Changes in electrophysiological markers of cognitive control after administration of galantamine

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ABSTRACT

The healthy brain is able to maintain a stable balance between bottom-up sensory processing and top-down cognitive control. The neurotransmitter acetylcholine plays a substantial role in this. Disruption of this balance could contribute to symptoms occurring in psychosis, including subtle disruption of motor control and aberrant appropriation of salience to external stimuli; however the pathological mechanisms are poorly understood. On account of the role beta oscillations play in mediating cognitive control, investigation of beta oscillations is potentially informative about such mechanisms. Here, we used magnetoencephalography to investigate the effect of the acetylcholinesterase-inhibitor, galantamine, on beta oscillations within the sensorimotor region during both a sensorimotor task and a relevance–modulation task in healthy participants, employing a double blind randomized placebo controlled cross-over design. In the galantamine condition, we found a significant reduction in the post-movement beta rebound in the case of executed movements and also in a planned but not executed movement. In the latter case, the effect was significantly greater following task-relevant compared with irrelevant stimuli. The results suggest that the action of galantamine reduces the influence of top-down cognitive processing relative to bottom-up perceptual processing in a manner resembling changes previously reported in schizophrenia.

1. Introduction

In schizophrenia (Dima et al., 2009) and ADHD (Liddle et al., 2011), an emerging theme is the hypothesis that imbalance between internally generated and externally generated mental processes plays a cardinal role. It is likely that these disorders differ in their underlying cellular or molecular processes. However, understanding the mechanism by which the balance between internally and externally generated processes is maintained in healthy individuals is potentially of great relevance to understanding how such imbalances result in functional impairment in mental disorders, and also for rational approaches to developing improved treatments.

Neural oscillations (rhythmic electrophysiological activity in neural assemblies) are thought to play a core role in mediating both short and long range coordination between brain regions. Oscillations exist over a range of frequencies, typically separated into well-defined frequency bands (alpha, beta etc.). Converging evidence from recent studies suggests that activity in the lower frequencies (alpha (8–13 Hz) and

beta (13–30 Hz) range) is reflective of cognitive influence of e.g. attentional networks on primary cortices (Bastos et al., 2015; Fries, 2015). Conversely higher frequency (gamma band (> 30 Hz)) activity is thought to mediate stimulus driven processing. Such oscillations are accessible by non-invasive electrophysiological imaging techniques such as magnetoencephalography (MEG), offering a means to assess, non-invasively, the balance of internally and externally focussed processing.

Robust modulation of neural oscillations in sensorimotor cortex by sensory or motor tasks is well known; specifically initiation of movement generates a reduction of beta amplitude which is sustained throughout movement (beta desynchronization) and concomitant increase in gamma amplitude (Salmelin et al., 1995; Jurkiewicz et al., 2006; for a review see Pfurtscheller and Lopes Da Silva, 1999). Cessation of movement drives an increase (above baseline) of beta amplitude (termed the post movement beta 'rebound' (PMBR)). Our recent work shows that PMBR following a visually cued finger movement is reduced in schizophrenia (Robson et al., 2016) and further that this reduction

was greater in patients with greater illness severity, i. e. the greater a patient's severity of illness, the lower their beta rebound value. Supporting this, we have also shown that beta rebound amplitude correlates negatively with schizotypal personality traits in healthy participants (Hunt et al., personal communication).

Evidence indicates that post-movement beta rebound (PMBR) is associated with the process of maintaining or adapting the brain's internal model that controls movements based on a prediction of the consequences of those movements (Cao and Hu, 2016). Variation in the magnitude of PMBR is greater when the discrepancy between the actual consequence of an action and the intended consequence is small, and furthermore this effect is increased if the prior performance history indicates that errors provide information that is useful for updating the brain's internal model. Cao and Hu (2016) propose that high beta rebound is associated with the process of actively maintaining the current forward model that guides movement. Our finding of reduced PMBR in schizophrenia supports a hypothesis that there is impairment of the 'top-down' process by which anterior brain regions modulate perceptual or motor systems. Our previous work using a task designed to modulate the relevance (or salience) of a stimulus showed that in schizophrenia there was a decrease in the amplitude of the beta rebound in response to a task-relevant stimulus (Liddle et al., 2016a,b), consistent with decreased influences of cognitive attribution of salience, which we interpret as reflective of top-down processing. We bear in mind that alternative hypotheses regarding the specific role of beta and gamma oscillations propose that gamma band oscillations are reflective of higher order cognition, and beta band oscillations index sensorimotor processing (Gaetz & Cheyne 2006, Jensen et al., 2005).

