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Changes in electrophysiological markers of cognitive control after administration of galantamine

Lauren E. Gascoyne[a,*], Karen J. Mullinger[a], Siân E. Robson[a], Jyothika Kumar[b], George C. O'Neill[a], Lena Palaniyappan[c], Peter G. Morris[a], Elizabeth B. Liddle[b], Matthew J. Brookes[a], Peter F. Liddle[b,*]

[a] Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy, University of Nottingham, University Park, Nottingham, UK
[b] Institute of Mental Health, Jubilee Campus, University of Nottingham, Nottingham, UK
[c] Department of Psychiatry & Robarts Research Institute, University of Western Ontario & Lawson Health Research Institute, London, ON, Canada

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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

* Corresponding authors.
E-mail addresses: lauren.gascoyne@nottingham.ac.uk (L.E. Gascoyne), peter.liddle@nottingham.ac.uk (P.F. Liddle).

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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.