Theta/delta coupling across cortical laminae contributes to semantic cognition.

Short title: Theta/delta interactions in semantic processing

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Running head: Cross frequency coupling in semantic cognition.

Abstract

Rhythmic activity in populations of neurons is associated with cognitive and motor function. Our understanding of the neuronal mechanisms underlying these core brain functions has benefitted from demonstrations of cellular, synaptic and network phenomena leading to the generation of discrete rhythms at the local network level. However, discrete frequencies of rhythmic activity rarely occur alone. Despite this, little is known about why multiple rhythms are generated together or what mechanisms underlie their interaction to promote brain function. One overarching theory is that different temporal scales of rhythmic activity correspond to communication between brain regions separated by different spatial scales. To test this we quantified the cross-frequency interactions between two dominant rhythms – theta and delta activity - manifest during MEG recordings of subjects performing a word-pair semantic decision task. Semantic processing has been suggested to involve the formation of functional links between anatomically disparate neuronal populations over a range of spatial scales and a distributed network was manifest in the profile of theta-delta coupling seen. Furthermore, differences in the pattern of theta-delta coupling significantly correlated with semantic outcome. Using an established experimental model of concurrent delta and theta rhythms in neocortex we show that these outcome-dependent dynamics could be reproduced in a manner determined by the strength of cholinergic neuromodulation. Theta-delta coupling correlated with discrete neuronal activity motifs segregated by cortical layer, neuronal intrinsic properties and long-range axonal targets. Thus, the model suggested that local, interlaminar neocortical theta-delta coupling may serve to coordinate both cortico-cortical and cortico-subcortical computations during distributed network activity.

Keywords

Cross frequency coupling, semantic processing, delta rhythm, theta rhythm

New and Noteworthy

Here we show, for the first time, that a network of spatially distributed brain regions can be revealed by cross-frequency coupling between delta and theta frequencies in subjects using MEG recording during a semantic decision task. A biological model of this cross-frequency coupling suggested an

interlaminar, cell-specific division of labour within neocortex may serve to route cortico-cortical and cortico-subcortical information flow to promote such spatially distributed, functional networks.

Introduction

Rhythmic electrical activity in discrete frequency bands accompanies a broad range of motor, affective and cognitive processes in the brain. Evidence for a direct, causal role in cognitive processing has been postulated for some time (e.g. Basar et al., 2001), with different frequencies involved to different extents in different tasks. For example, gamma rhythms organise primary sensory information to facilitate higher-order processing (Fries, 2015); beta rhythm generation correlates with task performance requiring short-term memory and prediction (Arnal & Giraud, 2012); alpha rhythms control access to stored memories (Klimesch, 2012); theta rhythms appear to be required for sequential processing of sensory information (Remondes & Wilson, 2013); delta rhythms appear vital for semantic processing (Harmony, 2013). Where the information is available, these rhythms appear to have an origin in subsets of neurons in local cortical and thalamic circuits (Roopun et al., 2008), but the temporal organisation they impart onto local circuit outputs is vital for control of information flow within the wider cortical mantle (e.g. Akam & Kullmann, 2010; Li et al., 2017).

Having a large library of rhythms available to local cortical circuits makes for a complex temporal landscape. However, the situation is further complicated by observations showing that discrete rhythms are rarely generated alone. Coexistence of multiple frequencies of activity, each temporally interacting with one another, is a common feature of brain dynamics (Lakatos et al., 2005) but we understand little about the mechanisms that facilitate these interactions, nor the computational advantages they may impart: Do they just represent a simple additive process, with one brain region involved simultaneously in multiple cortical processes, or is there synergy at work, with the presence of multiple, interacting rhythms superadditive for cortical function? There is increasing evidence for the latter, leading to the current working hypothesis that different frequencies of rhythm chaperone cortical communication on different spatial scales (Kopell et al., 2000; Canolty & Knight, 2010).

To address this issue we use a semantic cognition task to quantify changes in the outcome-dependent pattern of interaction between the two cardinal rhythms involved (theta and delta frequency activity). Semantic cognition assigns meaning to the storm of sensory inputs we experience during wakefulness (Corbett et al., 2009) and has been shown to involve interaction between many brain regions on multiple spatial scales (Binder et al., 2009). Functional neuroimaging studies suggest a ‘hub and spoke’-like structure to semantic representation networks (Patterson et

al., 2007). Activity locally seen within hub regions (e.g. Mollo et al., 2017) provides amodal rendering of semantic information (e.g. anterior temporal lobe, ATL) and comparators to prior schema leading to appropriate behavioural responses (e.g. posterior middle temporal gyrus, intraparietal sulcus; pMTG, IPS). This local activity needs to be distributed over broader spatial scales for appropriate semantic cognition to take place. Interaction between the above hub regions and language centers (LIFG, Sharot et al., 2012), executive control regions (Duncan, 2010) and parietal areas involved in polymodal sensory integration, attention and spatial cognition is also required (AG, Binder et al., 2009).

Flow of information between different regions involved in the semantic network most likely depends upon theta and delta frequency temporal patterns. Evidence for a role for theta-alpha rhythms (5-12 Hz) in semantic processing has been seen both in general in cortex (Klimesch et al., 1994) and specifically in ATL (van Ackeren & Rueschemeyer, 2014). Indirect evidence also suggests an involvement of activity at delta frequency: The N400 component of event related potentials – thought to represent a phase-resetting of on-going delta rhythms (van Petten & Luka, 2006) – is a marker for semantic cognition (Koelsch et al., 2004) and communication between frontal and parietal regions of semantic relevance is mediated by delta rhythms (1-4 Hz) during decision tasks (Nacher et al., 2013). The decision-making component of semantic processing also suggests importance for theta and delta rhythms: Activity across the theta-delta bands (2-9 Hz) relates to models of activity in which neurons coding for a particular outcome receive increasing levels of excitation over time (i.e. a 'ramp' of synaptic input) (Wang, 2002; Purcell et al., 2010; Hunt et al., 2012). In addition, iterative switching between discrete neuronal activity states at approximately theta frequency correlates with decision-making in frontal regions (Rich & Wallis, 2016).