While investigation of biochemical abnormalities in schizophrenia has been strongly focussed on the neurotransmitters, dopamine and glutamate, abnormalities of other neurotransmitters, including acetylcholine (Ach), are a topic of continuing research (Higley and Picciotto, 2014). In relation to the balance between top-down and bottom-up signalling, Ach is of particular interest. Cholinergic transmission promotes the cortical processing of sensory input, while decreasing the influence of internally generated signals by suppressing excitatory top-down connections (Hasselmo and Giocomo, 2006). However increased cholinergic activity does not merely promote bottom-up signalling from sensory areas at the expense of all top-down signalling from anterior brain regions. The complex role of the cholinergic system in attention has been reviewed by Sarter et al. (2005). Inputs from prefrontal cortex to cholinergic neurons in basal forebrain nuclei such as the nucleus basalis, modulate the extensive projections of those cholinergic neurons to other brain regions in a manner that enhances processing of attention-demanding signals while filtering out irrelevant information. In other circumstances, increased cholinergic drive from the basal forebrain nuclei can impair performance. Turchi and Sarter (2001) reported that in rats, increase of ACh input to cerebral cortex, stimulated by infusion of the glutamatergic agonist, NMDA, in the nucleus basalis, led to increased errors of commission in a sustained visual attention task, apparently reflecting impaired top-down cognitive control.

In rats, ACh plays a role in mediating increased attention to a sensory stimulus in circumstances where the stimulus does not reliably predict subsequent task-relevant events, compared to circumstances where the stimulus is predictive of subsequent events (Bucci et al., 1998). This is consistent with the interpretation that ACh shifts attention towards bottom-up sensory signals and away from top-down predictive signals. This effect of ACH signalling contrasts with the phenomenon of PMBR in humans in situations where the predictability of the outcome of a joy-stick movement is manipulated by the experimenter unbeknownst to the participant making the movement (Tan et al., 2016). In such situations, the magnitude of the PMBR is greater when the participant can be more confident that the movement has achieved its intended effect. This suggests that the magnitude of PMBR is an indicator of greater confidence in the top-down forward model

guiding the movement.

Although it is necessary to be cautious in making predictions based on observations of different types of task in different species, the contrast of the observed effects of ACh on attention to stimuli with inconsistent predictive power in rats, with the observed increase in PMBR when the human participant can have greater confidence that the movement has achieved its intended effect, suggests that enhancement of cholinergic transmission might diminish PMBR by virtue of discounting top-down prediction in favour of attention to bottom-up sensory signals. If this prediction were to be confirmed if it would add confidence to the proposal that PMBR is an index of top-down control.

In the present study we used MEG, recorded during both a simple sensorimotor and a cognitive task, to assess the effect of the anti-cholinesterase inhibitor, galantamine, on neural oscillations. By inhibiting the metabolism of Ach, galantamine is expected to enhance cholinergic neurotransmission. By virtue of shifting the balance away from internally generated (top-down) processing towards external (stimulus driven or bottom up) processing, we hypothesised that galantamine would produce a reduction in the post-event beta rebound.

2. Methods

2.1. Design and participants

Forty-two individuals took part in the study. Two tasks were employed. The first was a simple visually cued movement similar to that used in previous schizophrenia research (Robson et al., 2016; termed the visuo-motor task). The second was a cognitive task, a relevance modulation task in which motor response had to be suppressed in the majority of relevant trials (Liddle et al., 2016a,b). Following removal of subjects, due to either failure to complete the full set of data acquisitions, or poor data quality, 32 participants (mean age 23.5 (SD 2.7), 14 Female) were included in the visuo-motor task and 36 participants (mean age 23.6 (SD 2.5), 14 Female) were included in the relevance modulation task.

The study took place over two scanning days scheduled one week apart, comprising a double blind within-subjects randomized control trial with administration of 8 mg of galantamine on one day and a placebo on the other day. Stratified randomisation by age and sex was used to assign participants to "galantamine first" or "placebo first" groups. Both pills looked identical. Pills were administered 1.5 h before MEG scanning took place. Participants were asked to fast for 2 h and avoid caffeine for 12 h prior to taking the pill at both sessions. Participants were fully informed of the potential for the drug to cause side effects such as nausea and dizziness, and throughout the study visit the researcher asked the participants about any symptoms they were feeling and how severe they were. All participants gave written informed consent to take part in accordance with the Declaration of Helsinki. The study was approved by the University of Nottingham Medical School Research Ethics Committee.

2.2. MEG tasks and data acquisition

2.2.1. Visuo-motor task

A red dot on a grey background was presented in the upper right screen quadrant, and the participants were asked to fixate on this throughout the experiment. Each trial comprised presentation of a static, vertical square wave grating (15 degree visual angle, 3 cycles per degree) in the centre of the screen, appearing in the lower left peripheral vision of the participant for 1.5–2 s. This visual presentation was followed by 8–8.5 s of fixation with no grating. The time intervals were jittered randomly. Participants were instructed to make a single right index finger abduction as soon as the grating disappeared. Electromyography (EMG) was recorded using electrodes placed on the first dorsal interosseous muscle of the right hand. 70 trials in total were recorded for each participant.

2.2.2. Relevance modulation task

The relevance modulation (RM) task involves manipulation of stimulus relevance to elicit neural responses linked to behavioural salience. The paradigm consisted of eight blocks of trials. In each block, there were two types of stimuli: images of butterflies and images of ladybirds (ladybugs), and two types of block: butterflies-relevant and ladybirds-relevant (see Liddle et al. (2016a,b) for example images). Blocks lasted for 90 s, including instructions, and consisted of 40 stimuli (20 butterfly images, 20 ladybird images). These blocks were followed by a 25 s rest period during which time the participant was required to look at a fixation cross. Stimulus duration was 800 ms, with a minimum inter-trial interval of 1300 ms, which had a mean random jitter of 200 ms to avoid entrainment.

