ELSEVIER

Neuropsychologia 46 (2008) 1542–1548

NEUROPSYCHOLOGIA

www.elsevier.com/locate/neuropsychologia

# Stress modulation of visuomotor binding

Lorenza S. Colzato *, Wouter Kool, Bernhard Hommel

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

Received 7 August 2007; received in revised form 4 January 2008; accepted 14 January 2008
Available online 19 January 2008

**Abstract**

The primate cortex represents perceived and produced events in a distributed way, which calls for a mechanism that integrates their features into coherent structures. Animal, drug, and patient studies suggest that the local binding of visual features is under muscarinic–cholinergic control, whereas visuomotor binding seems to be driven by dopaminergic pathways. Consistent with this picture, we present evidence that the binding of visual features and actions is modulated by stress, induced by the cold pressure test (CPT), which causes an excessive dopamine turnover in prefrontal cortex. The impact of stress was restricted to the task-relevant visuomotor binding, supporting claims that dopamine affects the maintenance of task-relevant information in working memory. The outcome pattern, including the impact of the personality trait extraversion, suggests that the relation between dopamine level and visuomotor performance follows an inverted U-shaped function, with strongest binding being associated with average dopamine levels.


*Keywords:* Binding problem; Visuomotor binding; Neuronal synchronization; Dopamine; Stress

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). It has been suggested that the binding problem may be solved in terms of temporal coding, based on the selective synchronization of time-resolved neuronal responses (Eckhorn et al., 1988; Engel, Kreiter, Schillen, & Singer, 1992; Gray, König, Engel, & Singer, 1989; von der Malsburg, 1981, 1999). According to this view, the action potentials of neurons coding the features of the same object are synchronized, while being uncorrelated to the responses of neurons coding for the features of other objects. This view is supported by the evidence that neurons act as coincidence detectors, since synchronous synaptic inputs are more effective than asynchronous ones in eliciting spikes of the neurons on which they converge (Abeles, 1991). Temporal neural codes may be read out in terms of these coincidence detection properties. Many recording studies from the visual cortex of cats and monkeys have shown that the selective synchronization of oscillatory neuronal discharges may plausibly be involved in visual grouping and segregation (e.g. Castelo-Branco et al., 2000; Eckhorn et al., 1988; Gray et al., 1989), as well as in action planning (e.g., Pfurtscheller, Pregenzer, & Neuper, 1994; for an overview, see MacKay, 1997). In particular, action-contingent synchronization has been observed between motor and somatosensory areas of the monkey (Murthy & Fetz, 1992, 1996), and across the visual and parietal cortex and the parietal and the motor cortex of the cat (Roelfsema, Engel, König, & Singer, 1997).

## 1. Neuromodulation of visuomotor binding

In recent years evidence accumulates that at least two neurotransmitter systems are involved in binding features and the creation of temporal coherence between cell populations: the muscarinic–cholinergic system, which seems associated to perceptual binding (Colzato, Erasmus, & Hommel, 2004; Colzato, Fagioli, Erasmus, & Hommel, 2005; Rodriguez, Kallenbach, Singer, & Munk, 2004), and the dopaminergic system, which seems to drive the integration of action-related information (Schnitzler & Gross, 2005).

Neuropsychological and neurophysiological investigations (see for a review: Murray, Bussey, & Wise, 2000) have, in large part, identified the neural network that underlies the rapid acquisition and use of arbitrary visuomotor mappings, which

* 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).

0028-3932/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropsychologia.2008.01.006

consists of parts of the premotor and prefrontal cortex, the hippocampal system, and the basal ganglia (BG). In particular, the BG, a main way station in the dopamine relay system, are known to play a substantial role in stimulus–behavior integration (Gurney, Prescott, & Redgrave, 2001). Consistent with this scenario, Colzato, van Wouwe, and Hommel (2007a) showed recently that the binding of visual and action features is increased through the presentation of positive-affect inducing pictures, which can be assumed to stimulate the dopaminergic system (Ashby, Isen, & Turken, 1999; Holroyd & Coles, 2002; Mark, Blander & Hoebel, 1991; Robbins & Everitt, 1995; Suri, 2002). Along the same lines, Colzato, van Wouwe, and Hommel (2007b) observed a positive correlation between the strength of binding between visual and action features and spontaneous eyeblink rate (EBR)—a marker of dopaminergic functioning (Blin, Masson, Azulay, Fondarai, & Serratrice, 1990). Moreover, recent findings from our lab suggest a role of dopamine D1 receptors in binding perception and action (Colzato & Hommel, 2008). Our results show that cannabis, which primarily targets dopaminergic D1 receptors (Diana et al., 1998; Gessa et al., 1998), but not cocaine use, which mainly targets D2 receptors (Volkow, Fowler, & Wang, 1999), affects the strength of the binding between task-relevant stimulus features and the response.