Given these proposed roles for theta and delta frequency activity in semantic cognition we then use a local circuit, biological model of these rhythms (Carracedo et al., 2013) to identify possible *cellular* origins for their pattern of interaction. The profile of theta/delta interaction changes during the semantic task could be accurately reproduced in this local circuit model. The known connectivity properties of the cellular substrates identified by the model support the 'different rhythms – different spatial scales' hypothesis (Canolty & Knight, 2010) and suggest further refinement: Different frequencies of rhythm interact to coordinate cortico-cortical and cortico-subcortical functional connectivity.

Methods

Participants.

17 healthy, female, right-handed native English speakers (mean age 23.3 years, age range 20–35 years) with normal or corrected-to-normal vision participated in this study under written consent and following ethical approval (York Neuroimaging Centre, University of York).

Task.

The task is shown schematically in Fig 2a. Stimuli were adapted from Badre et al (2005) and involved sequential visual presentation of word pairs with varying levels of association. Subjects were requested to consider whether the word pairs were semantically related. Subjects were not aware of this aspect of the task structure. Related word combinations were selected using the Edinburgh Associative Thesaurus to identify words that were produced frequently together by 22% of participants. Unrelated word combinations were created by shuffling these data sets and removing coincidentally related pairs. The words were all nouns with a concreteness rating >500 as specified in the MRC psycholinguistic database (Wilson, 1988). Each word appeared once in both the related and unrelated conditions. Red fixation lines were always present on the screen, with words shown in light grey on a dark grey background (as in Fig 2a). The screen was positioned 75 cm from the viewer and the image projected in a way that words subtended 1 degree vertically and 5 degrees horizontally at the retina. First word presentation occurred 800 ms into the task for a duration of 200 ms. The second word presentation occurred at 1150 ms, again for 200 ms. The trial length was 3550 ms with a jitter of between 0 – 1000 ms between adjacent trials. 10% of trials were catch trials where participants were cued via a question mark on the screen to press a button to indicate whether the words in the pair were related. These trials were used to monitor reaction time (RT) performance and the behavioural response of interest: semantic decision ('related' vs. 'unrelated') for each subject/word pair. The catch trial and following trial were excluded from further analyses to avoid contamination from motor artefacts.

Data acquisition.

High resolution T1-weighted MR structural scans (method adapted from Kozinska et al., 2001) were acquired on a GE 3.0T Signa Excite HDX with an image resolution of 1.13mm and used for MEG co-registration. MEG data was acquired using a 4D Neuroimaging Magnes 3600 Whole Head 248 Channel SQUID Magnetometer based system. Co-registration was achieved with a Polhemus Fastrak (Colchester, VT 05446, USA) and 5 fiducial coils allowed for movement tracking. Data was acquired in a dark, magnetically isolated room and at a sample rate of 678.17 Hz (low-pass filtered to 200 Hz). Raw MEG data is available on request from beth.jefferies@york.ac.uk.

Virtual electrodes.

"Virtual electrodes" were constructed using a Linearly Constrained Minimum Variance beamformer using the technique described by van Veen (1997). The spatial filters were constructed using a covariance matrix calculated from all of the data and a multiple-spheres forward model (Huang 1999). Following co-registration with each subject's structural MRI scan coordinates were specified in standard MNI space, with individual coordinate spaces transformed to standard space. The first PCA component of the three orientations was used to create timeseries data. The extraction of beamformed data, and the analyses below, were performed using the York Neuroimaging Analysis Framework (publicly available at http://vcs.ynic.york.ac.uk/docs/naf/index.html) and standard Matlab signal processing routines.

Selection of regions of interest.

A 3D lattice of points was constructed across the whole brain with 5 mm spacing, and beamformers (above) were used to compute the total power at each point using the Neural Activity Index (NAI) (van Veen, 1997). This approach was used to assess any changes in magnitude of the two frequencies of interest (theta and delta rhythms, Fig 3b). However, owing to combinatorial issues and computational demand, more detailed spatiotemporal analyses were performed on a much smaller number of sites chosen for their precedented involvement – in terms of task- and state-dependent significant fMRI activations - in visual primary sensory (Banko et al., 2011) and semantic processing (eg. Visser et al., 2010). Regions involved in control, default, memory and network switching tasks (eg. Christoff et al., 2009) were also included for comparison.

Chosen coordinates for left (L) and right (R) hemispheres were as follows (numbered in bold according to the matrices shown in Fig. 2): **1**) medial frontal gyrus (LMFG: -27, 23, 48); **2**) angular gyrus (LAG: -41, -60, 29); **3**) posterior medial temporal gyrus (LpMTG: -64, -20, -9); **4**) posterior cingulate cortex (LPCC: -7, -52, 26); **5**) dorso-medial prefrontal cortex (LdMPFC: -7, 49, 18); **6**) ventro-medial prefrontal cortex (LvMPFC: -6, 52, -2); **7**) anterior temporal lobe superior temporal gyrus (LATL_aSTG: -57, 6, -18); **8**) anterior insular cortex (LAIC: -30, 18, 4); **9**) posterior insular cortex (LPIC: -36, 4, -2); **10**) inferior parietal sulcus (LIPS: -43, -50, 46); **11**) posterior inferior frontal gyrus (LpIFG: -47, 21, 18); **12**) left hippocampus (LHIPP: -25, -32, -18); **13**) left primary visual cortex (LV1: -15, -96, 6); **14**) medial frontal gyrus (RMFG: -27, 23, 48); **15**) right angular gyrus (RAG: 41, -53, 26); **16**) right posterior mid-temporal gyrus (RpMTG: 64, -20, -9); **17**) right posterior cingulate cortex (RPCC: 7, -46, 26); **18**) right dorsomedial prefrontal cortex (RdMPFC: 7, 49, 18); **19**) right ventromedial prefrontal cortex (RvMPFC: 10, 50, 0); **20**) right anterior temporal lobe/superior temporal gyrus (RATL_aSTG:

57, 9, -18); **21**) right anterior insular cortex (RAIC: 34, 16, 4); **22**) right posterior insular cortex (RPIC: 38, 5, -2); **23**) right inferior parietal sulcus (RIPS: 52, -60, 44); **24**) right posterior inferior frontal gyrus (RpIFG: 47, 18, 18); **25**) right hippocampus (RHIPP: 32, -40, -16); **26**) right primary visual cortex (RV1: 15, -96, 6).