Subjects were instructed before each block that either the butterflies or the ladybirds would be the relevant stimuli in that block, and to ignore the interleaving irrelevant stimuli. The eight blocks were presented alternately in the pattern: B–L–B–L–B–L–B–L (where B = butterflies-relevant and L = ladybirds-relevant). For the butterflies-relevant blocks, participants were shown a colour-filled line drawing of a target butterfly with a specific shape, inner wing colour, and outer wing colour at the start of the block and instructed to press a button every time they saw a butterfly that matched the target on all three attributes, while ignoring the interleaved images of ladybirds. In the ladybirds-relevant condition, an image was a target if there were equal numbers of red and yellow ladybirds. The ladybirds were positioned and oriented randomly on each stimulus presentation and the total number of ladybirds ranged between four and six. Participants were instructed to press a button for a target ladybird image, while ignoring the interleaving images of butterflies. For both block-types (butterflies-relevant and ladybirds-relevant) the probability of a target being presented was 0.05, a value set intentionally low so as to ensure close attention to the stimuli while minimizing target trials. All participants were given a full explanation and demonstration of the task outside the scanner. During the demonstration participants practiced watching out for the target stimuli and were asked afterwards to make sure they were able to identify them, although no button presses were made during the practice. Note that, for analysis, all trials in which a response was made were eliminated, leaving only relevant trials in which a button press was successfully supressed.

2.2.3. MEG data acquisition

MEG data were acquired using a 275-channel CTF MEG system (MISL; Coquitlam, BC, Canada) in synthetic 3rd order gradiometer configuration; at a sampling rate of 600 Hz. Subjects were positioned supine. To ascertain the location of the head within the MEG helmet, three head position indicator (HPI) coils were attached to the subject at the nasion and preauricular points. These were energised throughout the experiment in order to continuously track the subjects' head position. To allow co-registration of brain anatomy to the MEG sensor geometry, a measurement of the locations of the HPI coils relative to the scalp surface was created using a 3D digitiser (Polhemus; Colchester, VT). Anatomical head images were acquired using a 7 T Philips MRI scanner (T$_1$ weighted; MPRAGE sequence; 1 mm^3 resolution). Co-registration of MEG data to anatomical MRI was achieved by matching the digitised head surface to the equivalent surface extracted from the MRI.

2.3. Data pre-processing

MEG data were inspected visually and pre-processed by a single experienced experimenter who was blinded to the drug and placebo conditions. Data were filtered between 1 and 150 Hz, and synthetic 3rd order gradiometer noise cancellation applied. Any trials deemed to contain excessive interference, for example generated by muscles or eye movement, were removed. For the both tasks, trials/blocks in which the subject's head moved > 5 mm (Euclidean distance) from its starting position were excluded.

For the visuomotor task, data were epoched to include the last 1.5 s of visual grating, and 7 s of rest, in order to account for jitter in the original trials. Processed trials were therefore 8.5 s long, comprising 0–1.5 s of visual grating stimulation and 1.5–8.5 s of no stimulation. Only trials containing EMG abductions that were 3 standard deviations larger than the mean amplitude of the EMG signal, and that occurred within a time window of $1.6 < t < 2.5$ s were included (i. e. within 1 s of the visual grating offset allowing 1 ms for initiation of movement). Overall, these preprocessing steps resulted in a mean trial number per participant of 61 for both drug (SD 8) and placebo (SD 6); these trials were taken forward for further analysis. There was no significant difference in the number of drug and placebo trials as measured using a related-samples Wilcoxon signed rank test ($Z = -0.383$, $p = .702$).

For the relevance modulation task, relevant and irrelevant trials were epoched into 2 s windows from the onset of the stimulus. Trials containing button presses were excluded from the analysis. Inspection of the input signal from the button box showed that button presses occurred only in relevant trials, but may have occurred erroneously (i.e. a response may have been made to a non-target trial). To make the number of relevant and irrelevant trials equivalent within each dataset, the irrelevant trial following each button press was also removed. These preprocessing steps resulted in a mean trial number (out of a potential 160 trials) per participant of 147 (SD 18) for drug and 138 (SD 30) for placebo for both relevant and irrelevant conditions. A related-samples Wilcoxon signed rank test showed that the difference in the number of trials between drug and placebo conditions was not significant ($Z = -1.074$, $p = .283$).