Even though the available evidence may be taken to point to a linear relationship between visuomotor binding and dopamine level, there are reasons to assume that this relationship may actually follow an inverted U-shaped function. According to Goldman-Rakic and colleagues (Goldman-Rakic, Muly, & Williams, 2000; Muly, Szigeti, & Goldman-Rakic, 1998), it is an average dopamine level that allows for the best cognitive performance, whereas too high or too low levels impair cognitive processes. This effect is explained by the existence of gamma-amino-butyric acidergic (GABAergic) interneurons with D1 (dopamine) receptors and inhibitory input to cortical pyramidal cells, which are related to cognitive performance. At moderate levels of dopamine release the function of these pyramidal cells (but not of the interneurons) is enhanced, which leads to better performance as compared to lower levels. But at high levels of dopamine release, the GABAergic inhibitory interneurons also get excited and start projecting the neurotransmitter GABA onto the pyramidal cortical cells. This provides them with inhibitory input, leading to impaired performance (Goldman-Rakic et al., 2000).

## 2. Purpose of study

The present study aimed at reconciling the available evidence in humans that visuomotor binding increases linearly with increasing dopaminergic activity (Colzato et al., 2007a, 2007b), with animal evidence (Goldman-Rakic et al., 2000; Muly et al., 1998) that the level of dopaminergic activity and the efficiency of dopaminergically driven processes may follow an inverted U-shaped function.

Exposure to stress increases the release of glucocorticoids (Sapolsky, Romero, & Munck, 2000), which in turn enhances catecholamine (dopamine and norepinephrine) activity (Arnsten, 1998). However, there is evidence for a direct link between stress and increased dopaminergic activity especially in the mesocortical dopaminergic system (Deutch & Roth, 1990; Thierry, Tassin, Blanc, & Glowinski, 1976). In the monkey and the rat, stress causes an excessive turnover of dopamine in the prefrontal cortex (PFC), resulting in cognitive impairments (Arnsten & Goldman-Rakic, 1998; Murphy, Arnsten, Goldman-Rakic, & Roth, 1996). In humans, stress (induced by the cold pressure test (CPT) described below) impairs the processing of context information, presumably by disrupting dopaminergic supply to the dorsolateral PFC (Colzato, van Wouwe, van den Wildenberg, Elzinga, & Hommel, submitted for publication).

The first goal of our study was, thus, to explore the effects of stress (by means of the CPT) on visuomotor binding. Given that stress results in excessive dopamine levels and that the level of dopaminergic activity and the efficiency of visuomotor processes may follow an inverted U-shaped function, we thought that stress may produce a *decrease* of binding-related effects.

A second aim of our study was to determine under which circumstances, if any, dopamine modulates binding effects. Previous research (e.g., Hommel, 1998) showed that the strength of binding depends on the task-relevance of the respective feature dimension: stimulus features from task-relevant, and therefore attended dimensions affect later performance more strongly than features from task-irrelevant dimensions, suggesting that at least some aspects of the creation and/or the retrieval of bindings are under attentional control. Braver, Barch, and Cohen (1999) have suggested that dopamine is critically involved in the maintenance of task-relevant information. If stress causes an excessive dopamine turnover in the PFC and if the latter is associated with focusing on task-relevant information, we would expect that the relationship between stress and visuomotor binding is more pronounced with, or even restricted to the integration of task-relevant stimulus and response features.

A third aim of the study was to explore whether personality traits might mediate the interaction between stress, dopamine, and visuomotor binding. Research suggests a positive correlation between the personality trait neuroticism and dopamine (Lee et al., 2004), while extraversion seems to be related to suboptimal levels of dopaminergic activity (for a review, see Rammsayer, 1998). This suggests that personality and the amount of visuomotor binding are related but, considering that behavioral effects might be a nonlinear function of dopamine levels, that this relationship is further mediated by stress.

As behavioral marker for feature-integration processes we employed a variant of the task developed by Hommel (1998), which measures both visual–visual and visuomotor binding (see Fig. 1 and Section 3 for more details). As a well-established stressor we used the CPT (von Baeyer et al., 2005), in which participants briefly immerse a hand in cold water.

In sum, we expected that, first, stress, which produces excessive dopamine turnover, would decrease the strength of visuomotor binding (i.e., the size of effects indicative of stimulus–response binding). Second, given that dopamine is assumed to be involved in increasing the maintenance of task-relevant information (Braver et al., 1999), we speculated that stress might affect binding only for the task-relevant stimulus feature shape, that is, with the size of the shape–response binding

