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SHORT COMMUNICATION
Caffeine, but not nicotine, enhances visual feature binding

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Abstract

The distributed organization of the human visual cortex calls for a mechanism that integrates and binds the features of a perceived event, and neural synchronization is a prime candidate to serve that purpose. Animal studies suggest that synchronization in the visual cortex is enhanced by the muscarinic cholinergic system. Here we show that in healthy humans the binding of shape and colour, and of shape and location, of visual objects is increased by stimulating the muscarinic cholinergic system (caffeine consumption) but not by stimulating the nicotinic cholinergic system (nicotine consumption). Binding across perception and action is unaffected by either manipulation, suggesting a specific link between the visual system and the muscarinic cholinergic system.

Introduction

When we are facing multiple objects, a red apple and a yellow banana, say, the features of these objects are coded and processed in different cortical areas, yet what we perceive are well integrated objects and not mere bundles of attributes. The human brain thus seems to employ some kind of feature-binding mechanism which integrates the neural patterns coding the features belonging to a given event and makes us validly perceive that bananas are yellow but not red (Treisman, 1996). One candidate for such a mechanism are conjunction detectors, that is, neural units that are selective for the presence of particular feature combinations (Mozer, 1991; Riesenhuber & Poggio, 1999). Coding by means of conjunction detector makes sense for processing highly probable, evolutionarily important feature conjunctions. However, excessive numbers of conjunction detectors would be necessary to code any arbitrary feature combination, suggesting that frequently changing feature relations are processed in a different way (Singer, 1994; Colzato *et al*., 2004; Hommel, 2004). Better suited for this case seems to be the neural coupling of cell populations (Abeles, 1991; Engel & Singer, 2001), which is assumed to be achieved by coordinating and synchronizing the firing rates of cells referring to the same event, i.e. feature conjunctions may be coded spontaneously through the temporal coherence of their neural codes.

The possible role of neural synchronization in binding features within the visual and the motor system has been implicated in many studies. Apart from numerous animal studies (Abeles, 1991; Engel & Singer, 2001; Roelfsema *et al*., 1997), transient increases in synchronization in the gamma frequency range have been observed in healthy humans in visual tasks such as figure–ground discrimination (Engel & Singer, 2001), switching between bistable visual figures (Keil *et al*., 1999), and the retention of visual patterns in short-term memory (Tallon-Baudry *et al*., 1999) Motor tasks have revealed similar relationships between synchronization and integrative cognitive processes such as the planning of multifeatured actions (Hari & Salenius, 1999).

Although the available evidence points to a link between neural synchronization and feature binding, it remains unclear how and under which circumstances synchronization emerges, which makes it difficult to appreciate its true functional role. A potentially important observation in this context is the finding that, in the cat, neocortical synchrony in the gamma band ($\approx$ 30–70 Hz) is enhanced by muscarinic cholinergic agonists and disrupted by antagonists (Rodriguez *et al*., 2000, 2001, 2004). Empirical evidence for this link is consistent with Colzato *et al*. (2004), who observed in humans that alcohol, which is known to cause hypoactivity of the cholinergic system (Sanna *et al*., 1994; Minami *et al*., 1997), impairs feature binding in visual perception but not binding across perception and action. This fits with the hypothesis that the binding of visual features is driven by the muscarinic cholinergic system (Metherate *et al*., 1992; Rodriguez *et al*., 2000, 2001, 2004).

The aim of the present study was to set up a specific test of this hypothesis in healthy human subjects: can it be demonstrated that, first, cholinergic agonists increase the binding of visual features but not of other features and that, second, this increase is specifically driven by agonists of the muscarinic but not the nicotinic cholinergic system? The two agonists we compared were caffeine and nicotine. The behavioural effects of caffeine have been attributed to several neuromodulatory systems, including dopaminergic, GABA, serotinergic, cholinergic and noradrenergic pathways (Nehlig *et al*., 1992). However, there is evidence for a direct muscarinic cholinergic link between caffeine and the processing and short-term memory of visual information.