2.4. Source analysis

Following pre-processing, data were source reconstructed using adaptive spatial filtering (beamforming) (Robinson and Vrba, 1999; Van Veen et al., 1997) with source space locations of interest informed by a cortical atlas. The cortex was parcellated using the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) from which subcortical regions of interest (ROIs) had been removed, leaving 78 cortical ROIs (Gong et al., 2009). Individual anatomical MRIs were first segmented to remove the skull and scalp using the brain extraction tool (BET; Smith, 2002) in the fMRIB software library (FSL; Jenkinson et al., 2012). Our AAL parcellation (which was initially defined in MNI space) was then transformed to each participant's individual anatomy using the fMRIB Linear Image Registration Tool (FLIRT; Jenkinson et al., 2012). For each of the 78 AAL regions, voxels were defined on a regular 4 mm grid across the whole cortical volume, and the LCMV beamformer estimated time course of activity derived for each voxel. A Gaussian weighting function of ~17 mm was applied to the voxel grid signals within each region to derive a single regional time course biased towards the centre of mass (Brookes et al., 2016). For beamforming, data covariance was calculated using a frequency window extending from 1 to 150 Hz using a 4th order Butterworth filter, and a time window which included the whole experiment (Brookes et al., 2008). The covariance matrix was regularised using the Tikhonov method with a regularisation parameter equivalent to 5% of the maximum eigenvalue of the unregularised covariance matrix. The forward calculation was based upon a dipole approximation (Sarvas, 1987) and a multiple local spheres head model (Huang et al., 1999). Dipole orientation was calculated using a non-linear search for optimum signal to noise ratio (SNR). Where necessary, beamformer time courses were sign flipped to account for arbitrary polarity of the source orientation calculation.

The beamformer was used initially to derive a spatial map, representing change in oscillatory power induced by movement in the visuo-motor task, within the beta (13–30 Hz) band. For each region, beamformer projected data were frequency filtered to the band of interest; a Hilbert transform was used to derive the analytic signal, and the analytic signal used to compute the amplitude envelope (termed

Hilbert envelope) of oscillations (see also O'Neill et al. (2015)). For the visuo-motor task, an active window was defined as 2–2.5 s (relative to the trial start) to encompass the beta desynchronization and a control window of 3–3.5 s defined to encompass the beta rebound. These windows were chosen as they represent the largest difference in power change across the task. We then computed the mean Hilbert envelope in both windows, and normalised the difference by the value in the control window to yield a measure of fractional change in oscillatory amplitude induced by the movement. This was done for all AAL regions. Maps were averaged across participants and used to confirm that the largest beta effects were in the left somatosensory AAL region. The left somatosensory AAL region was used as the predefined ROI for further analysis of the relevance modulation task, allowing for direct comparison of the movement and non-movement conditions within the same region in each participant.

2.5. Time-frequency analysis

To further assess task-related change in neural oscillatory amplitude, time-frequency spectrograms (TFS) were created for the left somatosensory AAL region for both tasks. For each subject, the beamformer projected time course for this region was frequency filtered into 31 overlapping bands in the 1–150 Hz range. For each band the Hilbert envelope was calculated and averaged across trials. For the visuo-motor task, a resting baseline signal for each frequency band was estimated as the mean Hilbert envelope value in the 6.5–8 s window, and subtracted from the remaining time course. For the relevance modulation task, a resting baseline signal was calculated as a grand average of the last 20 s of each block (i. e. during the rest period), resulting in one resting value per participant for each frequency band; these values were subtracted from the resulting relevant and irrelevant time courses. Individual bands were concatenated in frequency to create time frequency spectrograms, which were then averaged across participants for each drug condition (galantamine, placebo). For further visualisation, we computed time courses of the frequency band of interest (beta: 13–30 Hz) by averaging across the applicable rows of the TFS with the baseline values added back in; these time courses were plotted showing mean and standard error over subjects in the galantamine and placebo conditions.

2.6. Statistical analysis

After visualisation of the time courses, we tested for a statistically significant effect of drug condition on movement-induced response. For the visuo-motor task, we computed (for each participant) the mean value of the Hilbert amplitude in a window encompassing the event-related beta desynchronization (2–3 s), a window encompassing the rebound (3–4 s) and a baseline window (7–8 s). The beta desynchronisation and rebound values are henceforth presented relative to resting baseline. We tested for a difference in these two sets of values, across drug conditions (i. e. between galantamine and placebo) using a two-sided Wilcoxon signed rank test of the null hypothesis that a change in the Hilbert envelope originated from a distribution with a median of zero when measured independently for all subjects. Bonferroni correction was applied to account for comparisons across the two windows (desynchronisation and rebound), creating a significance threshold criterion of $p = .025$.

To test for the statistical significance of the effect of drug condition on the planned movement response relating to the difference between a relevant and irrelevant stimulus, we computed (for each participant) the mean value of the Hilbert amplitude in a window encompassing the stimulus presentation (0–0.8 s) and the post-stimulus window (1–2 s) relative to baseline in both the relevant and irrelevant trials, and in the galantamine and placebo conditions separately. The baseline value was calculated as the grand average value across all 8 blocks of 25 s baseline window. We then used a repeated measures ANOVA to investigate any

interaction effects of relevance (2 factor levels: relevant and irrelevant) and drug condition (2 factor levels: galantamine and placebo). This was undertaken separately for the desynchronisation and rebound for the beta band values. Post-hoc tests of simple and main effects were conducted as necessary.