Analysis.

Pre-processing: For each trial/subject, beamformed channels containing movement artefacts, eye blinks and external noise were excluded leaving 70-130 trials for each condition (related or unrelated word pairs) for each subject. Data epochs for each trial (length 3350 ms, see 'task' above) were then filtered from 0.5-45 Hz using a zero-phase, finite impulse response filter (Matlab) to preserve both phase information and the original sample rate (678.17 Hz) for analysis of temporal structure. For analyses focussing on theta and delta rhythms we first identified the subject mean modal peak frequencies in the timseseries data epochs from 1st stimulus presentation to RT. These were 5.2 Hz (used as the theta frequency reference) and 2.5 Hz (delta frequency) (see Fig. 3a). For theta/delta phase-amplitude coupling analyses band-pass filtered timeseries were generated from 4.5-7.5 Hz and 1.0 – 4.0 Hz.

Region activation: Changes in event-related potentials (ERPs), particularly the N400 component, have been linked to semantic processing previously (Koelsch et al., 2004). We therefore quantified stimulus-induced deviations from baseline (the first 800 ms of each trial prior to presentation of the 1st stimulus) as magnitude changes above threshold in the virtual electrode data. Threshold was defined by analysing the distribution for all virtual electrode activity for each subject and set at two standard deviations above the baseline mean (i.e. above the 5% significance level, Fig. 1a). This method captured both the initial ERP and any subsequent, significant deviations leading up to the decision time (i.e. 800 ms – RT for each trial/subject. Regions shown to be active during the task in general (at any time from presentation of 1st stimulus to RT) were then subdivided according to each subject's semantic decision ('related' or 'unrelated') on a trial-by-trial basis.

Temporal cross-covariances: Two measures of pairwise temporal relationships between virtual electrode activity were used on the data epoch between 1st stimulus presentation to RT. Firstly, synchrony is recognised as a key mechanism used by the cortex to code for properties of sensory stimuli (Gray et al., 1989). We calculated pairwise synchrony as the mean magnitude of the crosscovariogram around 0 ms (-25ms to +25 ms) lag for each pair of electrodes (Fig 1b) using the signal processing toolbox in Matlab. Data were Hamming windowed with window length of 300 ms and overlap of 285 ms. Secondly, covariance between electrode pairs at theta frequency –

particularly with half a theta cycle temporal separation – has been demonstrated as a signature of functional connectivity between brain regions (Mizuseki et al., 2009). We therefore took the magnitudes of the pairwise crosscovariogram around +96 ms and -96 ms (192 ms = 5.2Hz – the mean theta frequency for this subject cohort). These were meaned between 25 ms either-side of these phase values. Pairwise synchrony and theta covariance thresholds were again set at 2 standard deviations over the mean crosscovariance data distribution.

Phase-amplitude coupling (PAC): More complex temporal signatures, particularly cross-frequency coupling, are known to play an important role in long-range network function during cognition (Canolty & Knight, 2010). We therefore focussed on interactions between the two dominant frequencies expressed between stimulus presentation and RT: Delta-theta coupling was quantified using the method described in Kramer & Eden (2013) using meaned traces from each region node for each subject. Electrode data was band-pass filtered to extract activity in the delta band and theta band based on the cohort mean delta and theta frequencies (e.g. see above and Fig. 3a). The absolute component of the Hilbert transform of the theta channel was plotted relative to the phase of each delta period between stimulus presentation and response time (2-5 delta periods per subject/electrode). This method exposed any changes in theta rhythm magnitude relative to the concurrent delta rhythm phase (Fig.1c). Analysis data is presented on a linear plot to demonstrate any changes in the PAC profile for each task outcome. A false-detection-rate analysis (Storey & Tibshirani, 2003) was then performed to extract any statistical differences from shuffled theta channel data ($P>0.05$) and the significant PAC scores displayed on polar plots (e.g. Figs. 4 & 7). Raw data for this analysis was selected to meet the criteria suggested by Aru et al., 2015 for cross-frequency analysis in all aspects except 'input-related non-stationarities' – phase reset could not be discounted as it is a fundamental property of the delta and theta rhythms and vital for their role in cognition (Cobb et al., 1995; Calderone et al., 2014, see discussion).

In vitro model: Cognitively-relevant phenomena in human EEG, MEG and fMRI datasets are often modelled to suggest underlying network mechanisms. Neural, computational and statistical models have been applied to semantic cognition (Ralph et al., 2017) but rarely inform with sufficient objectivity and biological detail to suggest cell- and local network-level mechanisms. This is particularly pertinent when considering the origin of brain dynamic signatures of cognitive relevance for two reasons: Firstly, the minimum network substrates underlying known mechanisms of brain rhythms are all, to date, contained in local circuits anatomically smaller than the maximum spatial and/or temporal resolution of non-invasive techniques; Secondly, the different neuronal subtypes

involved in generation of different rhythms have different anatomical projection profiles which limit – and thus point towards - their possible involvement in communication across multiple, distributed regions (see discussion). Coupled delta and theta rhythms have been modelled at the local circuit level previously in rodent association cortical regions anatomically corresponding to areas known to be involved in human semantic cognition (Carracedo et al., 2013). In this model the two coexistent rhytms were generated locally by subnetworks involving neurons with very different long-range projection profiles: Regular spiking neurons (RS, theta) projecting purely cortico-cortically and intrinsic bursting neurons (IB, delta) projecting subcortically (Groh et al., 2010; Kim et al., 2015). We therefore used this model to identify possible neuronal substrates for semantic decision-related changes in theta/delta coupling in local circuits. We then related model data to the 'different frequencies – different spatial scales' hypothesis.

