Shaham, N, Burak Y. Submitted Slow Diffusive Dynamics in a Chaotic Balanced Neural Network [17].

In Press

Grodzinsky, Y, Deschamps I, Shapiro LP. In Press Patients with Broca’s aphasia and Young Children can reconstruct elided VPs [23].

2016


The basal ganglia (BG) network has been divided into interacting actor and critic components, modulating the probabilities of different state-action combinations through learning. Most models of learning and decision making in the BG focus on the roles of the striatum and its dopaminergic inputs, commonly overlooking the complexities and interactions of BG downstream nuclei. In this study, we aimed to reveal the learning-related activity of the external segment of the globus pallidus (GPe), a downstream structure whose computational role has remained relatively unexplored. Recording from monkeys engaged in a deterministic three-choice reversal learning task, we found that changes in GPe discharge rates predicted subsequent behavioral shifts on a trial-by-trial basis. Furthermore, the activity following the shift encoded whether it resulted in reward or not. The frequent changes in stimulus-outcome contingencies (i.e., reversals) allowed us to examine the learning-related neural activity and show that GPe discharge rates closely matched across-trial learning dynamics. Additionally, firing rates exhibited a linear decrease in sequences of correct responses, possibly reflecting a gradual shift from goal-directed execution to automaticity. Thus, modulations in GPe spiking activity are highest for attention-demanding aspects of behavior (i.e., switching choices) and decrease as attentional demands decline (i.e., as performance becomes automatic). These findings are contrasted with results from striatal tonically active neurons, which show none of these task-related modulations. Our results demonstrate that GPe, commonly studied in motor contexts, takes part in cognitive functions, in which movement plays a marginal role.


The myelin g-ratio is defined as the ratio of the inner to the outer diameter of the myelin sheath. This ratio provides a measure of the myelin thickness that complements axon morphology (diameter and density) with high specificity for assessment of demyelination in diseases such as multiple sclerosis. Previous work has shown that an aggregate g-ratio map can be computed using a formula that combines axon and myelin density measured with quantitative MRI. In this work, we computed g-ratio weighted maps in the cervical spinal cord of nine healthy subjects. We utilized the 300 mT/m gradients from the CONNECTOM scanner for estimating the fraction of restricted water (fr) with high accuracy using the CHARMED model. Myelin density was estimated using the lipid and macromolecular tissue volume (MTV) method, derived from normalized proton density (PD) mapping. The variability across spinal level, laterality and subject were assessed using a three-way ANOVA. The average g-ratio value obtained in the white matter was 0.76 +/- 0.03, consistent with previous histology work. Coefficients of variation of fr and MTV were respectively 4.3% and 13.7%. fr and myelin density were significantly different across spinal tracts (p = 3x10(-7) and 0.004 respectively) and were positively correlated in the white matter (r = 0.42), suggesting shared microstructural information. The g-ratio did not show significant differences across tracts (p=0.6). This study suggests that fr and myelin density can be measured in vivo with high precision and that they can be combined to produce a map robust to free water pool contamination such as cerebrospinal fluid or veins and weighted by the myelin g-ratio. Potential applications include the study of early demyelination in multiple sclerosis and the quantitative assessment of remyelination drugs.


When attention is directed to stimuli in a given modality and location, information processing in other irrelevant modalities at this location is affected too. This spread of attention to irrelevant stimuli is often interpreted as superiority of location selection over modality selection. However, this conclusion is based on experimental paradigms in which spatial attention was transient whereas intermodal attention was sustained. Furthermore, whether modality selection affects processing in the task-relevant modality at
irrelevant locations remains an open question. Here, we addressed effects of simultaneous spatial and intermodal attention in an EEG study using a balanced design where spatial attention was transient and intermodal attention sustained or vice versa. Effects of spatial attention were not affected by which modality was attended and effects of intermodal attention were not affected by whether the stimuli were at the attended location or not. This suggests not only spread of spatial attention to task-irrelevant modalities but also spread of intermodal attention to task-irrelevant locations. Whether spatial attention was transient or sustained did not alter the effect of spatial attention on visual N1 and Nd1 responses. Prestimulus preparatory occipital alpha band responses were affected by both transient and sustained spatial cueing, whereas late poststimulus responses were more strongly affected by sustained than by transient spatial attention. Sustained but not transient intermodal attention affected late responses (>200 msec) to visual stimuli. Together, the results undermine the universal superiority of spatial attention and suggest that the mode of attention manipulation is an important factor determining attention effects.


