It is generally believed that during economic decisions, striatal neurons represent the values associated with different actions. This hypothesis is based on a large number of electrophysiological studies, in which the neural activity of striatal neurons was measured while the subject was learning to prefer the more rewarding action. Here we present an alternative interpretation of the electrophysiological findings. We show that the standard statistical methods that were used to identify action-value neurons in the striatum erroneously detect the same action-value representations in unrelated neuronal recordings. This is due to temporal correlations in the neuronal data. We propose an alternative statistical method for identifying action-value representations that is not subject to this caveat. We apply it to previously identified action-value neurons in the basal ganglia and fail to detect action-value representations. In conclusion, we argue that there is no conclusive evidence for the generally accepted hypothesis that striatal neurons encode action-values.

Stimulus-specific adaptation (SSA) occurs when neurons decrease their responses to frequently-presented (standard) stimuli but not, or not as much, to other, rare (deviant) stimuli. SSA is present in all mammalian species in which it has been tested as well as in birds. SSA confers short-term memory to neuronal responses, and may lie upstream of the generation of mismatch negativity (MMN), an important human event-related potential. Previously published models of SSA mostly rely on synaptic depression of the feedforward, thalamocortical input. Here we study SSA in a recurrent neural network model of primary auditory cortex. When the recurrent, intracortical synapses display synaptic depression, the network generates population spikes (PSs). SSA occurs in this network when deviants elicit a PS but standards do not, and we demarcate the regions in parameter space that allow SSA. While SSA based on PSs does not require feedforward depression, we identify feedforward depression as a mechanism for expanding the range of parameters that support SSA. We provide predictions for experiments that could help differentiate between SSA due to synaptic depression of feedforward connections and SSA due to synaptic depression of recurrent connections. Similar to experimental data, the magnitude of SSA in the model depends on the frequency difference between deviant and standard, probability of the deviant, inter-stimulus interval and input amplitude. In contrast to models based on feedforward depression, our model shows true deviance sensitivity as found in experiments.
According to the synaptic trace theory of memory, activity-induced changes in the pattern of synaptic connections underlie the storage of information for long periods. In this framework, the stability of memory critically depends on the stability of the underlying synaptic connections. Surprisingly however, synaptic connections in the living brain are highly volatile, which poses a fundamental challenge to the synaptic trace theory. Here we review recent experimental evidence that link the initial formation of a memory with changes in the pattern of connectivity, but also evidence that synaptic connections are considerably volatile even in the absence of learning. Then we consider different theoretical models that have been put forward to explain how memory can be maintained with such volatile building blocks.

Uncovering structural regularities and architectural topologies of cortical circuitry is vital for understanding neural computations. Recently, an experimentally constrained algorithm generated a dense network reconstruction of a ~0.3-mm 3 volume from juvenile rat somatosensory neocortex, comprising ~31,000 cells and ~36 million synapses. Using this reconstruction, we found a small-world topology with an average of 2.5 synapses separating any two cells and multiple cell-type-specific wiring features. Amounts of excitatory and inhibitory innervations varied across cells, yet pyramidal neurons maintained relatively constant excitation/inhibition ratios. The circuit contained highly connected hub neurons belonging to a small subset of cell types and forming an interconnected cell-type-specific rich club. Certain three-neuron motifs were overrepresented, matching recent experimental results. Cell-type-specific network properties were even more striking when synaptic strength and sign were considered in generating a functional topology. Our systematic approach enables interpretation of microconnectomics ?big data? and provides several experimentally testable predictions.
performing a waiting task. Electrophysiological recordings from two regions necessary for this behavior, medial prefrontal cortex (mPFC) and secondary motor cortex (M2), revealed an unexpected functional dissociation. Both areas encoded deterministic biases in action timing, but only M2 neurons reflected stochastic trial-by-trial fluctuations. This differential coding was reflected in distinct timescales of neural dynamics in the two frontal cortical areas. These results suggest a two-stage model in which stochastic components of action timing decisions are injected by circuits downstream of those carrying deterministic bias signals.