For both tasks, in order to rule out any confound of drug side effects, we undertook a supplementary analysis using the drug side-effect data for all participants, directly comparing those that experienced side effects and those that did not. Results showed no significant difference in neural activity between those with drug side effects and those without in both tasks (see Appendix A for method and results).

3. Results

3.1. Visuo-motor task

Fig. 1 shows results for our visuo-motor paradigm, for both galantamine and placebo conditions. Fig. 1A shows task-induced relative change in beta amplitude across all 78 AAL regions. Results show clearly that, as expected, beta modulation was observed in bilateral primary sensorimotor regions, with the largest effect in left postcentral gyrus (left somatosensory AAL region).

Fig. 1B shows the baseline corrected time-frequency spectrograms from left postcentral gyrus (primary somatosensory cortex), in which the expected beta band desynchronisation and rebound in response to a movement are observable. The upper panel shows the case for the galantamine condition whilst the centre panel shows the case for the placebo. The lower panel shows the placebo case subtracted from the galantamine case in a difference spectrogram. These same data are also visualised in Fig. 1C, in which the line plots show the averaged time courses in both conditions. Note that in Fig. 1B and C there is a clear decrease in beta rebound in response to galantamine. The desynchronisation (2–3 s) and rebound (3–4 s) windows were compared to a baseline value taken from the end of the trial (7–8 s) for the paired galantamine and placebo conditions. A Wilcoxon signed rank test was used to check for significant differences between the two group conditions for desynchronisation, rebound and baseline power. Comparing mean (over time) amplitudes for the rebound across conditions using a non-parametric Wilcoxon signed rank test, the observed difference in mean values was shown to be significant ($Z = -2.278$, $p = .02$). Relative to baseline, the mean rebound value for the galantamine condition was 75.52 (SD 175.8) nAm oscillatory amplitude and for the placebo condition 133.97 (SD 205.3) nAm. There was no significant effect of galantamine on the amplitude during the desynchronization window in the beta band ($Z = -0.402$, $p = .69$). There was also no significant difference in the baseline windows ($Z = -1.636$, $p = .10$).

3.2. Relevance modulation task

Fig. 2 shows time frequency spectra and time courses for beta band modulation during the relevance modulation task, in the galantamine and placebo conditions. The left somatosensory AAL region was used as the region of interest to allow direct comparison with the visuo-motor task.

Once again a difference in beta modulation is generated by galantamine, in which the magnitude of the beta rebound is clearly reduced compared to placebo, in the relevant case. This was tested statistically using values relative to resting baseline: For the beta rebound component, there was a significant interaction between the drug factor and the relevance factor, $F(1,35) = 6.3$, $p = .017$. Pair-wise comparisons showed that there was a significant effect of drug on the beta rebound, with galantamine showing a mean difference of -69.43 (SEM 20.44) nAm compared to the placebo ($p = .002$) and also a significant effect of relevance on the beta rebound, with the relevant condition showing a mean difference of 31.49 nAm (SEM 7.48) compared to the irrelevant condition ($p = .0002$). Conversely, for the beta
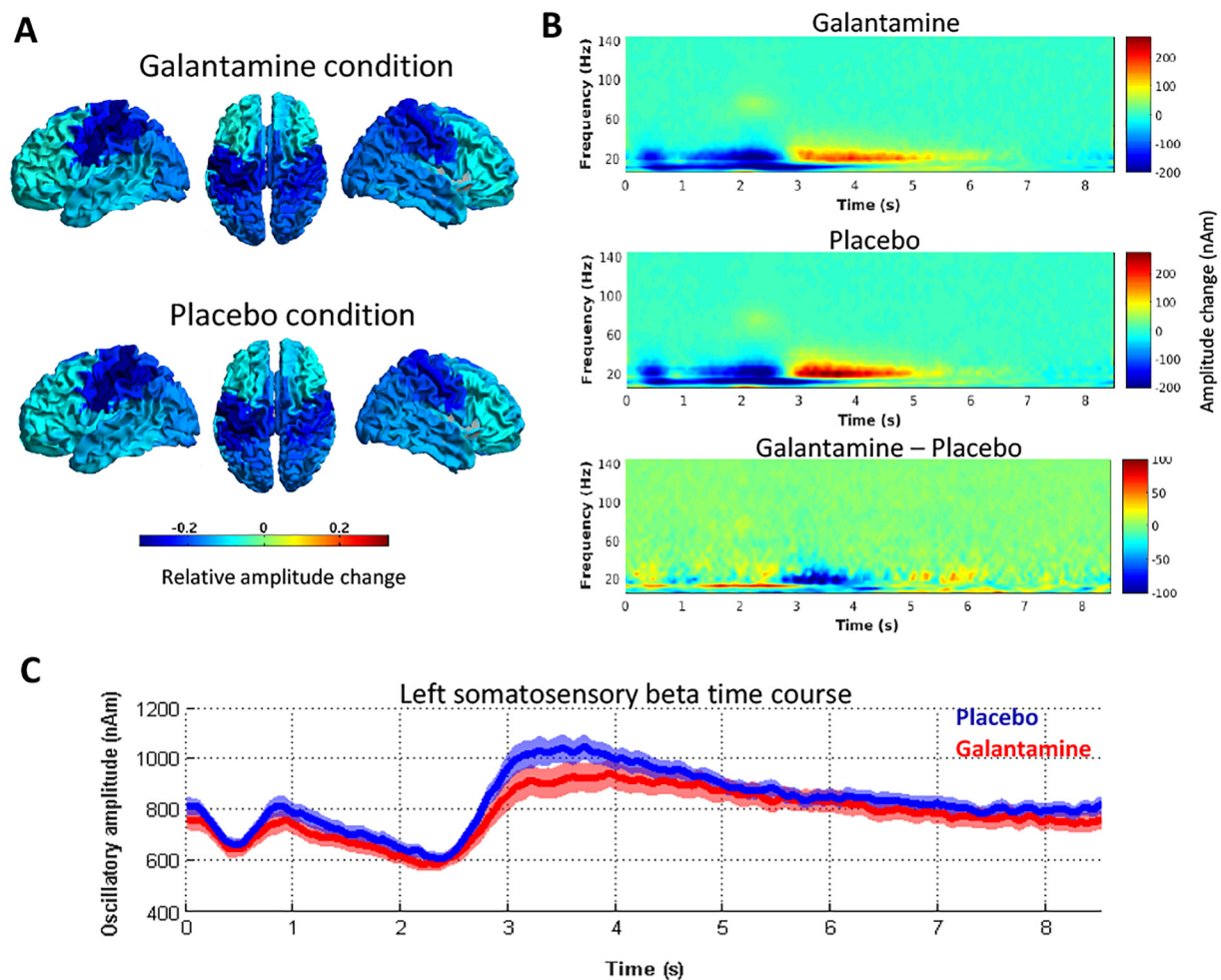
Fig. 1. Visuomotor task results: A) Beamformer source reconstructions, at 78 AAL regions, of cortical beta (13–30 Hz) amplitude changes for the motor task. All images contrast an active window during movement (2–3 s) and a comparison window during the rebound (3–4 s). B) Time frequency spectrograms (baseline corrected) for left sensory AAL region in the galantamine (top) and placebo (middle) conditions. The lower panel shows the difference between these for visualisation. C) Hilbert envelope time courses in the beta band, baseline uncorrected. The red time course shows the galantamine condition, the blue time course shows the placebo condition. Note that in both B and C a marked reduction in the amplitude of the beta rebound with galantamine is observed.