An individual's genetic makeup plays an important role in determining susceptibility to cognitive aging. Identifying the specific genes that contribute to cognitive aging may aid in early diagnosis of at-risk patients, as well as identify novel therapeutics targets to treat or prevent development of symptoms. Challenges to identifying these specific genes in human studies include complex genetics, difficulty in controlling environmental factors, and limited access to human brain tissue. Here, we identify Hp1bp3 as a novel modulator of cognitive aging using a genetically diverse population of mice and confirm that HP1BP3 protein levels are significantly reduced in the hippocampi of cognitively impaired elderly humans relative to cognitively intact controls. Deletion of functional Hp1bp3 in mice recapitulates memory deficits characteristic of aged impaired mice and humans, further supporting the idea that Hp1bp3 and associated molecular networks are modulators of cognitive aging. Overall, our results suggest Hp1bp3 may serve as a potential target against cognitive aging and demonstrate the utility of genetically diverse animal models for the study of complex human disease.


Pluripotent self-renewing embryonic stem cells (ESCs) have been the focus of a growing number of high-throughput experiments, revealing the genome-wide locations of hundreds of transcription factors and histone modifications. While most of these datasets were used in a specific context, all datasets combined offer a comprehensive view of chromatin characteristics and regulatory elements that govern cell states. Here, using hundreds of datasets in ESCs, we generated colocalization maps of chromatin proteins and modifications, and built a discovery pipeline for regulatory proteins of gene families. By comparing genome-wide binding data with over-expression and knockdown analysis of hundreds of genes, we discovered that the pluripotency-related factor NR5A2 separates mitochondrial from cytosolic ribosomal genes, regulating their expression. We further show that genes with a common chromatin profile are enriched for distinct Gene Ontology (GO) categories. Our approach can be generalized to reveal common regulators of any gene group; discover novel gene families, and identify common genomic elements based on shared chromatin features.

Deouell, LY. 2016 Microsaccades mediate a bottom-up mechanism for cross-frequency coupling in early visual cortex (Commentary on Lowet et al.). The European journal of neuroscience.
Neuronal responses characterized by regular tuning curves are typically assumed to arise from structured synaptic connectivity. However, many responses exhibit both regular and irregular components. To address the relationship between tuning curve properties and underlying circuitry, we analyzed neuronal activity recorded from primary motor cortex (M1) of monkeys performing a 3D arm posture control task and compared the results with a neural network model. Posture control is well suited for examining M1 neuronal tuning because it avoids the dynamic complexity of time-varying movements. As a function of hand position, the neuronal responses have a linear component, as has previously been described, as well as heterogeneous and highly irregular nonlinearities. These nonlinear components involve high spatial frequencies and therefore do not support explicit encoding of movement parameters. Yet both the linear and nonlinear components contribute to the decoding of EMG of major muscles used in the task. Remarkably, despite the presence of a strong linear component, a feedforward neural network model with entirely random connectivity can replicate the data, including both the mean and distributions of the linear and nonlinear components as well as several other features of the neuronal responses. This result shows that smoothness provided by the regularity in the inputs to M1 can impose apparent structure on neural responses, in this case a strong linear (also known as cosine) tuning component, even in the absence of ordered synaptic connectivity.