First, caffeine impacts the muscarinic cholinergic but not the nicotinic cholinergic system (Sorimachi *et al*., 1992). Cholinergic systems are under tonic inhibitory control by endogeneous adenosine, as suggested by observations of an increase of adenosine extracellular concentrations in the basal forebrain cholinergic areas of the behaving cat during prolonged wakefulness (Porkka-Heiskanen *et al*., 1997), and of dramatic decreases in waking induced by the perfusion of

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adenosine into the same regions (Portas *et al*., 1997). Also, the state of prolonged sustained wakefulness can be mimicked by increasing adenosine levels in basal forebrain cholinergic regions but not by increasing those levels in noncholinergic areas (Porkka-Heiskanen *et al*., 1997). Given that caffeine (and other xanthines) are adenosine antagonists, it thus makes sense to assume that they unfold their arousing impact by reducing the amount of inhibition adenosine exerts on cholinergic pathways. Moreover, evidence that the cholinergic impact on cortical states is mainly muscarinic (Lamour *et al*., 1982) suggests a central role of muscarinic cholinergic pathways in linking caffeine to information processing.

Second, a number of studies suggest that the impact caffeine exerts on the muscarinic cholinergic system eventually targets visual processes. Monkey studies have shown that systemic injections of scopolamine, a muscarinic cholinergic antagonist, impair the encoding of new visual objects but have little effect during recognition (Aigner & Mishkin, 1986; Aigner *et al*., 1991). In humans, the intake of caffeine attenuates the scopolamine-induced impairment of, among other things, perceptual sensitivity in visual search, visual short-term memory, and reading (Riedel *et al*., 1995). At the same time, caffeine does not modulate the impact of scopolamine on simple and choice reaction time, suggesting that caffeine has a specific effect on visual processing via muscarinic cholinergic pathways (cf. Smith *et al*., 2003). Consistent with this interpretation, a recent PET study in humans using a visual task provides evidence that muscarinic cholinergic effects modulate visual attribute processing (Mentis *et al*., 2001). In particular, muscarinic action was found to predominate in striate cortex (Brodmann Area 17) and lateral visual association areas (18 and 19), whereas nicotinic action predominated in the thalamus and inferior parietal regions (areas 39 and 40). In contrast to caffeine, nicotine is well known to induce cholinergic facilitation via nicotinic but not muscarinic receptors.

In view of this evidence, we assumed that, first, caffeine would act via muscarinic cholinergic pathways and nicotine via nicotinic cholinergic pathways and that, second, enhancing muscarinic but not nicotinic action would affect visual feature binding. Accordingly, we expected caffeine but not nicotine intake to affect the behavioural measure of feature integration we used, and this effect to be specific to visual binding.

We adopted the task from Hommel (1998), which involves the repetition of task-related and -unrelated visual features and of the response (see Fig. 1). The standard findings are interactions involving (i) the task-related stimulus features (e.g. shape, if and only if it signals the response; location, if and only if the responses are spatially defined); (ii) the nonspatial stimulus features (e.g. shape and/or colour); and (iii) the response (for an overview, see Hommel, 2004). These interactions all follow the same pattern: performance is impaired in partial-repetition trials, that is, if one stimulus feature (or the response) is repeated (e.g. S1 shape = S2 shape), while the other is not (e.g. S1 colour ≠ S2 colour or R1 ≠ R2). This demonstrates that the mere co-occurrence of a feature–feature or feature–response conjunction is sufficient to create a temporary binding of the respective feature codes, a kind of 'event file' (Hommel, 1998, 2004; Hommel & Colzato, 2004). Reactivating one member of this binding (as with feature repetition) spreads activation to other members, which calls for a time-consuming rebinding process in partial-repetition trials. Most important for our purposes, these partial-repetition costs can be taken to indicate feature–feature and feature–response binding, which is why we chose them as behavioural markers. Along the lines described above we thus expected caffeine and nicotine consumption to decrease partial-repetition costs for shape–colour conjunctions and for shape–location conjunctions (i.e. visual–visual bindings), but not for shape–response or location–response conjunctions.