Briefly, horizontal and thalamocortically-oriented slices (450 μm thick) containing parietal cortex were taken from male Wistar rats (150-300g) according to the UK Home Office Animals (Scientific Procedures) Act 1986. Slices were transferred to an interface chamber and perfused with oxygenated artificial cerebrospinal fluid (aCSF) (in mM: 126 NaCl, 3 KCl, 1.25 NaH_2PO_4, 0.6mM $MgSO_4$, 1.2 $CaCl_2$, 24 $NaHCO_3$ and 10 glucose) at 32 °C. Delta rhythms occurred spontaneously and persistently in the presence of 2-6 μM carbachol – an analogue of acetylcholine. Extracellular field recordings were performed with aCSF-filled glass micropipettes (2-5 MΩ) and were bandpass filtered at 0.1Hz to 300Hz to provide a local reference for the neocortically generated delta rhythm. Intracellular recordings were performed with 2M potassium acetate-filled glass micropipettes (50-150MΩ) and were low-pass filtered to 2.5kHz. Neuron subtypes were quantified by response to depolarising current step (0.2 nA, 200 ms) from resting membrane potential. Statistical analysis of excitatory synaptic inputs (EPSPs) and action potential (AP) outputs was performed with a repeat measures ANOVA to examine the effects of experimental condition (different concentrations of carbachol) over delta phase. Significant (using FDR test) coupling between the field delta rhythm and EPSP/AP profiles are displayed in polar plots (Fig. 7).

Results

Basic ERP electrophysiology revealed sensory task-dependent but not semantic interpretation-dependent brain regions. No significant differences in behavioural performance were seen between each semantic interpretation ($P<0.05$, Fig. 2a,b). Similarly, the magnitude of the suprathreshold event related potential (ERP) changes also showed no correlation with behavioural performance. A

spatiotemporal sequence of regional activations was seen for each subject distributed around the time of second stimulus presentation (Fig. 2ci). However, while no set of regions active at any time between stimulus presentation and RT was common to all subjects when analysed by semantic outcome (word-pairs seen as related or unrelated), a set of regions showed activation (>2SD above baseline) in response to task in general in all subjects (Fig. 2cii). These regions were all posterior and consisted of bilateral primary visual, posterior cingulate and parietal areas along with both hippocampi, though measurement from this deep-lying structure with non-invasive methods is notoriously unreliable (Fig. 2ciii). No involvement of the frontal or temporal semantic regions used for analysis was exposed using this basic measure of local activity. Thus, region activation alone failed to capture the semantic decision-making process.

Theta/delta spectral content dominated the epoch between stimulus presentation and response but did not associate with semantic interpretation. The above data demonstrated that different semantic decision outcomes did not associate with magnitude changes in ERP in the individual regions analysed here. However, data also showed dominant, spectrally discrete delta and theta frequency peaks during the time from stimulus presentation to behavioural response (Fig. 3ai,ii). Band-pass filtering of these delta (1-4 Hz) and theta (4.5-7.5 Hz) components revealed no significant global differences in power in the time-period from presentation of the stimuli to a 'related' and 'unrelated' behavioural response when averaging across all subjects (Fig 3b, $P>0.05$). The presence of rhythmic activity is a known substrate for communication between brain regions vital for cognition (Fries, 2015). While rhythm power may be relevant in some cases, the key property of such rhythms is to provide a temporal framework with which to coordinate activity over cortical distance. We therefore next examined basic measures of this temporal framework associated with delta and theta rhythms.

Pairwise regional covariance metrics also revealed task- but not semantic interpretation-dependent networks. We measured the degree of synchrony from broadband signals as a measure of pairwise regional communication between regions (Gray et al., 1989). Significant ($P<0.05$) pairwise regional synchrony values for each correlation mean showed sequences of co-activation from 1st word presentation to behavioural response for each subject (Fig. 3ci). A small number of local region pairs in frontal and parietal areas correlated with task for >15/17 subjects (94%, Fig. 3ci,iii). However, no long-range correlations were apparent (Fig. 3ciii) nor, again, did synchrony between any set of region pairs correlate with either 'related' or 'unrelated' semantic outcome for all subjects (Fig. 3ci).

The above observations demonstrated that both the strongest ERP responses and the most broadband-synchronous region pairs did not correspond with either the core semantic network structure revealed by fMRI studies (see introduction), or the nature of the semantic decision made on presentation of the word pairs. We therefore next examined the precedented pattern of theta-mediated functional connectivity – the half theta period phase separation of activity between regions (Mizusaki et al., 2009). Again, no common set of region pairs correlated with semantic interpretation (Fig. 3di). However, compared to the 0 ms synchrony metric (Fig. 3c), a greater number of region pairs were shared by >15/17 subjects (94%) when considering semantic task alone. Connected regions formed a distributed network involving medial prefrontal cortex, medial frontal gyrus, hippocampus, visual cortex and temporal areas. Unlike the region pairs revealed by absolute synchrony, these regions have been shown previously to be vital for semantic processing - ATL-aSTG, pMTG, IFG, dmPFC, IPS, AG (Whitney et al., 2011; Jefferies, 2013), Fig. 3diii), executive control - vmPFC, MFG, memory - both left and right hippocampi, and task-associated primary sensory processing - left and right V1 (Fig. 3diii). The resulting network was far more global than that seen for zero lag/lead synchrony alone (Fig 3ciii vs. Fig 3diii) and consisted of region pairs with highly significant, greater anatomical separation ($P<0.01$, n=6,15).