Lee, J, Joshua M, Medina JF, Lisberger SG. 2016 Signal, Noise, and Variation in Neural and Sensory-Motor Latency. Neuron. Analysis of the neural code for sensory-motor latency in smooth pursuit eye movements reveals general principles of neural variation and the specific origin of motor latency. The trial-by-trial variation in neural latency in MT comprises a shared component expressed as neuron-neuron latency correlations and an independent component that is local to each neuron. The independent component arises heavily from fluctuations in the underlying probability of spiking, with an unexpectedly small contribution from the stochastic nature of spiking itself. The shared component causes the latency of single-neuron responses in MT to be weakly predictive of the behavioral latency of pursuit. Neural latency deeper in the motor system is more strongly predictive of behavioral latency. A model reproduces both the variance of behavioral latency and the neuron-behavior latency correlations in MT if it includes realistic neural latency variation, neuron-neuron latency correlations in MT, and noisy gain control downstream of MT.

Atlan, G, Terem A, Peretz-Rivlin N, Groysman M, Citri A. 2016 Mapping synaptic cortico-claustral connectivity in the mouse. The Journal of comparative neurology. The claustrum is an intriguing brain structure, featuring the highest connectivity per regional volume in the brain. It is a thin and elongated structure enclosed between the striatum and the insular cortex, with widespread reciprocal connections with the sensory modalities and prefrontal cortices. Retinotopic and somatotopic organizations have been described in the claustrum, and anatomical studies in cats, monkeys, and rats have demonstrated topographic organization of cortico-claustral connections. In this study, we mapped the projections from cortical modalities (visual, auditory, somatosensory, motor and olfactory), and prefrontal regions (anterior cingulate cortex and orbitofrontal cortex) to the claustrum in mice. Utilizing expression of a virally-encoded synaptic anterograde tracer, AAV-SynaptoTag, followed by 3-dimensional reconstruction of the cortical projections, we performed a comprehensive study of the organization of these
projections within the mouse claustrum. Our results clearly demonstrate a dorsoventral laminar organization of projections from the sensory cortices to the claustrum, whereas frontal inputs are more extensive and overlap with the inputs from the sensory cortices. In addition, we find evidence in support of a core/shell organization of the claustrum. We propose that the overlap between the frontal inputs and the inputs from the sensory modalities may underlie executive regulation of the communication between the claustrum and the cortical modalities. This article is protected by copyright. All rights reserved.


Patient-specific models of anatomical structures and pathologies generated from volumetric medical images play an increasingly central role in many aspects of patient care. A key task in generating these models is the segmentation of anatomical structures and pathologies of interest. Although numerous segmentation methods are available, they often produce erroneous delineations that require time-consuming modifications.


Predictive coding theories posit that neural networks learn statistical regularities in the environment for comparison with actual outcomes, signaling a prediction error (PE) when sensory deviation occurs. PE studies in audition have capitalized on low-frequency event-related potentials (LF-ERPs), such as the mismatch negativity. However, local cortical activity is well-indexed by higher-frequency bands [high-? band (H?): 80-150 Hz]. We compared patterns of human H? and LF-ERPs in deviance detection using electrocorticographic recordings from subdural electrodes over frontal and temporal cortices. Patients listened to trains of task-irrelevant tones in two conditions differing in the predictability of a deviation from repetitive background stimuli (fully predictable vs. unpredictable deviants). We found deviance-related responses in both frequency bands over lateral temporal and inferior frontal cortex, with an earlier latency for H? than for LF-ERPs. Critically, frontal H? activity but not LF-ERPs discriminated between fully predictable and unpredictable changes, with frontal cortex sensitive to unpredictable events. The results highlight the role of frontal cortex and H? activity in deviance detection and PE generation.

Environmental rhythms potently drive predictive resource allocation in time, typically leading to perceptual and motor benefits for on-beat, relative to off-beat, times, even if the rhythmic stream is not intentionally used. In two human EEG experiments, we investigated the behavioral and electrophysiological expressions of using rhythms to direct resources away from on-beat times. This allowed us to distinguish goal-directed attention from the automatic capture of attention by rhythms. The following three conditions were compared: (1) a rhythmic stream with targets appearing frequently at a fixed off-beat position; (2) a rhythmic stream with targets appearing frequently at on-beat times; and (3) a nonrhythmic stream with matched target intervals. Shifting resources away from on-beat times was expressed in the slowing of responses to on-beat targets, but not in the facilitation of off-beat targets. The shifting of resources was accompanied by anticipatory adjustment of the contingent negative variation (CNV) buildup toward the expected off-beat time. In the second experiment, off-beat times were jittered, resulting in a similar CNV adjustment and also in preparatory amplitude reduction of beta-band activity. Thus, the CNV and beta activity track the relevance of time points and not the rhythm, given sufficient incentive. Furthermore, the effects of task relevance (appearing in a task-relevant vs irrelevant time) and rhythm (appearing on beat vs off beat) had additive behavioral effects and also dissociable neural manifestations in target-evoked activity: rhythm affected the target response as early as the P1 component, while relevance affected only the later N2 and P3. Thus, these two factors operate by distinct mechanisms.


