Cholinergic Enhancement of Visual Attention and Neural Oscillations in the Human Brain

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Summary

Cognitive processes such as visual perception and selective attention induce specific patterns of brain oscillations [1–6]. The neurochemical bases of these spectral changes in neural activity are largely known, but neuromodulators are thought to regulate processing [7–9]. The cholinergic system is linked to attentional function in vivo [10–13], whereas separate in vitro studies show that cholinergic agonists induce high-frequency oscillations in slice preparations [14–16]. This has led to theoretical proposals [17–19] that cholinergic enhancement of visual attention might operate via gamma oscillations in visual cortex, although low-frequency alpha/beta modulation may also play a key role. Here we used MEG to record cortical oscillations in the context of administration of a cholinergic agonist (physostigmine) during a spatial visual attention task in humans. This cholinergic agonist enhanced spatial attention effects on low-frequency alpha/beta oscillations in visual cortex, an effect correlating with a drug-induced speeding of performance. By contrast, the cholinergic agonist did not alter high-frequency gamma oscillations in visual cortex. Thus, our findings show that cholinergic neuromodulation enhances attentional selection via an impact on oscillatory synchrony in visual cortex, for low rather than high frequencies. We discuss this dissociation between high- and low-frequency oscillations in relation to proposals that lower-frequency oscillations are generated by feedback pathways within visual cortex [20, 21].

Results

Neural processing of sensory signals originating from an attended location is thought to be enhanced by changes in oscillatory neural activity. Low-frequency alpha and beta oscillations in attended neuronal representations can be suppressed even before an expected stimulus appears (and enhanced for unattended) [5, 6]. This is thought to reflect up- and downregulation in the excitability of relevant neuronal populations [22]. Conversely, stimulus induced high-frequency gamma oscillations for attended neuronal representation are enhanced [1–4] and this is thought to increase their efficacy in driving postsynaptic neurons engendering privileged access to further processing stages [1, 23]. As for oscillations in general, the neurochemical pathways supporting these spectral changes are unknown but theoretical proposals suggest that an enhancement in high-frequency gamma oscillations is driven by cholinergic activity [17–19]. However, alpha oscillations are also known to be influenced by cholinergic neuromodulation [24–27].

Here we tested the impact of a cholinergic pharmacological intervention on brain oscillations during an attentional task in humans. Specifically, we recorded magnetoencephalography (MEG) while participants performed a spatial visual attention task (Figure 1), either under treatment with physostigmine [10, 11] as a cholinergic agonist or under placebo.

We recruited 16 participants who underwent both drug and placebo sessions (counterbalanced order) during this task. A central precue at trial start indicated which hemifield should be attended for a subsequently presented bilateral pair of gratings (see Figures 1B and 1C). The task was to discriminate orientation (clockwise or anticlockwise tilt relative to diagonal, titrated to yield ~90% accuracy) for the attended hemifield on each trial.

Under physostigmine, performance was faster than placebo (mean 779.8 ms versus 819.2 ms, mean speeding of 39.4 ms) without accuracy cost (mean 90% correct under physostigmine, 89% for placebo, n.s.). This difference was significant for reaction time (RT, $t = -1.84, p < 0.05$), when the order of drug and placebo was taken into account, as well as for inverse efficiency (combining RT and accuracy into a single value [28], $t = -2.52, p < 0.05$), and for the latter this was significant also without taking the order-effect into account ($t = -1.97, p < 0.05$). Thus, the drug improved performance, extending previous demonstrations that cholinergic enhancement can improve attentional processing.

We performed a time-frequency (t-f) analysis on MEG time courses projected onto the cortical surface, using a source-reconstruction method (see Supplemental Experimental Procedures) similar to previous studies [3, 4] to test the impact of the cholinergic agonist on well-known changes in oscillatory activity related to visuospatial attention. Directing attention to the left or right hemifield is known to suppress contralateral and/or increase ipsilateral alpha/beta activity [5, 6, 22], whereas gamma synchronization is enhanced [1–4] contralateral to the attended hemifield in visual cortex. Accordingly we tested for the expected symmetric attentional “hemispheric lateralization” effects in visual cortex (see Experimental Procedures for our formal symmetry constraint), then assessed any impact of physostigmine versus placebo upon either alpha/beta or gamma spatial attention effects.

Cholinergic Enhancement of Alpha/Beta Spatial Attention Effects

As expected [5, 6], alpha/beta hemispheric lateralization effects resulting from attended hemifield emerged in the preparatory cue period for occipital, parietal, and motor cortex (Figures 2A–2D), peaked around expected target onset, and then returned back to baseline levels. The novel result is that here alpha/beta spatial attention effects on visual cortex were enhanced by our cholinergic manipulation, being more pronounced under physostigmine than placebo...
No Cholinergic Modulation of Gamma Attention Effects in Visual Cortex

Consistent with previous reports [1–4], we found lateralized effects due to attended hemifield on gamma activity for visual cortex (p < 0.0001, uncorrected), extending into lateral occipital and ventral occipito-temporal cortex; see Figure 3. These gamma spatial attention effects emerged rapidly after stimulus onset and then endured for ~500 ms. But note that these gamma attention effects were clearly not enhanced by physostigmine here, being highly reproducible in both the drug and placebo sessions (see Figure 3), with no significant difference (p > 0.2, was actually for slightly reduced gamma attentional effects under physostigmine). Likewise, stimulus-related visual gamma responses, due merely to onset of the visual gratings independent of attended hemifield, were also unaffected by physostigmine (see Figure S2). We note for completeness (and to show that gamma elsewhere could be affected) that there was a clear enhancement of a poststimulus-induced gamma-band response in frontal cortex (p < 0.01, uncorrected, see Figure S2). The impact of the drug on oscillations in early visual cortex was thus highly specific for the alpha/beta bands.