desynchronisation, there was no significant interaction between the drug factor and relevance factor, $F(1,35) = 0.689$, $p = .41$. There were main effects for drug ($F(1,35) = 9$, $p = .005$) and for relevance ($F(1,35) = 22.6$, $p = .00003$). A Wilcoxon signed rank test showed that there was no significant difference in the baseline values between galantamine and placebo conditions ($Z = -1.23$, $p = .22$). In summary, these results indicate that there is a significant difference in the beta rebound amplitude for the placebo condition in the relevant trials, indicating that that, in agreement with our visuo-motor data, galantamine reduces the beta rebound amplitude.

4. Discussion

This study investigated the effect of the cholinergic agent galantamine on neural oscillations in healthy participants. In accord with our hypothesis we found decreased beta rebound following movement in the visuo-motor task. Similarly, in the relevance modulation task, the enhancement of PMBR during relevant trials compared with irrelevant trials observed in the placebo condition, was reduced in the galantamine condition despite the absence of an overt motor response.

4.1. Is PMBR an index of post-event evaluation of action?

It has been proposed that beta rebound reflects local processes such

as promoting re-establishment of the status quo in the motor cortex after the execution of a movement (Engel and Fries, 2010) but more recently it has been proposed to be an index of long-range integrative processes, such as the maintenance of the forward model that guides movement (Cao and Hu, 2016). The observation that a beta signal apparently arising from dorsolateral prefrontal cortex is time locked to the occurrence of errors in a cognitive control task such as the Ericson Flanker task, and predicts the degree of post-error slowing (Marco-Pallarés et al., 2008), suggests that top-down beta signals serve a general role in mediating adaptive responses subsequent to perceptuo-motor events.