Discriminating external from self-produced sensory inputs is a major challenge for brains. In the auditory system, sound localization must account for movements of the head and ears, a computation likely to involve multimodal integration. Principal neurons (PNs) of the dorsal cochlear nucleus (DCN) are known to be spatially selective and to receive multimodal sensory information. We studied the responses of PNs to body rotation with or without sound stimulation, as well as to sound source rotation with stationary body. We demonstrated that PNs are sensitive to head direction, and, in the presence of sound, they differentiate between body and sound source movement. Thus, the output of the DCN provides the brain with enough information to disambiguate the movement of a sound source from an acoustically identical relative movement produced by motion of the animal.

Jaffe-Dax, S, Lieder I, Biron T, Ahissar M. 2016 Dyslexics' usage of visual priors is impaired. Journal of vision. 16(9):10. Abstract

Human perception benefits substantially from familiarity, via the formation of effective predictions of the environment's pattern of stimulation. Basic stimulation characteristics are automatically retrieved and integrated into our perception. A quantitatively measurable manifestation of the integration of priors is known as "contraction to the mean"; i.e., perception is biased toward the experienced mean. We previously showed that in the context of auditory discrimination, the magnitude of this bias is smaller among dyslexic individuals than among good readers matched for age and general reasoning skills. Here we examined whether a similarly reduced contraction characterizes dyslexics' behavior on serial visual tasks. Using serial spatial frequency discrimination tasks, we found that dyslexics' bias toward the experiment's mean spatial frequency was smaller than that observed for the controls. Thus, dyslexics' difficulties in automatic detection and integration of stimulus statistics are domain-general. These difficulties are likely to impede the acquisition of reading expertise.

Seed-based functional connectivity (FC) of resting-state functional MRI data is a widely used methodology, enabling the identification of functional brain networks in health and disease. Based on signal correlations across the brain, FC measures are highly sensitive to noise. A somewhat neglected source of noise is the fMRI signal attenuation found in cortical regions in close vicinity to sinuses and air cavities, mainly in the orbitofrontal, anterior frontal and inferior temporal cortices. BOLD signal recorded at these regions suffers from dropout due to susceptibility artifacts, resulting in an attenuated signal with reduced signal-to-noise ratio in as many as 10% of cortical voxels. Nevertheless, signal attenuation is largely overlooked during FC analysis. Here we first demonstrate that signal attenuation can significantly influence FC measures by introducing false functional correlations and diminishing existing correlations between brain regions. We then propose a method for the detection and removal of the attenuated signal ("intensity-based masking") by fitting a Gaussian-based model to the signal intensity distribution and calculating an intensity threshold tailored per subject. Finally, we apply our method on real-world data, showing that it diminishes false correlations caused by signal dropout, and significantly improves the ability to detect functional networks in single subjects. Furthermore, we show that our method increases inter-subject similarity in FC, enabling reliable distinction of different functional networks. We propose to include the intensity-based masking method as a common practice in the pre-processing of seed-based functional connectivity analysis, and provide software tools for the computation of intensity-based masks on fMRI data. Hum Brain Mapp 37:2407-2418, 2016. © 2016 Wiley Periodicals, Inc.


The "arkypallidal" neurons of the globus pallidus (external segment) emit feedback GABAergic projections to the striatum. In this issue of Neuron, Mallet et al. (2016) show that "arkypallidal" neurons provide a Stop signal, suppressing the development of Go-related striatal activity.


