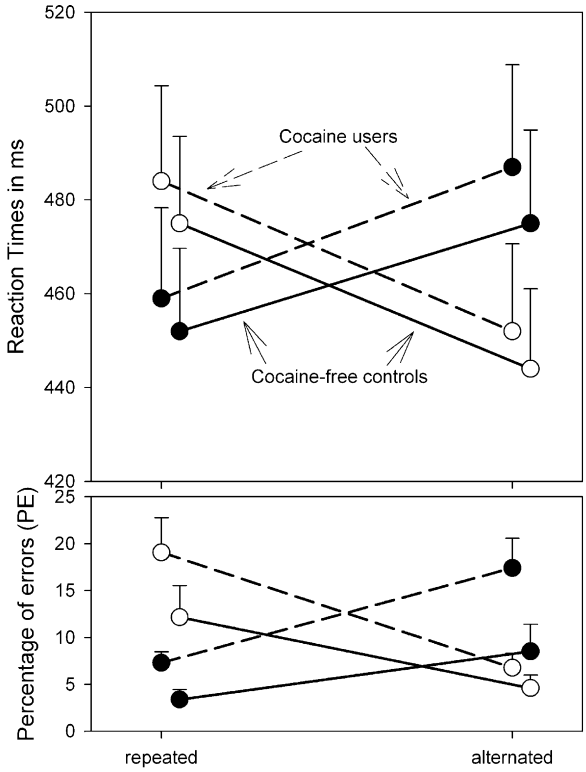

Fig. 3. Mean reaction times and error percentages for RT2 as a function of group (cocaine users = dotted line and cocaine-free controls = straight line), repetition vs. alternation of stimulus task-relevant feature and response. Vertical capped lines indicate standard error of the mean. Cocaine, compared to no use, did not affect the binding effect between orientation and response.

The error rates followed the same pattern: response interacted with orientation, location, and color. Both interactions were due to fewer errors when both features were repeated or both alternated, as compared to conditions where one feature but not the other was repeated. Group did not yield in the error rates any significant interaction.

3.2. Experiment 2 (cocaine)

Table 3 provides an overview of the ANOVA outcomes for RTs and PEs obtained for R2.

Experiment 2 replicated the first experiment for the most part. We obtained a significant main effect of location, which interact with group. This indicates that the cocaine-free controls showed a normal, significant IOR (−19 ms), $F(1, 11) = 16.86$, $p = .002$, which, however, was eliminated in recreational users of cocaine (−5 ms), $F(1, 9) = 1.59$, $p = .24$. Moreover, we obtained two-way interactions between orientation and location, orientation and color, between orientation and response, location and response. Most importantly, there was no evidence of any impact of group on the task-relevant visuomotor binding of orientation and response, $F < 1$. The error results mirrored RTs, yielding interactions between orientation and response, and between location and response, see Fig. 3.

4. Conclusions

Our findings show that cannabis, a drug targeting primarily the dopaminergic D1 system (Diana et al., 1998), affects the strength of the binding between task-relevant stimulus and response features, whereas cocaine, a drug targeting principally the dopaminergic D2 system (Volkow et al., 1999), has no effect on binding whatsoever. In contrast, cocaine use leads to the elimination of the otherwise robust IOR (replicating Colzato & Hommel, 2007), while no such impact was observed for cannabis. These findings are consistent with a crucial role of dopaminergic pathways in the visuomotor integration, but they go beyond previous observations in suggesting a specific role of dopaminergic D1 receptors. These types of receptors have been associated with working memory functions (Sawaguchi & Goldman-Rakic, 1991), which raises at least two possibilities of how the DA/D1 system might modulate visuomotor integration.

One possibility is that this system drives the neural synchronization that mediates visuomotor integration. Synchronization has been claimed to play a role in both visuomotor binding (Roelfsema, Engel, Koenig, & Singer, 1997) and working memory maintenance (Raffone & Wolters, 2001), and both of these functions have been suspected to be driven by dopaminergic systems (Sawaguchi & Goldman-Rakic, 1991; Schnitzler & Gross, 2005). Accordingly, it is possible that dopaminergic

D1 receptors are responsible for generating and/or maintaining the synchronized states underlying feature integration (cf., Castner & Williams, 2007). Another, not necessarily mutually exclusive, possibility is that D1 receptors play a role in updating stimulus–response bindings. In contrast to complete repetitions or alternations of stimulus–response conjunctions, partial repetitions require such an update, and there is evidence that dopaminergic pathways play a central role in updating cognitive representations (Braver & Cohen, 2000). Accordingly, it is possible that drugs targeting D1 receptors impair or slow down updating processes, which should result in larger partial-repetition costs as obtained in this study. Further neuromodular investigations testing acute effects, by means of highly selective D1 and D2 agonists as SKF 38393 and LY171555, would be useful to provide insights into which of these possibilities applies.

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