Furthermore, the findings of Tan et al. (2016) indicating that PMBR is greater when the participant has greater confidence that the movement has achieved its intended target, suggest the beta rebound reflects an assessment of the match between intention and achieved action. This observation raises the possibility that the reduction in beta rebound in the galantamine condition might reflect reduced confidence in the reliability of the prediction regarding movement outcome, such as would be anticipated if galantamine shifts the balance away from processing internal mental processes towards the processing of external stimuli. This interpretation is consistent with the proposal that acetylcholine enhances perceptual learning in circumstances in which consequences are uncertain by suppressing the use of outdated top-down cues and boosting bottom-up sensory processing (Yu and Dayan, 2005; Marshall
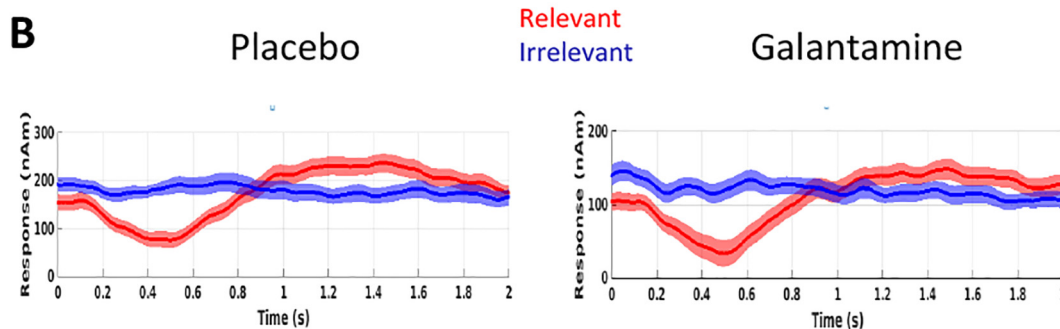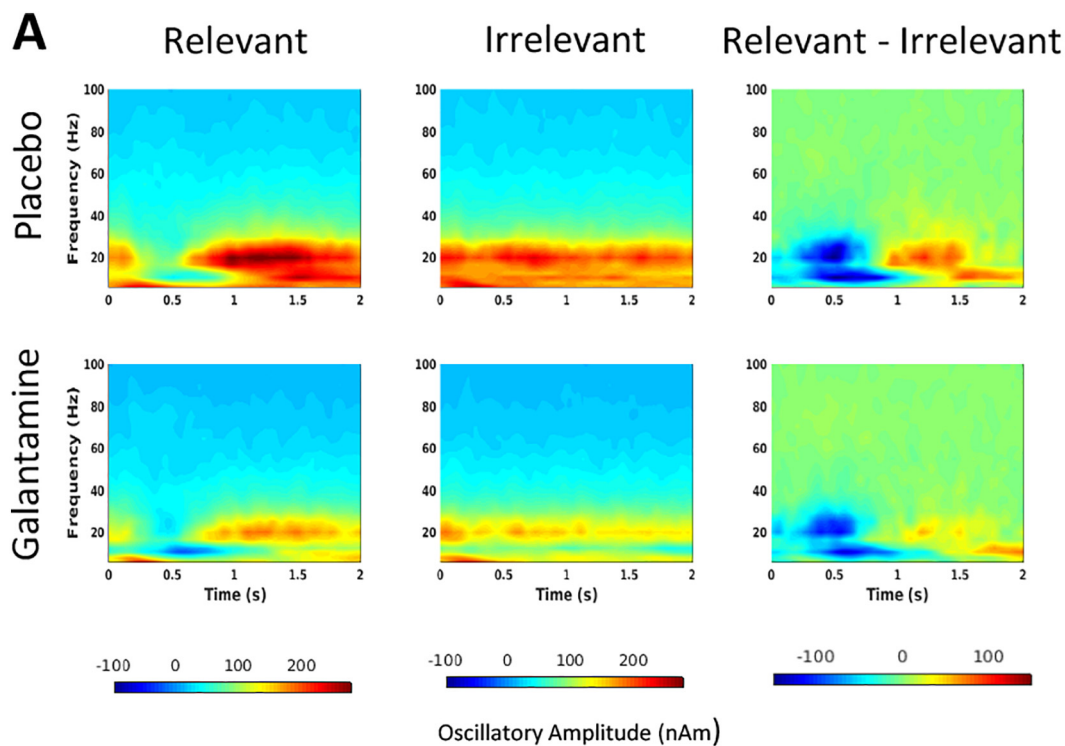
A

B

Fig. 2. Relevance Modulation Task Results A) Time frequency spectrograms for averaged relevant, irrelevant and difference spectrograms in the galantamine and placebo conditions for the beta band. B) Amplitude envelope time courses (without baseline subtraction) for the beta band. The red time course shows the relevant condition, the blue time course shows the irrelevant condition.

et al., 2016). We note the alternative hypotheses that Ach might modulate beta oscillations via cholinergic projections from subcortical regions (Kondabolu et al., 2016) or from basal forebrain nuclei but evidence regarding the pathways by which Ach exerts its influence on cerebral function is currently inconclusive (see Hasselmo and Sarter, 2011).

4.2. Beta rebound in the absence of overt motor response

In the relevance modulation task, our observation that beta rebound was significantly greater during relevant trials than irrelevant trials, despite the absence of an overt motor response in the placebo condition, confirms our earlier observation of a similar effect in healthy controls in the study by Liddle et al. (2016a,b) that employed the same task. This observation of greater beta rebound during task-relevant trials in which relevance is signalled by top-down processing, adds strength to the interpretation that beta rebound reflects top-down evaluative processing. Furthermore, the observation that galantamine reduced the magnitude of increase in beta rebound in relevant trials compared with irrelevant trials in this task provides further support for the interpretation that galantamine promotes bottom up processing at

the expense of top-down processing. The enhancement of attention to an external stimulus by Ach is especially marked when the stimulus is relevant or salient (Picciotto et al., 2012).