Phase amplitude coupling (PAC) between theta and delta rhythms predicted semantic interpretation. The above data established that temporal interactions associated with theta rhythms exposed a network of regions previously linked to semantic cognition. To investigate this further we next examined any relationship between the theta rhythmic activity and the other dominant component of the spectra revealed in Fig. 3a – the delta rhythm. Delta and theta rhythms show cross-frequency coupling during cognition (Lakatos et al., 2005), and cross-frequency coupling in general is thought to provide a temporal framework for coordinating local and distal cortical dynamics (Canolty & Knight, 2010). We therefore analysed the profile of theta coupling to the delta rhythm for each region. We used the mean, by region for each subject, delta rhythm phase from the left hemisphere only as a reference as we wanted to prevent possible interference from inter-hemispheric phase lags. The left hemisphere was chosen as previous studies have suggested a dominance of the left hemisphere in semantic processing (Vigneaua et al., 2006; Whitney et al., 2011). Plotting the absolute (magnitude) or the theta rhythm against this mean delta phase metric showed a switch from single to bi-modal peaks per delta period prior to a 'related' and 'unrelated' interpretation respectively. These data suggested a difference in local delta-theta phase-amplitude coupling for different semantic interpretations ($P<0.01$, Kologmorov-Smirnov, n=17, Fig. 4).

A biological model predicted the changes in PAC profile correlated with altered neocortical neuronal subtype outputs. It is notoriously difficult to assign a genuine biological process to cross frequency coupling phenomena using analytical models (Aru et al., 2015). To establish a possible neuronal network mechanism to the above modification of delta-theta PAC (Fig. 4) we used an *in vitro biological* model shown to capture delta-theta PAC previously. The model chosen generates local, concurrent neocortical theta and delta rhythms in isolated parietal cortex (Carracedo et al., 2013). The delta rhythm responses seen in the MEG datasets used here appeared as a consequence of stimulus-locked averaging of on-going delta rhythms in individual trials ('phase resetting', Fig. 5a,b) as seen previously for visual stimuli (Klein et al., 2016). It should perhaps be noted that delta rhythms are a prominent feature of both slow-wave sleep *and* waking (Hall et al., 2014), with amplitude differences relative to higher frequencies responsible for the subtle changes in the spectral power law behaviour (Wen & Liu, 2016). We therefore first established that the model could also demonstrate this phase resetting. Using thalamocortical slices, time-discrete (50 μs) thalamic stimulation (bipolar electrode, 10-100 μA) was extremely effective at phase resetting the persistent neocortical delta rhythm (Fig 5. c,d).

However, while phase reset is a fundamental response of on-going cortical rhythms to input, it is also a potential source of spurious cross-frequency coupling measures (Aru et al., 2015). We therefore designed a set of model conditions that attempted to capture potential differences in cortical dynamics associated with semantic interpretation *in the absence* of discrete inputs: The *in vitro* model is dependent on low, but non-zero, cholinergic neuromodulation. Acetylcholine levels in the cortex vary on a sub-second timescale and carry information about the subjective nature of sensory stimuli. This form of neuromodulation is positively correlated with stimulus presentation properties, the degree of novelty, saliency and the subject's degree of attention to the stimulus (Acquas et al., 1996; Baxter & Chiba, 1999). Thus we used different levels of cholinergic neuromodulation to explore the effects on the profile of concurrent theta-delta rhythm interactions in the three main principal neuron subtypes in deep and superficial neocortex (Fig. 6a).

Lower and higher levels of pharmacologically-induced cholinergic excitation (2 μM and 6 μM carbachol respectively) generated significantly different profiles of local delta rhythm-nested neuronal excitation (excitatory postsynaptic potentials - EPSPs) and response (action potential – AP - generation) in all 3 neuronal subtypes tested (Fig. 6). Intrinsically bursting (IB) neurons in layer 5 (the primary generators of the local neocortical delta rhythm) generated trains of action potentials overlying ramped excitatory synaptic inputs (EPSPs, Fig. 6d, Fig. 8). A small but significant decrease in outputs from these neurons was seen at higher cholinergic excitation ($P<0.05$).

In contrast, for regular spiking (RS) neurons in layers 5 and 2/3, both EPSP inputs and AP output probabilities became bimodal under higher cholinergic excitation, with dual EPSPs leading to dual, discrete periods of output generation (Figs.6b,c). These dual peaks in input and output were separated, on average, by one theta period within each accompanying delta period (L5 RS, 175 ± 12 ms, L2/3 RS, 205 ±25 ms) – an observation similar to the peak separation in the MEG cross-frequency coupling measures (Fig 4). MEG is thought to measure mean local dendritic current flow in populations of neurons throughout the cortical mantle. We therefore compared the model data with the subject data by pooling the mean EPSP profiles (Fig.7b) and spike probabilities (Fig. 7c) from all 3 neuron subtypes and compared to the global mean delta-theta PAC profile (Fig. 7a). The transition from single to dual peaks was significant in each case (FDR, $P<0.05$, Figs. 7aii-cii). In addition, no significant difference was seen between the corresponding model and human data cross-frequency coupling profiles: Those associated with 'related' or 'unrelated' semantic interpretations in subjects compared with model data in low- and high-cholinergic conditions respectively ($P>0.05$ for pooled mean EPSP and AP probability measures). This suggested that reaching an 'unrelated' interpretation for paired words involved cholinergically-mediated, dual state changes at theta frequency in RS neuron inputs/outputs temporally aligned to activity in delta-generating IB neurons (see discussion).