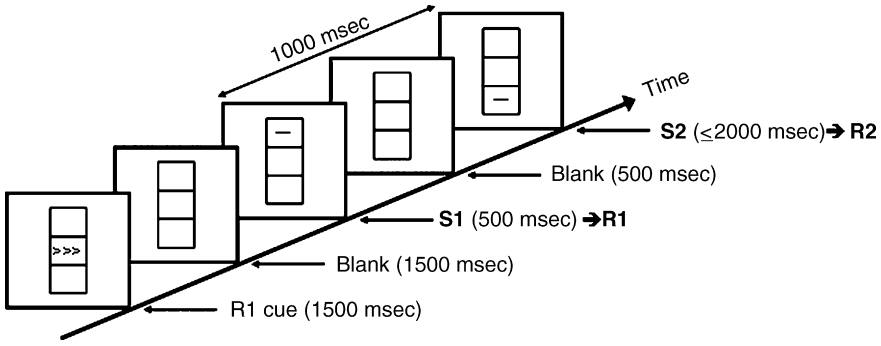


Fig. 1. Sequence of events in the present experiments (cf., Hommel, 1998). A response cue signaled a left or right key press (R1) that was to be prepared accordingly but to be delayed until presentation of S1, a red or green, vertical or horizontal line in a top or bottom box. S2 appeared 1 s later—another red or green, vertical or horizontal line in the top or bottom box. S2 shape signaled R2, also a speeded left or right key press. R2 speed and accuracy were analyzed as function of the repetition vs. alternation of stimulus shape, color, and location, and of the response. This task has a number of important characteristics: The identity of S1 does not matter for R1 (so that S1 and R1 can vary orthogonally) but varies in shape, location, and color. Given that S2 varies on the same dimensions and R2 can be the same as, or be different from R1, this design generates repetitions and alternations of all three stimulus features and of the response. In our design (S2) shape was the only task-relevant stimulus feature and response location the only relevant response feature, whereas color and stimulus location could safely be ignored. Performance in such a task commonly 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 (e.g., if shape repeats while location does not, or vice versa; or if shape repeats while the response does not, or vice versa). 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 event files the code of that feature has become a part of (Hommel, 1998, 2004). This creates conflict between the retrieved codes and those activated by the current response location of 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 shape and location stimulus feature) and visuomotor (e.g., integration of shape stimulus feature and response feature) binding.

effect. Moreover, we tested whether the efficiency of visuomotor binding would be systematically affected by extraversion and neuroticism, presumably mediated by stress.

## 3. Methods

### 3.1. Subjects

Seventeen students (8 women and 9 men, mean age = 20.53) served as subjects for partial fulfillment of course credit or a financial reward. Two participants were excluded because it turned out that they did not comply with the instructions given by the experimental protocol. All reported having normal or corrected-to-normal vision, and were not familiar with the purpose of the experiment. Written informed consent was obtained by all subjects; the protocol was approved by the local ethical committee (Leiden University, Institute for Psychological Research).

Following Elzinga and Roelofs (2005) and Colzato, van Wouwe, van den Wildenberg, et al. (submitted for publication) subjects were selected with the Mini-International Neuropsychiatric Interview (MINI; Lecrubier et al., 1997). The following exclusion criteria were applied: no Axis 1 psychiatric disorder (DSM-IV), including 'substance abuse'; no clinically significant medical disease; no use of medication (including oral contraceptives); being younger than 18 or older than 27 years old. All women participated during their late luteal phase[1] (days 21–25) of their menstrual cycle given that during this period stress-induced cortisol levels are not different between men and women (Elzinga & Roelofs, 2005; Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999).

Participants were asked to minimize their physical exercise during the hour before the experiment and to refrain from big meals, coffee, tea, drinks with a low pH, chocolate or chocolate milk, coke and alcohol starting 20:00 the evening before the experiment (all variables known to have an influence on cortisol levels). Compliance with these instructions was motivated by announcing that saliva samples would be taken.

[1] One female participated on the first day of her period on the second condition, due to an instable cyclus.

### 3.2. CPT

To induce stress we used the well-established CPT (von Baeyer et al., 2005). Participants were asked to immerse a hand in cold water (1–4 °C) for 1.5 min. Pumps circulating the cold water prevented the development of a microenvironment of warmer water around the hand of the participant. Ice cubes were used to cool the water and a perforated plastic separated the ice from the hands of the participants. In the control condition the same method was used with lukewarm water (20–25 °C).

### 3.3. Binding task

The actual experiment consisted of a 50-min condition in which subjects completed a version of the task adopted from Hommel (1998; see Fig. 1). Participants faced three gray, 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. While a right-pointing arrow informed the subject that the left key was to be pressed as soon as S1 appeared, a left-pointing arrow signaled a right key press.

S1 varied randomly in shape (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 shape, color, or location; i.e., subjects were encouraged to respond to the mere onset of S1.

R2 was a binary-choice reaction to the shape of S2 (vertical or horizontal), which also appeared in red or green, and in the top or bottom box, 1000 ms after S1 onset. Half of the subjects were thus to press the left key whenever S2 was a horizontal line (whatever the color or location) and the right key whenever S2 was a vertical line, while the other half received the opposite mapping. 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 measures of interest were reaction times and percent error rates for R2, as a function of whether R2 was or was not a repetition of R1 (a response repetition or alternation, that is) and whether the shape, color, or location of S2 was the same as in S1 (a shape, color, or location repetition or alternation). Each condition (control and stress) was composed of a factorial combination of the

two possible shapes, colors, and locations of S2, the repetition vs. alternation of shape, color, location, and the response, and three replications per condition ($2 \times 2 \times 2 \times 2 \times 2 \times 2 \times 2 \times 2 \times 3 = 384$).

### 3.4. Physiological and psychological measures

#### 3.4.1. Cortisol

Saliva samples were obtained using Salivettes (Sarstedt, Rommelsdorf, Germany). Saliva samples were stored at −18 °C before assaying (Dresden LabService GmbH, Dresden, Germany).

#### 3.4.2. Heart rate and blood pressure

Heart rate and systolic and diastolic blood pressure (SBP and DPB) were measured from the non-dominant arm with an OSZ 3 Automatic Digital Electronic Wrist Blood Pressure Monitor (Spiedel & Keller).