4.3. Parallels with schizophrenia

In both of the tasks employed in this study, the decrease in beta rebound in the galantamine condition relative to the placebo condition, was similar to the decrease in beta rebound observed in schizophrenia relative to controls, in our previous studies. Robson et al. (2016) reported diminished beta rebound following an executed motor act in the visuo-motor task in schizophrenia, while Liddle et al. (2016a,b) reported decreased beta rebound in relevant trials in the Relevance Modulation task in schizophrenia relative to that in controls. Although the similarity of the effect of galantamine with the effect observed in schizophrenia, is consistent with the proposal that in both situations there is a relative impairment of the top-down control of motor function, the similarity is puzzling in light of the fact that galantamine has cognitive enhancing properties in early Alzheimer's disease (Darreh-Shori et al., 2008; Sahoo et al., 2018).

However, given the role of acetylcholine in signalling anticipated

unreliability of predictive cues (Yu and Dayan, 2005) our findings are consistent with the proposal by Hemsley (1987) that a basic disturbance in schizophrenia is weakening of the influence of stored memories of regularities of previous input on current perception. More recently, Silverstein and Keane (2009) demonstrated that when top-down feedback is required to organize novel or weakly grouped stimuli, learning of perceptual organization tends not to occur in schizophrenia. Thus the observation of similarities between the effect of galantamine and the effect of suffering from schizophrenia on beta rebound might reflect similar weakening of the top- down influence. PMBR might indeed be useful index of impaired top-down processing in schizophrenia that can be elicited using a simple perceptual-motor task.

4.4. Contrast with physostigmine

The observed effects of galantamine contrast with those of the cholinesterase inhibitor physostigmine. Physostigmine produces a marked increase in the alpha/beta desynchronization during the performance of attention-demanding tasks in parietal and occipital regions, but shows less prominent effects on post-event beta synchronisation (Bauer et al., 2012). In contrast, our results show no effect on beta desynchronization during perceptual processing but an appreciably diminished post-event beta rebound. It should be noted that although both galantamine and physostigmine are cholinesterase inhibitors, galantamine also increases the responsiveness of cholinergic nicotinic receptors to ACh. By virtue of inhibiting the metabolism of ACh, both drugs would be expected to achieve pro-cholinergic effects via both muscarinic and nicotinic receptors, but the nicotinic effects might be expected to dominate with galantamine.

Appendix A. Investigating the influence of drug side effects

Table A1 shows the side effects experienced by the full study cohort, with some participants experiencing more than one side effect. In order to investigate the influence of drug side effects on results, we split the participant groups depending on whether they reported any drug side effects, or reported feeling 'fine' after taking the drug. There were some effects present in the placebo condition, however these were few and mild, and could be accounted for by caffeine withdrawal for example, so did not warrant explicit investigation. Participant numbers for each task are reported in Table A2.

5. Conclusion

In conclusion, our findings are consistent with the hypothesis that galantamine diminishes the effect of top-down influences on post-event adaptive processes in motor cortex, perhaps due to an increased attentional focus on the processing of external stimuli. The similarity of the effects of galantamine on beta rebound, with the diminution of beta rebound observed in schizophrenia suggests that further understanding of the mechanism of the effects of galantamine might enhance understanding of the pathophysiology of schizophrenia, and also of cognitive control deficits in ADHD.

Declaration of interest

LP reports personal fees from Otsuka Canada, SPMM Course Limited, UK, Canadian Psychiatric Association; book royalties from Oxford University Press; investigator-initiated educational grants from Janssen Canada, Otsuka Canada; travel support from Boehringer Ingelheim and Magstim Limited outside the submitted work.

Table A1

Symptom	Drug day (N)	Placebo day (N)
No symptoms	23	36
Nausea	9	–
Drowsy	3	3
Dizzy	9	–
Stomach pain	2	–
Lightheaded	2	2
Headache	1	1
Blurry vision	–	1
Heartburn	–	1
Overheating	1	–
Elevated heart rate	1	–
Adverse effects (vomiting, severe dizziness)	3	–

Table A2

Task	Felt 'fine' (N)	Drug side effects (N)
Visuo-motor	17	15
Relevance Modulation	21	15

Visuo-motor task

Using a series of 2-tailed Mann-Whitney U tests, we investigated the effect of galantamine side effects on the cortical responses. We compared the desynchronisation, rebound and baseline for beta frequency oscillations between the subset of participants with side effects and those without, only within the galantamine data (excluding the placebo data). For the beta frequency, there was no significant difference between the groups in the desynchronisation condition ($Z = -1.1114$, $p = .265$), the rebound condition ($z = -0.925$, $p = .355$), or the baseline ($z = -0.774$, $p = .439$).

Relevance modulation task

We used a mixed design ANOVA to compare the differences in the repeated measures components of desynchronization and rebound between the two independent galantamine groups (side effect and no side effect) in both the relevant and irrelevant conditions. There was no significant between subjects effect $F(1,34) = 1.3$, $p = .262$, indicating that there was no effect of galantamine side effect on the cortical responses for the relevance condition. Baseline values were tested separately, using a 2-tailed Mann-Whitney U test. There were no significant differences between the beta frequency baseline values for the side effect and no side effect groups ($z = -1.112$, $p = .911$).

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