4. Discussion

The data presented here demonstrate that theta and delta frequency dynamics dominate the spectral profile of cortical activity during semantic processing. Temporal coordination at theta frequency exposed the core regions of the semantic cognition network revealed by fMRI studies (see introduction). Additional temporally coupled regions exposed were the task-relevant primary sensory regions (bilateral V1), the hippocampi (but with the caveat that signal from deep structures can be unreliable) and key control regions involved in decision-making (MFG, vmPFC). The profile of delta-theta PAC within this network provided a predictor of semantic decision outcome in the word-pair task used here, with PAC profile in the period from stimulus presentation to RT showing dual peaks for unrelated decisions and single peaks for related decisions. Dual peaks in delta-theta PAC were reproduced in a biological model in a manner dependent on cholinergic neuromodulation suggesting multiple activations of cholinergically-excited theta-generating neurons were required to reach an 'unrelated' compared to a 'related' semantic decision. How could such a temporal pattern arise and how does it fit with current theories of the role of cross-frequency coupling in cognition?

Cross-frequency coordination of brain rhythms is a potent substrate for a broad range of cognitively-relevant processes (Hyafil et al., 2015), and the pattern of coordination may represent a range of different neuronal network architectures if it is assumed the phenomenon is biologically-generated. Unfortunately, apparent interactions can be generated non-biologically in many different situations related to data type, quality, analysis methods and external inputs (Aru et al., 2015). However, several observations do suggest the present observations were a consequence of a biological substrate:

a) The phase reset that generated the theta and delta average responses seen occurred on presentation of the first word not the second. This may explain why ERP measures alone exposed only the regions primarily receiving the sensory information (Fig. 2c) rather than those involved in the semantic task – insufficient information being presented at the time of phase-reset to perform any semantic computation.

b) The second word presentation was not time-locked to the intrinsic frequency of the delta rhythms or its nested theta rhythm – 350 ms (2.9 Hz) stimulus separation cf. 2.5 Hz and 5.2 Hz respectively.

c) The results presented were from all the delta/theta periods occurring from stimulus presentation to decision point. Pooling multiple periods of potentially cross-frequency coupled rhythms over time minimises any effects of time-discrete inputs (Aru et al., 2015).

d) Modelling the observed pattern of cross frequency coupling reproduced the results from human data with high fidelity in the *absence* of any time-discrete external inputs (Fig. 7).

In addition to using the model to help ablate any possible artefacts from sensory inputs contributing to the results, it also allowed us to speculate on the biological origins of the cross-frequency interactions seen. Despite the species, and temperature differences the model reproduced the same frequency range of theta seen in MEG data and slightly slower delta frequency. Pharmacological generation of theta/delta rhythms in this manner has been shown previously to work equally well in human and rodent tissue *in vitro* (Carracedo et al., 2013) and the data presented here suggest that the persistent rhythm in rat can be phase-reset in a similar manner to that seen in the human MEG data (Fig. 5): The consequent stimulus-locked delta rhythm survived for a longer time in the model than in subjects but this may be a consequence of the absence of further stimuli related to reaching the decision-point that may be present in the MEG trial data.

The overall change in PAC profile was remarkably similar in the model and human task-dependent data. In this respect the model predicted a highly discrete division of labour across the two, coupled

445 spectral components dominating the MEG signals. Theta rhythmicity, both in terms of excitatory
446 input and action potential output, was the sole property of regular spiking (RS) neocortical neurons.
447 These neurons are purely cortico-cortical in terms of their long-range projections: That is to say, they
448 communicate exclusively with their immediate neighbours *and* distal cortical regions directly. In
449 contrast, delta rhythmicity arises purely from layer 5 intrinsic bursting neurons (Carracedo et al.,
450 2013) and this principal neuron subtype projects to immediate neighbours *and* exclusively to distal
451 subcortical regions (Groh et al., 2010; Kim et al., 2015). In addition, the local mechanisms of
452 generation of these two rhythms are very different: The delta rhythm is generated in thalamus and
453 neocortex by synaptically coupled bursting neurons operating in networks controlled by $GABA_B$
454 receptor-mediated synaptic inhibition (Hughes et al., 1998; Carracedo et al., 2013) whereas the
455 theta rhythm (5-8 Hz) is generated by complex interactions between fast and slow $GABA_A$ receptor-
456 mediated inhibitory synaptic inputs to principal cells (Gillies et al., 2002).

457 This division of labour has at least two consequences for the dynamical differences shown here prior
458 to reaching a semantic decision: Firstly, the observed bimodal nature of deep and superficial layer RS
459 neuronal output probabilities, separated by one theta period, would suggest a role in reinforcing
460 interaction between local cortical layers. Reciprocal interactions between deep and superficial layers
461 has been proposed to represent a biological substrate for unsupervised learning and recall in layered
462 neural networks (Dayan et al., 1995; Carracedo et al., 2013). Longer range cortico-cortical
463 interactions at theta frequency are also suggested to underlie error detection with reference to
464 memory (Jensen & Tesche, 2002; Jacobs et al., 2006), and in prefrontal, medial frontal and parietal
465 areas (Luu et al., 2004; Trujillo & Allen, 2007; van Driel et al., 2012). These regions formed part of the
466 task-related circuit revealed by theta-related region coupling (Fig. 3d). This suggested a commonality
467 between error signalling and the 'actual vs. expected' nature of the comparison between 1^{st} and 2^{nd}
468 presented words in the task. The overt 'state-change'-like nature of the output probabilities in RS
469 neurons resembled activity patterns shown in orbitofrontal neurons during subjective decision-
470 making previously (Rich & Wallis, 2016) (Fig. 8).