Brain- Behavior Relations Induced by the Cholinergic Agonist

Finally we turned to possible relations between the neurophysiological effects and performance effects of our cholinergic intervention. We correlated the participant-by-participant drug effect on inverse efficiency scores (combining response speed and accuracy) to each of the neurophysiological effects described above (and as depicted in Figures 2, 3, S1, and S2) for the t-f windows shown. Note that these t-f windows had been selected independent of behavior, based either on attentional contrast in agreement with the literature or the difference between drug and placebo (Figures S1 and S2). The only significant brain-behavior relation observed was between drug-related performance speeding and the drug-induced poststimulus alpha spatial attention effects in the parieto-occipital sulcus (r = 0.65, p < 0.01). Although the effect in the extended time-frequency window in the lateral parts of parieto-occipital cortex as shown in Figures 2E and 2F were not significantly related to the behavioral effects, the poststimulus aspect (0–200 ms) was significant here, too (r = 0.52, p < 0.05). Given the limitation of this correlation to the poststimulus period, we further investigated whether this effect might by itself depend on any stimulus-evoked components but also checked on general effects of alpha/beta power irrespective of spatial attention. To this end we subtracted the stimulus-evoked field from the spectrograms (as in Figure S1) and computed a partial correlation analysis removing any general effects of alpha/beta power. Figure S3 shows the scatterplot for this analysis and reveals that the partial correlation for alpha lateralization in the parieto-occipital sulcus increased to r = 0.71 (p < 0.01) but decreased for the lateral aspects of parieto-occipital cortex (r = 0.41, p > 0.05). Thus, the key impact of the cholinergic agonist was upon alpha/beta oscillations modulated top-down by spatial attention in visual cortex. By contrast, gamma oscillations in visual cortex were unaffected.

Discussion

Here we demonstrate via a causal intervention with a cholinergic agonist (physostigmine) that cholinergic neuromodulation augments the top-down impact of spatial attention on...
oscillations in human visual cortex, specifically for low-frequency alpha/beta bands. Previous studies show that cholinergic agonists enhance the hemodynamic BOLD response [10, 11] to attended stimuli in visual cortex or spike-rates recorded invasively [13] in primary visual cortex but the studies had not examined oscillatory phenomena. Although our results show the same pattern of spatial attention effects as a previous MEG study on spatial attention [4]—contralateral suppression (or/and ipsilateral enhancement) of alpha/beta oscillations and contralateral enhancement of gamma oscillations—we show that a cholinergic enhancement via physostigmine boosts attentional alpha/beta effects in human visual cortex (Figure 2) but did not impact gamma effects in visual cortex (Figure 3; see also Figure S2). Moreover, the cholinergic impact on alpha/beta spatial attention effects were correlated to a drug-induced improvement in performance (Figure 4), such that strong attentional lateralization coincided with more efficient task processing, whereas any potential drug effect on visual gamma phenomena did not show such a correlation. Our alpha/beta findings provide a new line of evidence for the emerging view that low-frequency oscillations in visual cortex (and sensory cortex more generally) play a key role in gating sensory processing [6, 22, 31], auditory cortex of anesthetized animals [24, 25] after cholinergic manipulations, not from recordings in visual cortex during an attention task with a cholinergic intervention. Moreover, the one invasive study to date [32] that examined cholinergic modulation of visual cortex while recording oscillations (albeit in anesthetized cats, without any attention task) found no immediate effect on the visually driven gamma response, analogous to our results (Figure S2) for awake humans in a cognitive task that allowed us to document spatial attention effects also (Figure 3). Note that we did, however, find an enhanced gamma-band response (after grating onset) in right frontal cortex (Figure S2), a brain structure that is intimately involved in control of attention [33] although it did not correlate with the performance speeding here. Likewise, in rats, frontal gamma oscillations may also depend on cholinergic activation [34].