In situations of choice between uncertain options, one might get feedback on both the outcome of the chosen option and the outcome of the unchosen option ("the alternative"). Extensive research has shown that when both outcomes are eventually revealed, the alternative's outcome influences the way people evaluate their own outcome. In a series of experiments, we examined whether the outcome of the alternative plays an additional role in the decision-making process by creating expectations regarding the outcome of the chosen option. Specifically, we hypothesized that people see a good (bad) alternative's outcome as a bad (good) sign regarding their own outcome when the two outcomes are in fact uncorrelated, a phenomenon we call the "Alternative Omen Effect" (ALOE). Subjects had to repeatedly choose between two boxes, the outcomes of which were then sequentially revealed. In Experiments 1 and 2 the alternative's outcome was presented first, and we assessed the individual's prediction of their own outcome. In Experiment 3, subjects had to predict the alternative's outcome after seeing their own. We find that even though the two outcomes were in fact uncorrelated, people tended to see a good (bad) alternative outcome as a bad (good) sign regarding their own outcome. Importantly, this illusory negative correlation affected subsequent behavior and led to irrational choices. Furthermore, the order of presentation was critical: when the outcome of the chosen option was presented first, the effect disappeared, suggesting that this illusory negative correlation is influenced by self-relevance. We discuss
the possible sources of this illusory correlation as well as its implications for research on counterfactual thinking.


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Recent evidence from blind participants suggests that visual areas are task-oriented and sensory modality input independent rather than sensory-specific to vision. Specifically, visual areas are thought to retain their functional selectivity when using non-visual inputs (touch or sound) even without having any visual experience. However, this theory is still controversial since it is not clear whether this also characterizes the sighted brain, and whether the reported results in the sighted reflect basic fundamental a-modal processes or are an epiphenomenon to a large extent. In the current study, we addressed these questions using a series of fMRI experiments aimed to explore visual cortex responses to passive touch on various body parts and the coupling between the parietal and visual cortices as manifested by functional connectivity. We show that passive touch robustly activated the object selective parts of the lateral-occipital (LO) cortex while deactivating almost all other occipital-retinotopic-areas. Furthermore, passive touch responses in the visual cortex were specific to hand and upper trunk stimulations. Psychophysiological interaction (PPI) analysis suggests that LO is functionally connected to the hand area in the primary somatosensory homunculus (S1), during hand and shoulder stimulations but not to any of the other body parts. We suggest that LO is a fundamental hub that serves as a node between visual-object selective areas and S1 hand representation, probably due to the critical evolutionary role of touch in object recognition and manipulation. These results might also point to a more general principle suggesting that recruitment or deactivation of the visual cortex by other sensory input depends on the ecological relevance of the information conveyed by this input to the task/computations carried out by each area or network. This is likely to rely on the unique and differential pattern of connectivity for each visual area with the rest of the brain.

Deffains, M, Iskhakova L, Katabi S, Haber SN, Israel Z, Bergman H. 2016Subthalamic, not striatal, activity correlates with basal ganglia downstream activity in normal and parkinsonian monkeys. [174]. eLife. 5 Abstract

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The striatum and the subthalamic nucleus (STN) constitute the input stage of the basal ganglia (BG) network and together innervate BG downstream structures using GABA and glutamate, respectively. Comparison of the neuronal activity in BG input and downstream structures reveals that subthalamic, not striatal, activity fluctuations correlate with modulations in the increase/decrease discharge balance of BG downstream neurons during temporal discounting classical condition task. After induction of parkinsonism with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), abnormal low beta (8-15 Hz) spiking and local field potential (LFP) oscillations resonate across the BG network. Nevertheless, LFP beta oscillations entrain spiking activity of STN, striatal cholinergic interneurons and BG downstream structures, but do not entrain spiking activity of striatal projection neurons. Our results highlight the pivotal role of STN divergent projections in BG physiology and pathophysiology and may explain why STN is such an effective site for invasive treatment of advanced Parkinson's disease and other BG-related disorders.

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