OBJECTIVE: To evaluate whether full-term deliveries resulting in neonates diagnosed with hypoxic-ischemic encephalopathy are associated with a significant increase in the rate of subsequent unscheduled cesarean deliveries. METHODS: We conducted a retrospective chart review study and examined all deliveries in the Department of Obstetrics and Gynecology at Hadassah University Hospital, Mt. Scopus campus, Jerusalem, Israel, during 2009-2014. We reviewed all cases of hypoxic-ischemic encephalopathy in singleton, term, liveborn neonates and identified seven such cases, three of which were attributed to obstetric mismanagement and four that were not. We measured the rate of unscheduled cesarean deliveries before and after the events and their respective hazard ratio. RESULTS: Before a mismanaged delivery resulting in hypoxic-ischemic encephalopathy, the baseline rate of unscheduled cesarean deliveries was approximately 80 unscheduled cesarean deliveries for every 1,000 deliveries. In the first 4 weeks immediately after each of the three identified cases, there was a significant increase in the rate of unscheduled cesarean deliveries by an additional 48 unscheduled cesarean deliveries per 1,000 deliveries (95% confidence interval [CI] 27-70/1,000). This increase was transient and lasted approximately 4 weeks. We estimated that each case was associated with approximately 17 additional unscheduled cesarean deliveries (95% CI 8-27). There was no increase in the rate of unscheduled cesarean deliveries in cases of hypoxic-ischemic encephalopathy that were not associated with mismanagement. CONCLUSION: The increase in the rate of unscheduled cesarean deliveries after a catastrophic neonatal outcome may result in short-term changes in obstetricians’ risk evaluation.

Berman, S, West, K, Does, MD, Yeatman, JD, Mezer, AA. 2017. *Evaluating g-ratio weighted changes in the corpus callosum as a function of age and sex*. [Abstract](#) [Supplemental Digital Content](#)

Recent years have seen a growing interest in relating MRI measurements to the structural-biophysical properties of white matter fibers. The fiber g-ratio, defined as the ratio between the inner and outer radii of the axon myelin sheath, is an important structural property of white matter, affecting signal conduction. Recently proposed modeling methods that use a combination of quantitative-MRI signals, enable a measurement of the fiber g-ratio in vivo. Here we use an MRI-based g-ratio estimation to observe the variance of the g-ratio within the corpus callosum, and evaluate sex and age related differences. To estimate the g-ratio we used a model (Stikov, 2012; Duval et al., 2016) based on two different WM microstructure parameters: the relative amounts of myelin (myelin volume fraction, MVF) and fibers (fiber volume fraction, FVF) in a voxel. We derived the FVF from the fractional anisotropy (FA), and estimated the MVF by using the lipid and macromolecular tissue volume (MTV), calculated from the proton density (Mezer et al., 2013). In comparison to other methods of estimating the MVF, MTV represents a stable
parameter with a straightforward route of acquisition. To establish our model, we first compared histological MVF measurements (West et al., 2016) with the MRI derived MTV. We then implemented our model on a large database of 92 subjects (44 males), aged 7 to 81, in order to evaluate age and sex related changes within the corpus callosum. Our results show that the MTV provides a good estimation of MVF for calculating g-ratio, and produced values from the corpus callosum that correspond to those found in animals ex vivo and are close to the theoretical optimum, as well as to published in vivo data. Our results demonstrate that the MTV derived g-ratio provides a simple and reliable in vivo g-ratio-weighted (GR*) measurement in humans. In agreement with theoretical predictions, and unlike other tissue parameters measured with MRI, the g-ratio estimations were found to be relatively stable with age, and we found no support for a significant sexual dimorphism with age.


How does cortical tissue change as brain function and behavior improve from childhood to adulthood? By combining quantitative and functional magnetic resonance imaging in children and adults, we find differential development of high-level visual areas that are involved in face and place recognition. Development of face-selective regions, but not place-selective regions, is dominated by microstructural proliferation. This tissue development is correlated with specific increases in functional selectivity to faces, as well as improvements in face recognition, and ultimately leads to differentiated tissue properties between face- and place-selective regions in adulthood, which we validate with postmortem cytoarchitectonic measurements. These data suggest a new model by which emergent brain function and behavior result from cortical tissue proliferation rather than from pruning exclusively.