471 Secondly, the theta-frequency state changes seen in RS neurons were strongly phase-related to the
472 delta rhythm manifest in IB neurons. Outputs from this cell subtype target subcortical structures
473 such as colliculus, striatum and thalamus, all of which have been shown to be involved in decision-
474 making. The ramped inputs to IB neurons during delta in the model presented here closely
475 resembled those inferred from existing models of neuronal dynamics during decision-making (see
476 introduction, Hunt et al., 2012, Fig. 8). However, in these models the ascending ramp of magnitude
477 of excitation to 'decision' arises predominantly from the sensory input containing the 'values' used

for choice. How can this be replicated in a model that has no sensory input (the isolated parietal cortex preparation)? The nature of the model indicated that 'ramps' in excitatory synaptic input were generated locally within neocortex via feedforward interactions between slow (predominantly NMDA receptor-mediated) recurrent connections between adjacent IB neurons. This fits the known profile of excitatory connections to neocortical neurons: Only approximately 5% of inputs to neocortical cells arise from ascending cortical input, even in primary sensory areas (Peters & Payne, 1993), and it is considered extremely rare to find a neuron that actually responds to a single sensory stimulus or stimulus property (Abeles, 1988). The vast majority of inputs arise from local and distal cortical efferents (Young, 2000). Thus the 'ramp' of inputs is best considered an intrinsic property of cortical networks, with the cortical regional profile of sensory input dictating the onset and gradient of the 'ramp' - the degree and spatial extent of phase reset of the on-going delta rhythm (e.g. Fig. 3a).

The strong correlation between semantic decision outcome and the profile of theta-delta cross-frequency coupling suggested that the above two phenomena need to interact to perform this cognitive task. The model used here suggested that cholinergic neuromodulation was critical in shaping this interaction. While cholinergic responses are the rule rather than the exception in all neocortical neuron subtypes the converse – neocortical neurons influencing cholinergic neuronal excitability – is very rare. Interestingly, the one neocortical region shown to have a relatively strong influence on the magnitude of cholinergic neuronal activity is the orbitofrontal cortex (Do et al., 2016). This suggests a feedforward relationship between 'state-change' activity (i.e. periodic, theta frequency alterations in output probability (Rich & Wallis, 2016)) in this area and the extent of cholinergic drive mediating theta-frequency state changes in wider neocortex. Thus modulation of the model local circuit via cholinergic excitation may not be solely related to attention and stimulus novelty (Acquas et al., 1996), but also to the on-going activity associated with semantic processing within neocortex.

We suggest that state change (Rich & Wallis, 2016) and accumulator models (Wang, 2002) may therefore reflect two temporally coherent, exquisitely self-governing dynamic signatures of the same local neocortical circuits synergistically modifying both local and brain-wide neuronal activity prior to semantic decision. In the present data these dynamic signatures were manifest as theta and delta frequency rhythms arising from different neuronal subtypes. The projection profile of these neurons suggested that cross-frequency coupling may not be just facilitating simultaneous interactions over different spatial scales, but rather coordinating cortico-cortical and cortico-subcortical interactions. These rhythms represented the majority of the spectral content of the MEG

data between stimulus presentation and decision timepoint. However, they also occur coupled to faster frequencies (e.g. Lakatos et al., 2005) that have also been linked to semantic processing in key brain areas (Mollo et al., 2017). More comprehensive studies, over a broader dynamic range will therefore likely reveal much richer detail of the semantic decision process and the role of cross-frequency coupling in brain-wide communication in general.

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Figure legends.

Figure 1. Example of methods used to quantify activity alone and by phase of delta and theta oscillation. a) Example trace showing a single region's mean (over trials) response pattern. Activation of the region was quantified as deviations of the MEG signal greater than +2SD above the mean. Scale bar 2 nA.m, 200 ms. **bi)** Example cross-covariogram (meaned over trials) for a single pair of regions in one subject over the timecourse shown for a). Time-variant cross-covariance was taken either at 0 ms delay or one half a theta period delay. **bii)** Example of a time-variant cross-correlation at 0 ms from bi illustrating the thresholding used to define coactivation. Scale bar 0.2 normalised covariance units, 200 ms. **c)** Left panel: Example delta (black line) and theta (grey line) band-passed activity (1-4 Hz and 4.5-7.5 Hz respectively). Data shows the averages for all left cortical regions for one subject. Scale bar 0.5 nA.m, 200 ms. Right panel: Simulation of the effect of theta magnitude modulation (blue) by a single 'delta' gaussian. The resulting phase-amplitude coupling metric is shown in red.

Figure 2: Raw response magnitude demonstrates common regions related to subjective task performance but does not predict outcome. a) Pictorial examples from the task. **b**) Percentage errors and reaction times post second stimulus for all subjects for the two conditions – related (black) and unrelated (red). **ci)** An example of region activity changes with time. Data from one subject, averaged for 'related' trials is displayed as colormap where regions form each row (arranged by time to maximal response). Trial time is along the x-axis and MEG region activations (>2SD) are on the colour axis. Times for stimulus onset are shown as dashed lines. Note region numbers (y-axis) were reorganised by time of initial activation and do not represent the numbers given in methods. **cii)** Plot shows the number of active regions (>2SD from the mean signal from 0.8-2.0s) across subject. Note no regions were common to more than 7/17 subjects when considering outcome ('related' – black line, 'unrelated' – red line, 'related' and 'unrelated' – blue line). **ciii)** Map shows the location of each of the 10 regions found common to >15 subjects (94%) overlaid on a horizontal brain representation viewed from below.

Figure 3. Synchrony and theta covariance differentially demonstrate common region pairs related to subjective task performance but do not predict outcome. a) Average waveform (left) and spectrograms (right) for 4 example regions (LPCC, LAG, RAIC and RpMTG) averaged over all trials for one example subjects for the related (black) and unrelated (red) conditions. Scale bar = 200 ms, 2nA.m. **b**) Mean (by subject) difference between 'related' and 'unrelated' delta and theta power shown as colormap of percent difference calculated for each point of grid of beamformed nodes with 5mm spacing throughout the brain. Note none of these regional differences was significant