#### 3.4.3. Eysenck personality questionnaire revised short scale (EPQ-RSS) (Sanderman, Arrindell, Ranchor, Eysenck, & Eysenck, 1995)

The inventory was administered once, at the beginning of the first session. It provided measurements of the personality dimensions extraversion (E) and neuroticism (N). The E and N score could vary between 0 and 12.

### 3.5. Procedure and design

The study consisted of two sessions separated by 3–7 days, each one lasting for about 1 h. Each session was associated with either the CPT (stress condition) or the non-stressful lukewarm water (control condition). Half of the participants received the CPT in their first session, while this order was reversed for the other half. Therefore the order of stress and control conditions was counterbalanced between subjects.

To prevent any other time-of-day effects on cortisol levels and other measurements, both conditions started at the same time per participant. At every assessment point all physiological stress markers (saliva samples, HR, SBP, DBP) were measured. The experiment followed a placebo-controlled randomized counter-balanced within-subjects design.

The session comprised two parts; in the first part, a baseline assessment of physiological measures was followed by the non-dominant hand immersion in water (CPT or lukewarm). Five minutes later, the main (experimental) part was started with the visuomotor binding task, which lasted for 45 min. A second hand immersion and assessment of physiological measures took place 15 min into the binding task. In the session associated with the stress (CPT) condition only, a third assessment of physiological measures took place 15 min after the second CPT. Given that the RT task took 45 min to complete and given the duration of 30 min of the increased cortisol levels after a short-term stressor is presented (Sapolsky et al., 2000), we decided to split the reaction time task in two segments and to let the subjects perform two CPTs. By doing that we assured an increased cortisol level throughout the whole actual experiment.

### 3.6. Statistical analysis

First, separate five-way analyzes of variance (ANOVAs) with repeated measures were used to analyze the RTs and ERs with condition (stress vs. control), response (alternation vs. repetition), stimulus orientation (alternation vs. repetition), stimulus color (alternation vs. repetition), and stimulus location (alternation vs. repetition) as the within-subject factors.

Second, binding effects were calculated as the difference between the RTs for partial repetitions (feature *X* repeated and feature *Y* alternated, or vice versa) and the RTs for complete repetitions and "complete" alternations. That is, if features *X* and *Y* repeated and alternated, their binding effect $B_{XY}$ would be $B_{XY} = (RT_{X/alt,Y/rep} + RT_{X/rep,Y/alt})/2 - (RT_{X/rep,Y/rep} + RT_{X/alt,Y/alt})/2$. Binding effects thus correspond to the two-way interaction term of the respective features (and are thus immune to possible, but theoretically less relevant, main effects of feature repetition); a value close to zero means that the repetition effects of the two given features do not interact; a value greater than zero indicates a "binding-type" interaction of the sort described in the text. Third, we ran correlation analyzes that looked into the association between the individually calculated extraversion and neuroticism personality trait score for the EPQ-RSS, the second cortisol response (difference between first and third measurement), and the sizes of binding effects in visual perception (visual–visual binding) and across perception and action (visuomotor binding) for RTs and error rates. Finally, paired samples *t*-tests were performed to test whether the physiological stress markers were affected during the control and stress conditions. We adopted a significance level of $p < .05$ for all statistical tests and tested our hypothesis in four ways.

## 4. Results

### 4.1. Physiological measurements

Table 1 provides an overview of the mean score at different time points for cortisol level, HR, SBP and DBP for control and stress condition, respectively.

Paired samples *t*-tests were performed to test whether the physiological stress markers were affected during the control condition: cortisol level, $t = 1.57$, $p > .14$, HR, $t = 1.76$, $p > .09$, and SBP, $t = -.90$, $p > .38$, did not change significantly, while DBP, $t = 3.76$, $p < .01$, decreased significantly.

For the stress condition we ran separate one-way repeated measure ANOVAs. Cortisol levels, $F(1,14) = 25.15$, $p < .001$, increased, and HR, $F(1,14) = 5.07$, $p < .05$, decreased significantly, while SBP, $F(1,14) = 3.29$, $p > .06$, and DBP, $F(1,14) = 2.06$, $p > .16$, did not change throughout the stress condition.

Bonferoni corrected post hoc paired sample *t*-tests revealed that cortisol levels after the first stressor and after the second stressor were significantly higher than baseline levels, $t = -6.68$, $p < .001$. The difference between the first and second post-stressor measurements was not significant, $t = .513$, $p > .60$, an indication that our stress manipulation was successful and the increased cortisol level lasted for the whole actual experiment.

### 4.2. Binding task

Trials with missing or anticipatory responses (1.4%) were excluded from the analysis.