Maternal care is an indispensable behavioral component necessary for survival and reproductive success in mammals, and postpartum maternal behavior is mediated by an incompletely understood complex interplay of signals including effects of epigenetic regulation. We approached this issue using our recently established mice with targeted deletion of heterochromatin protein 1 binding protein 3 (HP1BP3), which we found to be a novel epigenetic repressor with critical roles in postnatal growth. Here, we report a dramatic reduction in the survival of pups born to Hp1bp3(-/-) deficient mouse dams, which could be rescued by co-fostering with wild-type dams. Hp1bp3(-/-) females failed to retrieve both their own pups and foster pups in a pup retrieval test, and showed reduced anxiety-like behavior in the open-field and elevated-plus-maze tests. In contrast, Hp1bp3(-/-) females showed no deficits in behaviors often associated with impaired maternal care, including social behavior, depression, motor coordination and olfactory capability; and
maintained unchanged anxiety-associated hallmarks such as cholinergic status and brain miRNA profiles. Collectively, our results suggest a novel role for HP1BP3 in regulating maternal and anxiety-related behavior in mice and call for exploring ways to manipulate this epigenetic process.


Anxiety-related and metabolic disorders are under intense research focus. Anxiety-induced microRNAs (miRNAs) are emerging as regulators that are not only capable of suppressing inflammation but can also induce metabolic syndrome-related processes. We summarize here evidence linking miRNA pathways which share regulatory networks in metabolic and anxiety-related conditions. In particular, miRNAs involved in these disorders include regulators of acetylcholine signaling in the nervous system and their accompanying molecular machinery. These have been associated with anxiety-prone states in individuals, while also acting as inflammatory suppressors. In peripheral tissues, altered miRNA pathways can lead to dysregulated metabolism. Common pathways in metabolic and anxiety-related phenomena might offer an opportunity to reclassify ‘healthy’ and ‘unhealthy’, as well as metabolic and anxiety-prone biological states, and inform putative strategies to treat these disorders.


BACKGROUND: Treatment of active ulcerative colitis is associated with incomplete efficacy, adverse events, and loss of response. Toll-like receptor-9 mediates innate and adaptive immune response toward intestinal microorganisms. The oral synthetic oligonucleotide toll-like receptor-9 modulator has demonstrated anti-inflammatory properties in colitis murine models and a satisfactory safety profile in humans. AIM: To evaluate the efficacy and safety of BL-7040 (a Toll-like receptor-9 modulator) in patients with moderately active ulcerative colitis. METHODS: Moderately active ulcerative colitis patients were included in this multicenter, open-label phase IIa trial. Concomitant mesalamine and steroids at a stable dose were allowed. Clinical outcome was evaluated using the Mayo score, histology, and mucosal cytokine levels. Side effects were registered. RESULTS: Sixteen out of 22 patients completed a 5-week treatment course and 2-week follow-up. Six patients discontinued the study, three of them due to adverse events. Clinical remission was observed in two patients (12.5 %), and clinical response as well as mucosal healing were achieved in half (50 %) of the patients, while all others remained stable. Furthermore, mucosal neutrophil (p = 0.002) and mucosal interleukin-6 levels (p = 0.046) were significantly reduced in responders compared to non-responders. Toll-like receptor-9 was well tolerated with only one unrelated to study drug serious adverse event (hemoglobin decrease) and 29 mild-to-moderate adverse events. CONCLUSIONS: Oral administration of the Toll-like receptor-9 agonist BL-7040 appeared efficacious, safe and well tolerated in patients with moderately active ulcerative colitis.


Trauma causes variable risk of posttraumatic stress symptoms (PTSS) owing to yet-unknown genome-neuronal interactions. Here, we report co-intensified amygdala and ventromedial prefrontal cortex (vmPFC) emotional responses that may overcome PTSS in individuals with the single-nucleotide polymorphism (SNP) rs17228616 in the acetylcholinesterase (AChE) gene. We have recently shown that in individuals with the minor rs17228616 allele, this SNP interrupts AChE suppression by microRNA (miRNA)-608,
leading to cortical elevation of brain AChE and reduced cortisol and the miRNA-608 target GABAergic modulator CDC42, all stress-associated. To examine whether this SNP has effects on PTSS and threat-related brain circuits, we exposed 76 healthy Israel Defense Forces soldiers who experienced chronic military stress to a functional magnetic resonance imaging task of emotional and neutral visual stimuli. Minor allele individuals predictably reacted to emotional stimuli by hyperactivated amygdala, a hallmark of PTSS and a predisposing factor of posttraumatic stress disorder (PTSD). Despite this, minor allele individuals showed no difference in PTSS levels. Mediation analyses indicated that the potentiated amygdala reactivity in minor allele soldiers promoted enhanced vmPFC recruitment that was associated with their limited PTSS. Furthermore, we found interrelated expression levels of several miRNA-608 targets including CD44, CDC42 and interleukin 6 in human amygdala samples (N=7). Our findings suggest that miRNA-608/AChE interaction is involved in the threat circuitry and PTSS and support a model where greater vmPFC regulatory activity compensates for amygdala hyperactivation in minor allele individuals to neutralize their PTSS susceptibility.