Methods and subjects

Eighteen volunteers took part in each study and served in two experimental sessions separated by 3–7 days. 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, Faculty of Social and Behavioural Sciences). Subjects in the caffeine group (habitual coffee consumers: 3–5 units per day on average) and in the nicotine group were in the age range of 20–30, healthy nonsmokers, not on medication or drugs, and without neurological or psychiatric history according to self-report. All experimental sessions were held in the morning to prevent time-of-day effects and the possible occurrence of withdrawal symptoms. Participants were asked to refrain 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 to have a normal night's rest. A double-blind, placebo-controlled, randomized cross-over design with counterbalancing of the order of conditions was used to avoid expectancy effects. Treatments were deceptive: subjects were led to believe that they were drinking regular coffee or keeping a nicotine patch each experimental session. Subjects' compliance was encouraged by taking a saliva sample (not further analysed) at the beginning of each

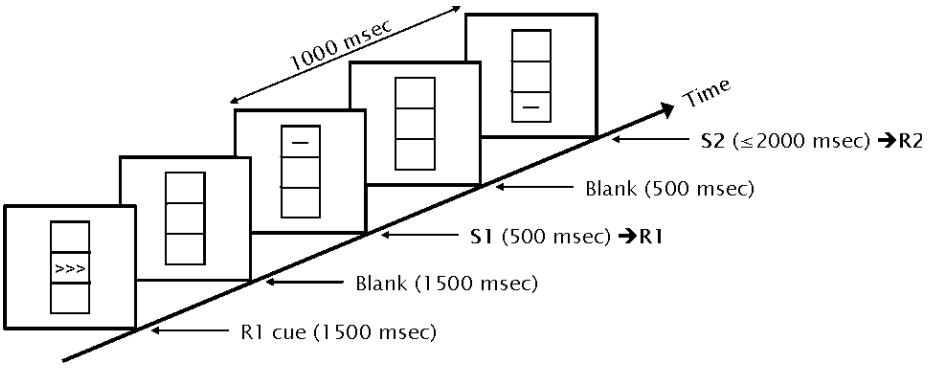

FIG. 1. Sequence of events in the present experiments (Hommel, 1998). A response cue signaled a left or right key press (R1) that was to be delayed until presentation of S1, a red or green, vertical or horizontal line in a top or bottom box. S2 appeared 1 s later: another red or green, vertical or horizontal line in the top or bottom box. S2 shape signaled R2, also a speeded left or right key press. R2 speed and accuracy were analysed as functions of the repetition vs. alternation of stimulus shape, colour and location, and of the response.