Our findings suggest that cholinergic enhancement affects oscillatory activity in specific frequency bands, but differentially for distinct brain regions. This may relate to differential distribution of cholinergic receptors [35] and/or regional differences in circuitry, e.g., laminar activation patterns. One potential explanation for this arises from recent monkey studies [20, 21]. These highlight that gamma synchrony in visual cortex...
involves superficial (supragranular) feedforward layers, whereas alpha/beta synchrony involves predominantly the deeper (infragranular) feedback receiving layers. In the context of the present finding of cholinergic influence on alpha/beta, but not gamma, oscillations within human visual cortex, this raises the intriguing possibility of cholinergic enhancement primarily impacting feedback layers in the context of visual attention [35, 36]. Feedback influences are presumably key to top-down attentional influences. Although some proposals [37, 7] have emphasized enhanced bottom-up processing because of cholinergic modulation, other accounts propose cholinergic enhancement of attentional influences [8–13]. Our neurophysiological findings for human visual cortex document an example of the latter influence, yet, interestingly, we see this effect to extend well into the poststimulus period, suggesting a cholinergic impact on the interaction of bottom-up and top-down influences.

The drug used here, physostigmine, influences both nico-
tinic and muscarinic receptors [8], and it may be of interest to further distinguish the specific contributions of these in future work. Nevertheless, physostigmine has proven useful for studying the impact of the cholinergic system on neural processing in many previous studies [8–11] and is of particular interest as a drug applicable to humans. The importance of our results is that they provide the first evidence on how the cholinergic system modulates cortical oscillations, in the context of a visuospatial attention task, illustrating the power and potential of combining neuropharmacology with MEG [38, 39] and documenting the importance of low-frequency (alpha/beta) oscillations for visual attention.

**Experimental Procedures**

**Participants**

Sixteen healthy male volunteers (mean age 25.6 years, SD 5.7 years) participated after informed consent in accord with ethical clearance. Participants trained on the task and then performed two MEG sessions: one under drug, one with placebo in a double-blind crossover design.

**Task**

Two visual gratings appeared, one in each hemifield centered at 8 degrees eccentricity (see Figure 1). Each trial started with a precue (central arrow pointing left or right for 500 ms) followed by a cue-target interval (length varied uniformly and unpredictably from 800 to 1200 ms), then onset of bilateral gratings for 500 ms. The task was to judge a tilt-offset for the grating in the cued hemifield (clockwise or counterclockwise relative to the diagonal), as indicated by pressing a right or left button with the corresponding index finger as quickly and accurately as possible. The actual tilt offset was titrated to yield ~90% correct performance; see Supplemental Experimental Procedures for further details.

**Procedure**

For the pharmacological MEG sessions, the responsible physician administered either the drug (0.01 mg physostigmine per kg bodyweight and infusion time and 0.2 mg glycopyrrolate as a peripheral antagonist; see Supplemental Information and [10, 11]) or the equivalent amounts of a saline solution for placebo via an intravenous line.

**Behavioral Data Analysis**

We performed a regression analysis on the difference between drug and placebo in RT with drug/placebo session order as a covariate. The same analysis was performed for inverse-efficiency behavioral scores [36], which combine RT and accuracy as RT divided by proportion correct.

**MEG Recording and Analysis**

MEG data were recorded continuously with a CTF Omega system at sampling rate of 600 Hz and analysis was primarily implemented with FieldTrip [40], unless stated. Procedures for recording, preprocessing, and artifact treatment followed previous work closely [1] as further described in Supplemental Experimental Procedures. For source reconstruction, we used a single-shell forward model [41] that was derived from the cortical sheets of each participant by a nonlinear warp of their brain to the MNI brain via SPM8 [42]. We used a beamforming approach [43, 44] to project the sensor data onto a (spatially) downsampled cortical grid representation. We then performed a time frequency analysis of the time courses on source level. For low-frequency bands (2.5–40 Hz), a wavelet analysis was computed and for the high-frequency bands, a multitaper analysis was computed.

**Analysis for Spatial Attention Effects**

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Analysis for Spatial Attention Effects

In order to minimize false positives, by design we implemented the following formal procedure to test here for symmetrically lateralized spatial attention...
Supplemental Information

Supplemental Information includes Supplemental Experimental Procedures, three figures, and one table and can be found with this article online at doi:10.1016/j.cub.2012.01.022.

Acknowledgments

This work was funded by the Wellcome Trust 087756/Z/08/Z. J.D. was a Royal Society Research Professor, M.B. had been funded by the Medical Research Council [G0500784], C.K. and H.J.H. were supported by Deutsche Forschungsgemeinschaft SFB 779, TP A2. The Wellcome Trust Centre for Neuroimaging is supported by core funding from the Wellcome Trust 091593/Z/10/Z.

Received: September 19, 2011
Revised: December 6, 2011
Accepted: January 11, 2012
Published online: February 2, 2012

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Figure 4. Brain-Behavior Relations

Scatterplots with regression lines showing significant correlation of drug impact on postural alpha/beta spectral power attention effects with inverse efficiency scores for lateral parts of parieto-occipital cortex (see Figures 2F, 2G, and S1).

(A) Correlation with the lateral parts of parieto-occipital cortex (Figure 2F, 10–20 Hz, 0–200 ms).

(B) Correlation with an ROI in the parieto-occipital sulcus (Figure S1), a structure tightly linked with alpha oscillations at the t-f window where the drug effect is maximal there (5–15 Hz, 0–350 ms).

Correlation of Physiological Measures with Behavior

We related the drug impact on inverse efficiency to the drug impact on those MEG results of interest already reported to avoid a blind search through the entire brain-time-frequency matrix.
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