The relationship between long-term cholinergic dysfunction and risk of developing dementia is poorly understood. Here we used mice with deletion of the vesicular acetylcholine transporter (VACht) in the forebrain to model cholinergic abnormalities observed in dementia. Whole-genome RNA sequencing of hippocampal samples revealed that cholinergic failure causes changes in RNA metabolism. Remarkably, key transcripts related to Alzheimer's disease are affected. BACE1, for instance, shows abnormal splicing caused by decreased expression of the splicing regulator hnRNPA2/B1. Resulting BACE1 overexpression leads to increased APP processing and accumulation of soluble Abeta1-42. This is accompanied by age-related increases in GSK3 activation, tau hyperphosphorylation, caspase-3 activation, decreased synaptic markers, increased neuronal death, and deteriorating cognition. Pharmacological inhibition of GSK3 hyperactivation reversed deficits in synaptic markers and tau hyperphosphorylation induced by cholinergic dysfunction, indicating a key role for GSK3 in some of these pathological changes. Interestingly, in human brains there was a high correlation between decreased levels of VACht and hnRNPA2/B1 levels with increased tau hyperphosphorylation. These results suggest that changes in RNA processing caused by cholinergic loss can facilitate Alzheimer's-like pathology in mice, providing a mechanism by which decreased cholinergic tone may increase risk of dementia.


Cholinergic vulnerability, characterized by loss of acetylcholine (ACh), is one of the hallmarks of Alzheimer's disease (AD). Previous work has suggested that decreased ACh activity in AD may contribute to pathological changes through global alterations in alternative splicing. This occurs, at least partially, via the regulation of the expression of a critical protein family in RNA processing, heterogeneous nuclear ribonucleoprotein (hnRNP) A/B proteins. These proteins regulate several steps of RNA metabolism, including alternative splicing, RNA trafficking, miRNA export, and gene expression, providing multilevel surveillance in RNA functions. To investigate the mechanism by which cholinergic tone regulates
hnRNPA2/B1 expression, we used a combination of genetic mouse models and in vivo and in vitro techniques. Decreasing cholinergic tone reduced levels of hnRNPA2/B1, whereas increasing cholinergic signaling in vivo increased expression of hnRNPA2/B1. This effect was not due to decreased hnRNPA2/B1 mRNA expression, increased aggregation, or degradation of the protein, but rather to decreased mRNA translation by nonsense-mediated decay regulation of translation. Cell culture and knock-out mice experiments demonstrated that M1 muscarinic signaling is critical for cholinergic control of hnRNPA2/B1 protein levels. Our experiments suggest an intricate regulation of hnRNPA2/B1 levels by cholinergic activity that interferes with alternative splicing in targeted neurons mimicking deficits found in AD.

SIGNIFICANCE STATEMENT: In Alzheimer's disease, degeneration of basal forebrain cholinergic neurons is an early event. These neurons communicate with target cells and regulate their long-term activity by poorly understood mechanisms. Recently, the splicing factor hnRNPA2/B, which is decreased in Alzheimer's disease, was implicated as a potential mediator of long-term cholinergic regulation. Here, we demonstrate a mechanism by which cholinergic signaling controls the translation of hnRNPA2/B1 mRNA by activation of M1 muscarinic type receptors. Loss of cholinergic activity can have profound effects in target cells by modulating hnRNPA2/B1 levels.