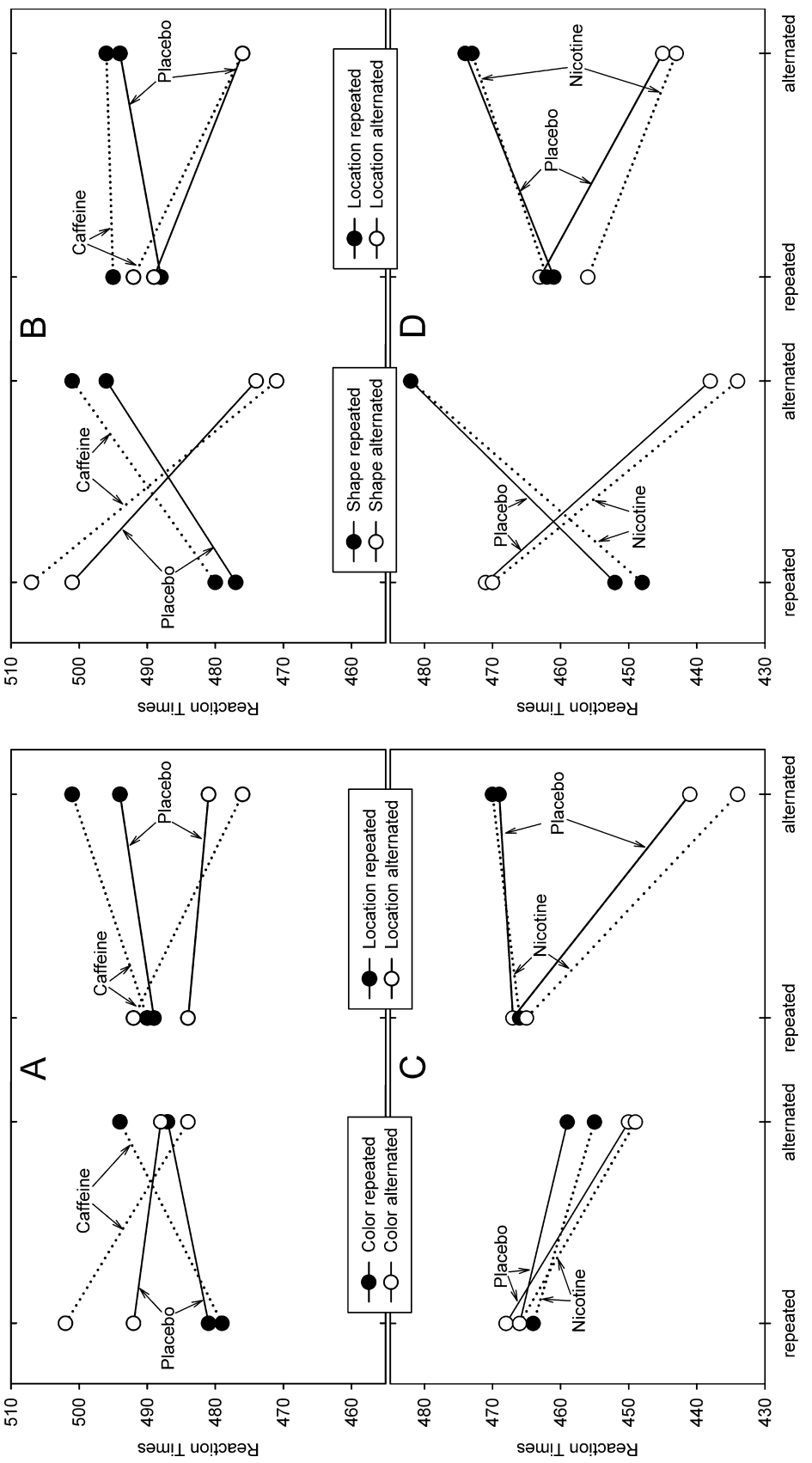

FIG. 2. Mean reaction time as a function of treatment and the repetition vs. alternation of (A and C, left) stimulus shape and stimulus colour, of (A and C, right) stimulus shape and stimulus location, of (B and D, left) response and stimulus shape and of (B and D, right) response and stimulus location. In each graph, ○ on the left and ● on the right side represent partial-repetition conditions (one stimulus feature is repeated while the other feature, or the response, is not; or vice versa), which are expected to produce worse performance, i.e. partial-repetition costs. (A and B) Caffeine study: feature–feature bindings are indicated by interactions between shape and location and between shape and colour (all $P < 0.001$), feature–response bindings by interactions between shape and response, location and response, and colour and response (all $P < 0.001$). Importantly, caffeine intake increased shape-location and shape–colour interactions (all $P < 0.05$) but not response–related interactions (all $P > 0.19$). Main effects were obtained for location ($P < 0.01$) and colour ($P < 0.05$). Error rates (not shown) followed the same pattern: reliable interactions were obtained for shape and location ($P < 0.05$), shape and response ($P < 0.005$), and location and response ($P < 0.003$), all showing the same partial-repetition-cost profile as reaction times. Apart from a location–repetition effect ($P < 0.05$), treatment produced a main effect ($P < 0.05$) but was not involved in any interaction. (C and D) Nicotine study: feature–feature bindings are indicated by interactions between shape and location ($P < 0.001$) and between shape and colour ($P < 0.05$), feature–response bindings by interactions between shape and response, and location and response (all $P < 0.001$). Importantly, nicotine did not modify any of these interactions (all $P > 0.25$). Main effects were obtained for location ($P < 0.001$) and shape ($P < 0.05$). Error rates followed the same pattern: apart from a location–repetition effect ($P < 0.01$), reliable interactions were obtained for colour and location ($P < 0.005$), shape and response and location and response (all $P < 0.001$), all showing the same partial-repetition-cost profile as reaction times.