The five-way ANOVA revealed an important significant condition × shape × response interaction, $F(1,14) = 5.61$, $p = .033$,

Table 1
Means of score at three different time points for cortisol level, heart rate, systolic blood pressure (SBP) and (diastolic blood pressure) DBP as a function of condition (stressed vs. unstressed)

| Physiological measurements | Unstressed | Stressed |
|---|---|---|
| Cortisol 1 | 5.80 | 10.79 |
| Cortisol 2 | 4.91 | 19.05 |
| Cortisol 3 | – | 18.02 |
| Heart rate 1 | 75.00 | 78.07 |
| Heart rate 2 | 70.21 | 76.14 |
| Heart rate 3 | – | 70.57 |
| SBP 1 | 123.93 | 121.50 |
| SBP 2 | 117.71 | 115.71 |
| SBP 3 | – | 111.00 |
| DBP 1 | 69.07 | 68.50 |
| DBP 2 | 64.50 | 66.07 |
| DBP 3 | – | 65.43 |

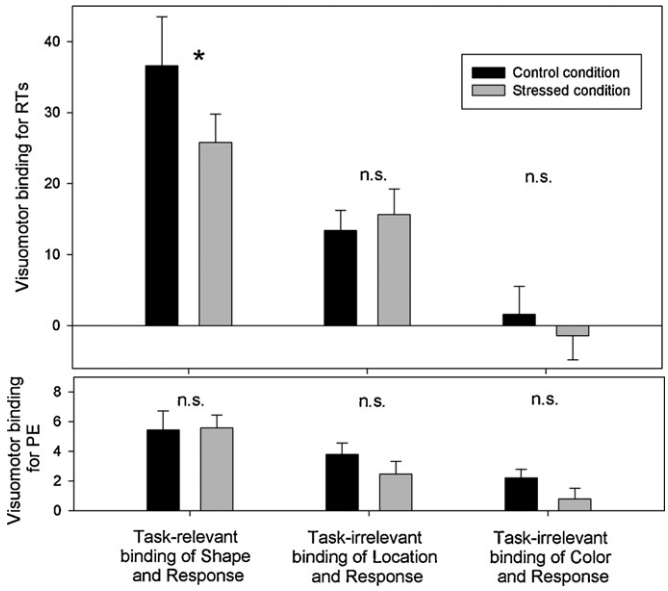


Fig. 2. Effects indicating stimulus–response binding in reaction times and error rates (on R2), for stress and control conditions. Vertical capped lines atop bars indicate standard error of the mean. n.s.: non-significant. *$p = .033$.

for RTs but not the PEs, which is depicted in Fig. 2. It can be seen that bindings for shape (the only task-relevant stimulus feature) and response, and for stimulus location and response, were significant, while the bindings for color and response were not. Apart from a significant condition x shape interaction, $F(1,14) = 10.79$, $p = .005$, for RTs, no other interaction involving condition was significant for RTs or PEs.

Further, replicating earlier findings (Hommel, 1998; Hommel & Colzato, 2004), RTs revealed significant interactions between shape and location (repetition), $F(1,14) = 11.33$, $p = .005$, color and location, $F(1,14) = 5.16$, $p = .039$, shape and response, $F(1,14) = 36.49$, $p = .0001$, and response and location, $F(1,14) = 30.77$, $p = .0001$—repeating one but not the other feature slowed down responding.

The PEs followed the same pattern: significant interactions were obtained between shape and response, $F(1,14) = 40.95$, $p = .005$, and location and response, $F(1,14) = 17.73$, $p = .05$, color and response, $p = .006$, due to fewer errors in conditions where the stimulus feature and the response were both repeated or both alternated, as compared to conditions where one was repeated but the other was not. Moreover, a significant main effect of location was found, $F(1,14) = 5.54$, $p = .034$, which entered a three-way interaction with shape and color, $F(1,14) = 7.60$, $p = .015$, due to a decrease of the location-by-color interaction if shape was repeated. Again, these effects were not modified by condition.

In order to test the hypothesis of an inverted U-shape relationship between PFC DA levels and visuomotor task performance, we analyzed the stress-induced change in the strength of shape–response binding in RTs as a function of the strength of shape–response binding in the control condition. If dopamine levels and binding strength are really related by a U-shaped function, one would expect that stress would *increase* binding strength in people with a relatively low dopamine baseline

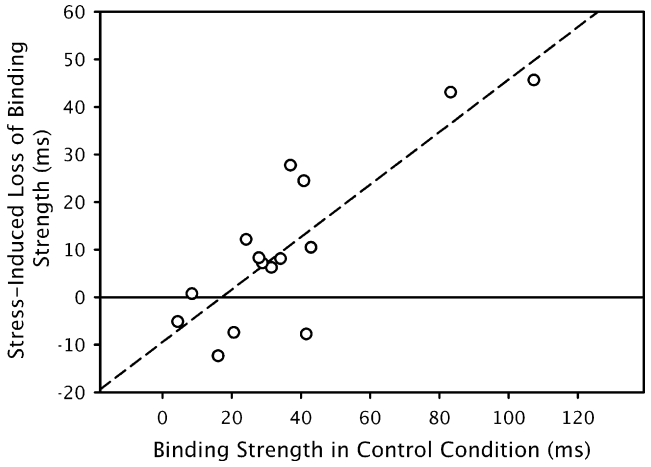


Fig. 3. The individual stress-induced decreases in the shape–response binding (loss of binding strength) as a function of the size of the shape–response binding effect in the control condition.