Semiconductor-metal hybrid nanoparticles manifest efficient light-induced spatial charge separation at the semiconductor-metal interface, as demonstrated by their use for hydrogen generation via water splitting. Here, we pioneer a study of their functionality as efficient photocatalysts for the formation of reactive oxygen species. We observed enhanced photocatalytic activity forming hydrogen peroxide, superoxide, and hydroxyl radicals upon light excitation, which was significantly larger than that of the semiconductor nanocrystals, attributed to the charge separation and the catalytic function of the metal tip. We used this photocatalytic functionality for modulating the enzymatic activity of horseradish peroxidase as a model system, demonstrating the potential use of hybrid nanoparticles as active agents for controlling biological processes through illumination. The capability to produce reactive oxygen species by illumination on-demand enhances the available peroxidase-based tools for research and opens the path for studying biological processes at high spatiotemporal resolution, laying the foundation for developing novel therapeutic approaches.


Parkinson's disease (PD) involves motor symptoms reflecting the progressive degeneration of dopaminergic neurons in the substantia nigra. However, diagnosis is only enabled late in the disease, limiting treatment to palliative assistance. Here, we review recently generated transcriptional profiling datasets from blood and brain RNA of human PD cohorts and animal models that may offer unprecedented progress in PD research. Specifically, advanced analysis techniques demonstrated functionally inter-related underlying impairments of RNA metabolism and neuroimmune signalling processes. Identifying novel biomarkers in serum and nucleated blood cells, including protein networks and non-coding RNAs can drive discovery of the molecular mechanisms involved and reveal new targets for therapeutic intervention, posing a dual diagnosis/treatment opportunity for limiting the exacerbation of neuroinflammatory events in PD.

Emerging evidence demonstrates association of depression with both immune malfunctioning and worsened course of diverse aging-related diseases, but there is no explanation for the pathway(s) controlling this dual association. Here, we report that in post-reproductive and evolutionarily 'blind' years, depression may weaken pathogen-host defense, compatible with the antagonistic pleiotropy hypothesis. In 15,532 healthy volunteers, depression scores associated with both inflammatory parameters and with increased circulation cholinesterase activities, implicating debilitated cholinergic blockade of inflammation as an underlying mechanism; furthermore, depression, inflammation and cholinesterase activities all increased with aging. In the entire cohort, combined increases in inflammation and the diabetic biomarker hemoglobin A1c associated with elevated depression. Moreover, metabolic syndrome patients with higher risk of diabetes showed increased cholinesterase levels and pulse values, and diabetics presented simultaneous increases in depression, inflammation and circulation cholinesterase activities, suggesting that cholinergic impairment precedes depression. Our findings indicate that dys-functioning cholinergic regulation weakens the otherwise protective link between depression and pathogen-host defense, with global implications for aging-related diseases.


Numerous animal species emit vocalizations in response to various social stimuli. The neural basis of vocal communication has been investigated in monkeys, songbirds, rats, bats, and invertebrates resulting in deep insights into motor control, neural coding, and learning. Mice, which recently became very popular as a model system for mammalian neuroscience, also utilize ultrasonic vocalizations (USVs) during mating behavior. However, our knowledge is lacking of both the behavior and its underlying neural mechanism. We developed a novel method for head-restrained male mice (HRMM) to interact with non-restrained female mice (NRFM) and show that mice can emit USVs in this context. We first recorded USVs in a free arena with non-restrained male mice (NRMM) and NRFM. Of the NRMM, which vocalized in the free arena, the majority could be habituated to also vocalize while head-restrained but only when a female mouse was present in proximity. The USVs emitted by HRMM are similar to the USVs of NRMM in the presence of a female mouse in their spectral structure, inter-syllable interval distribution, and USV sequence length, and therefore are interpreted as social USVs. By analyzing the vocalizations of NRMM, we established criteria to predict which individuals are likely to vocalize while head fixed based on the USV rate and average syllable duration. To characterize the USVs emitted by HRMM, we analyzed the syllable composition of HRMM and NRMM and found that USVs emitted by HRMM have a higher proportion of USVs with complex spectral representation, supporting previous studies showing that mice social USVs are context dependent. Our results suggest a way to study the neural mechanisms of production and control of social vocalization in mice using advanced methods requiring head fixation.

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 Jerusalem Brain Sciences Building will provide a state-of-the-art research and teaching facility for the Edmond and Lily Safra Center for Brain Sciences.

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