experimental session. Placebo and dose caffeine and nicotine quantities corresponded to 250 mg lactose and 250 mg caffeine (≈ 3 cups of coffee) and 0 and 7 mg nicotine (≈ 1 cigarette), respectively.

Subjects completed a version of the task adapted from Hommel (1998); see Fig. 1. They 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 (three left- or right-pointing arrows in the middle box) that preceded the trigger stimulus S1 by 3000 ms. S1 varied randomly in shape (a thin vertical or horizontal line), colour (red or green) and location (top or bottom box). R1 was to be carried out as soon as S1 appeared, independent of its shape, colour 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 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 shapes, colours and locations of S2, the repetition vs. alternation of shape, colour, location, and the response, and three replications per condition.

Results

After excluding trials with missing (< 1500 ms) or anticipatory (< 200 ms) responses, mean reaction times (RTs) and proportions of errors for R2 (i.e. the response to S2) were analysed as a function of treatment (placebo vs. treatment) and the repetition vs. alternation of response (R1 → R2), stimulus shape, colour, and location (S1 → S2). ANOVAs were performed by using a five-way design for repeated measures. Figure 2 shows the results from Caffeine and Nicotine groups comparing treatment with placebo conditions. We replicated the earlier finding (Hommel, 1998; Hommel & Colzato, 2004) of a shape–colour and a shape–location interaction in both groups: repeating the shape of a stimulus but not its colour or its location incurred a partial-repetition cost (see Fig. 2A and B). However, these two interactions were only affected by caffeine intake but not by nicotine. We also replicated the common interactions between response and shape, and between response and location in both groups (see Fig. 2C and D). Importantly, none of these effects was modified by treatment.

Discussion

Our findings show that intake of caffeine, but not of nicotine, increased the binding of visual features while both drugs spared cross-domain bindings between visual features and manual responses. This observation lends support to the hypothesis that feature binding in visual cortex is associated with neural synchronization enhanced by the muscarinic cholinergic system (Rodriguez *et al*., 2000, 2001, 2004). Whereas the apparently selective link between synchronization and muscarinic receptors is consistent with animal studies on both neocortical and hippocampal synchronization (e.g. Fellous & Sejnowski, 2000; Rodriguez *et al.*, 2004), it remains to be determined why this link is selective for local visual feature binding. Interestingly, local integration processes within visual and motor cortex are commonly associated with synchronization frequencies in the gamma band (Engel & Singer, 2001), while interarea synchronization, such as in visuomotor integration (Roelfsema *et al*., 1997) or visual target selection (Gross *et al*., 2004), relies on lower frequencies in the beta band (≈ 13–30 Hz). It thus seems possible that drugs such as alcohol and caffeine exert (at least part of) their muscarinic cholinergic influence on visual processing by increasing and decreasing the variability of firing rates, respectively (cf. Borchard *et al*., 2000); this again might affect higher synchronization frequencies more than lower frequencies (Kopell *et al*., 2000) and, hence, local, intra-area bindings more than long-range interarea bindings.

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