(as stress would drive the dopamine level from a suboptimal towards a more optimal level) but *decrease* binding strength in people with a relatively high dopamine baseline (as stress would drive the dopamine level beyond the optimal level). This means that stress should increase the size of (shape–response) binding effects in subjects with a relatively small effect in the control condition but decrease the size of binding effects in subjects with a relatively large effect in the control condition. We thus computed the individual stress-induced loss of binding effect (shape–response binding effect in the control condition minus the shape–response binding effect in the stress condition) and correlated this value with the size of the individual binding effect in the control condition. As shown in Fig. 3, this correlation was highly significant, $r = .84$, $p < .001$, and followed the expected pattern: Stress resulted in a "positive loss" (gain, that is) in "weak binders" but in considerable losses in "strong binders".

### 4.3. Personality traits

Pearson correlation coefficients showed a significant correlation between extraversion and task-relevant visuomotor binding (shape and response) only in the stress, $r = .590$, $p = .021$, but not in the control condition, $r = .201$, $p = .472$. However, this relationship was lost after partial correlations controlling for the effects of the second cortisol response with which extraversion also correlated significantly, $r = .555$, $p = .032$. All other correlations were not significant (all $p$ values >.9).

## 5. Discussion

Our methodology using the CPT was successful in inducing stress as evidenced by cortisol responses and the physiological measures. We found that stress caused by the CPT impaired binding-related effects (our 1st goal), and that this impairment was restricted to the integration of task-relevant stimulus and response features as shown in Fig. 2 (our 2nd goal). Stress was unrelated to task-irrelevant visuomotor and visual–visual bindings. Given that stress causes excessive DA turnover in the PFC

and impairs PFC cognition (Arnsten & Goldman-Rakic, 1998; Murphy et al., 1996), these results support the hypothesis that binding features across perception and action is driven by the dopaminergic system (Colzato et al., 2007a) – presumably by modulating neural synchronization (Schnitzler & Gross, 2005) – while perceptual binding is linked to the muscarinic–cholinergic system (Colzato et al., 2005; Rodriguez et al., 2004).

Given that experimental evidence in animals shows that the level of dopaminergic activity and the efficiency of dopaminergically driven processes follow an inverted U-shaped curve (Goldman-Rakic et al., 2000; Muly et al., 1998), we considered that the current dopamine level and visuomotor binding may be similarly related. Indeed, consistent with this idea we found that the size of the binding effect in the control condition predicts whether this effect increases or decreases under stress. As shown in Fig. 3, stress was associated with binding gains in subjects with weak binding in the control condition, but resulted in significant binding losses in subjects with strong binding in the control condition. This pattern suggests that stress, is related to task-relevant visuomotor binding according to an inverted U-shaped function; it seems that stress, and by extension PFC DA release, drives performance to more optimal levels in people with a low baseline binding but away from optimal levels in those with a higher baseline binding.

A similar conclusion can be drawn, at least preliminarily, from our observation that extraversion is positively correlated with task-relevant visuomotor binding. However, it is not possible to exclude that this relationship was probably mediated by stress, since it was reliable only in the stress condition, and it was no longer significant after controlling for the effects of cortisol, with which extraversion was also positively related. Given that the responsivity to changes in dopamine activity is lower in extraverts than in introverts (Rammsayer, 1998), inducing stress may improve cognitive performance in extraverts but impair performance in introverts.

Our observation that stress impacts visuomotor binding fits our previous demonstrations that task-relevant visuomotor binding is predicted by EBR (Colzato et al., 2007b) and selectively enhanced through positively charged pictures (Colzato et al., 2007a), and is consistent with the idea that dopamine is crucial for maintaining task-relevant information (Braver et al., 1999). In those studies, increases in DA activity were presumably elicited using positively charged pictures or were indicated with higher EBR. As opposed to the present study however, those studies, showed increased rather than decreased task-relevant visuomotor binding with increasing DA levels. Given that participants with extraordinarily high EBRs were not considered in the blink study, it makes sense to assume that the sample investigated was biased towards the lower end of the EBR scale. Assuming that EBR represents dopaminergic activity, this implies that the mean of the sample must have been biased towards the left, ascending side of the curve. If so, EBRs lower than the mean were associated with rather low dopamine levels and EBRs higher than the mean mostly (though not exclusively) with higher dopamine levels—hence the positive correlation between EBR and visuomotor binding. A comparable logic may apply to the pictures study. Normal, unaroused students may be more likely to fall onto the ascending part of the curve, so that seeing positively charged pictures would tend to increase dopamine levels, at least as compared to negative pictures—hence the positive correlation.

It is thus possible that positive correlations were obtained because the implicated dopamine levels were relatively low, so that previous studies have mainly tapped into the left part of the putative inverted U-shaped curve. Even if, this interpretation is preliminary, we suggest that it nicely fits the available evidence and merits further exploration. A limitation of this study is the indirect nature of the PFC DA release by the CPT; it is not to exclude the role of other stress-related catecholamines such as noradrenaline (even if noradrenaline has not yet been implicated in binding processes) or the participation of other stress-related areas as the amygdala in the CPT-induced loss of task-relevant visuomotor binding. Therefore, the hypothesis of an interaction between visuomotor binding and PFC DA levels requires more direct investigation using different paradigms. One such possibility is, for example, to examine the effect of catechol-omethyltransferase (COMT) polymorphism Val158Met on task-relevant visuomotor binding both at baseline and after tolcapone administration, since tolcapone is known to influence baseline PFC DA activity.