when corrected for multiple comparisons (FWE p<0.05 in SPM). **ci)** Pairwise, normalised cross-covariance between regions demonstrated trajectories of synchrony above threshold (>2SD) from stimulus presentation (inset). Note region numbers (y-axis) were reorganised by time of initial activation and do not represent the numbers given in methods. Main graph shows number of region pairs with correlations > 2 SD above mean for each behavioural outcome. No synchronous region pairs were common to >8 subjects when separated into outcome ('related' – black line, 'unrelated' – red line). 0 ms synchrony showed only 5 region pairs interacted in >15 subjects when considering task (blue line). **cii**) cross-covariance matrix of all region pairs, colormapped onto commonality across the subject pool. **ciii**) Location of each of the 5 region pairs common to >15 (94%) of subjects. **di)** Theta covariance between regions demonstrated trajectories from stimulus presentation (inset). Main graph shows number of region pairs with theta-lagged correlations > 2 SD above mean for each behavioural outcome. Theta covariance showed 14 region pairs interacted in >15 subjects when considering task (blue line). **dii**) cross-covariance matrix of all region pairs, colormapped onto commonality across subjects. Dark colours cf. light colours indicate commonality in greater numbers of subjects. **diii**) Location of each of the 14 region pairs common to >15 (94%) or subjects. Inset shows the distribution of inter-regional distances for interacting regions in each case. Note the significant (P<0.05) shift from short to long-distance functional connections when considering theta covariance (orange) vs. synchrony (purple).

Figure 4. The profile of delta/theta phase amplitude coupling predicted semantic interpretation. **P**hase-amplitude coupling of region-averaged data, filtered for theta magnitude (4.5 – 7.5 Hz), with reference to the mean delta rhythm phase. The cross-frequency coupling profiles were significantly different (P<0.05, n=17, Kologmorov-Smirnov) when comparing activity prior to a 'related' (black) vs.an 'unrelated' (red) interpretation. Inset shows significant PAC epochs polar plotted by delta phase.

Figure 5. Stimulus-induced delta rhythms are generated by phase reset. a. Example, non-averaged single traces from a single subject (n=92 trials). Upper figure shows the beamformed signal from LAG. Individual trial responses are shown in black, average in red. Stimuli were presented at the times indicated by the arrows. Middle figure shows a single example of raw data (black) and the corresponding filtered data (blue) to illustrate the continual presence of delta activity pre- and post trial. Lower figure shows the phase for each of the 92 signals (black) and the average phase (red). **b**. Spectrograms constructed from '**a**' in two different ways: Upper spectrogram shows the power in the broadband signal derived from the average of each single trial. Lower spectrogram shows the power from the averaged signal. Note the stimulus-induced delta power increase is only apparent

from the average signal, the actual delta activity is persistent. **c**. *In vitro* model of persistent delta rhythms reproduced the stimulus-induced phase reset of persistent delta rhythms. Upper figure shows the signal from parietal cortex aligned to electrical; stimulation of thalamus in thalamocortical slices. Individual signals shown in black, the stimulus-aligned average is shown in red. Lower figure shows the corresponding phase of the recorded oscillation. **d**. Phase reset plot for thalamic input to parietal cortex in the model. Note the highly linear, 'near absolute' nature of the phase reset.

Figure 6: Biological model of concurrent theta/delta activity reproduces MEG outcome-specific dynamics via altered cholinergic excitation. a) schematic of cells targeted in the *in vitro* parietal cortex slice. Regular spiking (RS) neurons were recorded in layer 2/3 and layer 5, Intrinsically bursting (IB) neurons were recorded in layer 5. Spontaneous delta activity was recorded in the presence of cholinergic agonist (carbachol) at two different concentrations (2 μM, black lines, 6 μM, red lines). **b**) Mean ± s.e.mean probability of action potential generation in layer 2/3 RS neurons binned according to phase of layer 5 field potential delta rhythm. Significantly larger action potential probabilities ($p<0.05$, n=10 replicates per N=5 slices/neurons) were seen for the higher level of cholinergic excitation from 30-90^{o} (asterisk). Example traces show activity at resting membrane potential (spikes, upper examples) and at -70 mV (EPSPs, lower examples). **c**) A similar profile of action potential output changes was seen when comparing outputs from layer 5 RS neurons. **d**) Action potential bursts dominated layer 5 IB neuron activity. Elevated cholinergic excitation significantly reduced these burst outputs (asterisk, $p<0.05$, n=10 replicates per N=5 slices/neurons).

Figure 7. Neuronal EPSP (input) and action potential generation (output) profiles match theta/delta cross-frequency coupling profile differences for 'related' vs. 'unrelated' semantic interpretations. Decision dependent differences in MEG theta-delta cross-frequency coupling (**a**) were not significantly different from the mean EPSP profiles (**b**) and Action potential (**c**) profiles pooled from all 3 neuron subtypes ($P>0.05$, Kologmorov-Smirnov, MEG 'related' vs. model lower cholinergic excitation (black), and MEG 'unrelated' vs. model higher cholinergic excitation (red). Lower graphs show polar plots for values in the upper-quartile range of the distribution. Note the presence of an additional peak later in the delta period when comparing the two outcomes/model conditions.

Figure 8. Biological model predicts theta rhythm involvement in cortico-cortical communication and delta rhythm involvement in cortical-subcortical communication. Upper panel: Layer 5 IB neuronal behaviour in the experimental model of coupled theta and delta activity displayed overt ramp-like EPSPs indicative of increasing synaptic drive during the active part of one delta rhythm duty cycle. This behaviour resembled that of accumulator neurons used to model decision-making.

These neurons are all subcortically-projecting in neocortex (Groh et al.,2010; Kim et al., 2015). Accumulator model figure was adapted from Hunt et al.,2012. **Lower panel:** Layer 5 and layer 2/3 RS neuronal behaviour in the experimental model showed state-like changes in action potential output probabilities driven by multiple EPSP inputs in a manner dependent on subsequent decision. Similar changes in the probability of neuronal activity were reported for frontal cortical neurons using linear discriminant analysis (LDA) of unit activity. LDA probability figure adapted from Rich & Wallis, 2016. RS neurons are exclusively cortico-cortical projecting neurons.