## Acknowledgments

We would like to thank Bernet Elzinga for her invaluable assistance in the Methods and Bart Verkuil for suggesting the link between stress and the CPT. We would like to thank also the anonymous reviewers, in particular Panos Bitsios.

## References

Abeles, M. (1991). *Corticonics: Neural circuits of the cerebral cortex*. Cambridge: Cambridge University Press.

Arnsten, A. F. T. (1998). Catecholamine modulation of prefrontal cortical cognitive function. *Trends in Cognitive Sciences*, *2*(11), 436–447.

Arnsten, A. F. T., & Goldman-Rakic, P. S. (1998). Noise stress impairs prefrontal cortical cognitive function in monkeys: Evidence for a hyperdopaminergic mechanism. *Archive of General Psychiatry*, *55*, 362–369.

Ashby, F. G., Isen, A. M., & Turken, U. (1999). A neuropsychological theory of positive affect and its influence on cognition. *Psychological Review*, *106*, 529–550.

Blin, O., Masson, G., Azulay, J. P., Fondarai, J., & Serratrice, G. (1990). Apomorphine-induced blinking and yawning in healthy volunteers. *British Journal of Clinical Pharmacology*, *30*, 769–773.

Braver, T. S., Barch, D. M., & Cohen, J. D. (1999). Cognition and control in schizophrenia: A computational model of dopamine and prefrontal function. *Biological Psychiatry*, *46*, 312–328.

Castelo-Branco, M., Goebel, R., Neuenschwander, S., & Singer, W. (2000). Neural synchrony correlates with surface segregation. *Nature*, *405*, 685–689.

Colzato, L. S., Erasmus, V., & Hommel, B. (2004). Moderate alcohol consumption in humans impairs feature binding in visual perception but not across perception and action. *Neuroscience Letters*, *360*, 103–105.

Colzato, L. S., Fagioli, S., Erasmus, V., & Hommel, B. (2005). Caffeine, but not nicotine enhances visual feature binding. *European Journal of Neuroscience*, *21*, 591–595.

Colzato, L. S., & Hommel, B. (2008). Cannabis, cocaine, and visuomotor integration: Evidence for a role of dopamine D1 receptors in binding perception and action. *Neuropsychologia*, *46*, 1570–1575.

Colzato, L. S., van Wouwe, N. C., & Hommel, B. (2007a). Feature binding and affect: Emotional modulation of visuo-motor integration. *Neuropsychologia*, *45*, 440–446.

Colzato, L. S., van Wouwe, N. C., & Hommel, B. (2007b). Spontaneous eye-blink rate modulates sensorimotor binding. *Neuropsychologia*, *45*, 2387–2392.

Colzato, L. S., van Wouwe, N. C., van den Wildenberg, W., Elzinga, B., Hommel, B. (submitted for publication). Stress and cognitive control: Dissociating effects on dorsolateral and ventromedial prefrontal cortex.

Deutch, A. Y., & Roth, R. H. (1990). The determinants of stress-induced activation of the prefrontal cortical dopamine system. *Progress in Brain Research*, *85*, 367–403.

Diana, M., Melis, M., & Gessa, G. L. (1998). Increase in meso-prefrontal dopaminergic activity after stimulation of CB1 receptors by cannabinoids. *European Journal of Neuroscience*, *10*, 2825–2830.

Eckhorn, R., Bauer, R., Jordan, W., Brosch, M., Kruse, W., Munk, M., et al. (1988). Coherent oscillations: A mechanism of feature linking in the visual cortex? Multiple electrode and correlation analyses in the cat. *Biological Cybernetics*, *60*, 121–130.

Elzinga, B. M., & Roelofs, K. (2005). Cortisol-induced impairments of working memory require acute sympathetic activation. *Behavioral Neuroscience*, *119*, 98–103.

Engel, A. K., König, P., Kreiter, A. K., Schillen, T. B., & Singer, W. (1992). Temporal coding in the visual cortex: New vistas on integration in the nervous system. *Trends in Neuroscience*, *15*, 218–226.

Gessa, G. L., Melis, M., Muntoni, A. L., & Diana, M. (1998). Cannabinoids activate mesolimbic dopamine neurons by an action on cannabinoid CB1 receptors. *European Journal of Pharmacology*, *341*, 39–44.

Goldman-Rakic, P. S., Muly, E. C., III, & Williams, G. V. (2000). D1 receptors in prefrontal cells and circuits. *Brain Research Review*, *31*, 295–301.

Gray, C. M., König, P., Engel, A. K., & Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature*, *338*, 334–337.

Gurney, K. N., Prescott, T. J., & Redgrave, P. (2001). A computational model of action selection in the basal ganglia I: A new functional anatomy. *Biological Cybernetics*, *84*, 401–410.

Holroyd, C. B., & Coles, M. G. H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine and the Error-Related Negativity. *Psychological Review*, *109*, 679–709.

Hommel, B. (1998). Event files: Evidence for automatic integration of stimulus–response episodes. *Visual Cognition*, *5*, 183–216.

Hommel, B. (2004). Event files: Feature binding in and across perception and action. *Trends in Cognitive Sciences*, *8*, 494–500.

Hommel, B., & Colzato, L. S. (2004). Visual attention and the temporal dynamics of feature integration. *Visual Cognition*, *11*, 483–521.

Kirschbaum, C., Kudielka, B. M., Gaab, J., Schommer, N. C., & Hellhammer, D. H. (1999). Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamic–pituitary–adrenal axis. *Psychosomatic Medicine*, *61*, 154–162.

Lecrubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., & Sheehan, K. H. (1997). The Mini-International Neuropsychiatric Interview (M.I.N.I.): A short diagnostic structured interview: Reliability and validity according to the CIDI. *European Psychiatry*, *12*, 224–231.

Lee, I. H., Cheng, C. C., Yang, Y. K., Yeh, T. L., Chena, P. S., & Chiub, N. T. (2004). Correlation between striatal dopamine D2 receptor density and neuroticism in community volunteers. *Psychiatry Research: Neuroimaging*, *138*, 259–264.

MacKay, W. A. (1997). Synchronized neuronal oscillations and their role in motor processes. *Trends in Cognitive Science*, *1*, 176–183.

Mark, G. P., Blander, D. S., & Hoebel, B. G. (1991). A conditioned stimulus decreases extracellular dopamine in the nucleus accumbens after the development of a learned taste aversion. *Brain Research*, *551*, 308–311.

Muly, E. C., III, Szigeti, K., & Goldman-Rakic, P. S. (1998). D1 receptor in interneurons of macaque prefrontal cortex: Distribution and subcellular localization. *Journal of Neuroscience*, *18*, 10553–10565.

Murphy, B. L., Arnsten, A. F. T., Goldman-Rakic, P. S., & Roth, R. H. (1996). Increased dopamine turnover in the prefrontal cortex impairs spatial working-memory performance in rats and monkeys. *Proceedings of the National Academy of Sciences of the United States of America*, *93*, 1325–1329.

Murray, E. A., Bussey, T. J., & Wise, S. P. (2000). Role of prefrontal cortex in a network for arbitrary visuomotor mapping. *Experimental Brain Research*, *133*, 114–129.

Murthy, V. N., & Fetz, E. E. (1992). Coherent 25- to 35-Hz oscillations in the sensorimotor cortex of awake behaving monkeys. *Proceedings of the National Academy of Sciences of the United States of America*, *89*, 5670–5674.

Murthy, V. N., & Fetz, E. E. (1996). Oscillatory activity in sensorimotor cortex of awake monkeys: Synchronization of local field potentials and relation to behavior. *Journal of Neurophysiology*, *76*, 3949–3967.

Pfurtscheller, G., Pregenzer, M., & Neuper, C. (1994). Visualization of sensorimotor areas involved in preparation for hand movement based on classification of mu and beta rhythms in single EEG trials in man. *Neuroscience Letters*, *181*, 43–46.

Rammsayer, T. H. (1998). Extraversion and dopamine: Individual differences in response to changes in dopaminergic activity as a possible biological basis of extraversion. *European Psychologist*, *3*, 37–50.

Robbins, T. W., & Everitt, B. J. (1995). Neurobehavioural mechanisms of reward and motivation. *Current Opinion in Neurobiology*, *6*, 228–236.

Rodriguez, R., Kallenbach, U., Singer, W., & Munk, M. H. (2004). Short and long-term effects of cholinergic modulation on gamma oscillations and response synchronization in the visual cortex. *Journal of Neuroscience*, *24*, 10369–10379.

Roelfsema, P. R., Engel, A. K., Koenig, P., & Singer, W. (1997). Visuomotor integration is associated with zero time-lag synchronization among cortical areas. *Nature*, *385*, 157–161.

Sanderman, R., Arrindell, W. A., Ranchor, A. V., Eysenck, H. J., & Eysenck, S. B. G. (1995). *Het meten van persoonlijkheidskenmerken met de Eysenck Personality Questionnaire (EPQ): Een handleiding*. Groningen: Stichting Drukkerij C. Regenboog.

Sapolsky, R. L., Romero, M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews*, *21*, 55–89.

Suri, R. E. (2002). TD models of reward predictive responses in dopamine neurons. *Neural Networks*, *15*, 523–533.

Schnitzler, A., & Gross, J. (2005). Normal and pathological oscillatory communication in the brain. *Nature Reviews Neuroscience*, *6*, 285–296.

Thierry, A. M., Tassin, J. P., Blanc, G., & Glowinski, J. (1976). Selective activation of the mesocortical DA system by stress. *Nature*, *263*, 242–244.

Treisman, A. (1996). The binding problem. *Current Opinion in Neurobiology*, *6*, 171–178.

von Baeyer, C. L., Piira, T., Chambers, C. T., Trapanotto, M., & Zeltzer, L. K. (2005). Guidelines for the cold pressure task as an experimental pain stimulus for use with children. *Journal of Pain*, *6*, 218–227.

von der Malsburg, C. (1981). *The correlation theory of brain function* (Internal report 81-2). Göttingen: Max Planck Institute for Biophysical Chemistry.

von der Malsburg, C. (1999). The what and why of binding: The modeler's perspective. *Neuron*, *24*, 95–104.

Volkow, N. D., Fowler, J. S., & Wang, G. J. (1999). Imaging studies on the role of dopamine in cocaine reinforcement and addiction in humans. *Journal of Psychopharmacology*, *13*, 337–345.