Publications


Sort by:

Submitted

Shaham, N, Burak Y. Submitted Slow Diffusive Dynamics in a Chaotic Balanced Neural Network [5].

In Press

Grodzinsky, Y, Deschamps I, Shapiro LP. In Press Patients with Broca’s aphasia and Young Children can reconstruct elided VPs [11].

2017


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.


2016

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.

Lin, T, Simchovitz A, Shenhar-Tsarfaty S, Vaisvaser S, Admon R, Hanin G, Hanan M, Kliper E, Bar-Haim Y, Shomron N et al. 2016 Intensified vmPFC surveillance over PTSS under perturbed microRNA-608/AChE interaction [58]. Transl Psychiatry. 6:e801. Abstract [59] 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.

Kaufer, D, Friedman A, Seidman S, Soreq H. 2016 Corrigendum: Acute stress facilitates long-lasting changes in cholinergic gene expression [65]. Nature. 531:126. Abstract [66] Kolinsky, B, Al-Onaizi M, Soreq L, Barbash S, Bekenstein U, Haberman N, Hanin G, Kish MT, Souza da Silva J, Fahnestock M et al. 2016 Cholinergic Surveillance over Hippocampal RNA Metabolism and Alzheimer's-Like Pathology [71]. Cereb Cortex. Abstract [72] 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 hnRNP2/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 hnRNP2/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.

Simchovitz, A, Soreq L, Soreq H. 2016 Transcriptome profiling in Parkinson’s leukocytes: from early diagnostics to neuroimmune therapeutic prospects [82].
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.


We hardly notice our eye blinks, yet an externally generated retinal interruption of a similar duration is perceptually salient. We examined the neural correlates of this perceptual distinction using intracranially measured ECoG signals from human visual cortex in 14 patients. In early visual areas (V1 and V2), the disappearance of the stimulus due to either invisible blinks or salient blank video frames ('gaps') led to a similar drop in activity level, followed by a positive overshoot beyond baseline, triggered by stimulus reappearance. Ascending the visual hierarchy, the reappearance-related overshoot gradually subsided for blinks but not for gaps. By contrast, the disappearance-related drop did not follow the perceptual distinction - it was actually slightly more pronounced for blinks than for gaps. These findings suggest that blinks' limited visibility compared with gaps is correlated with suppression of blink-related visual activity transients, rather than with 'filling-in' of the occluded content during blinks.

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.

Duval, T, Le?vy S, Stikov N, Campbell J, Mezer A, Witzel T, Keil B, Smith V, Wald LL, Klawiter E et al.. 2016. g-Ratio weighted imaging of the human spinal cord in vivo. NeuroImage. 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.

Shrem, T, Deouell LY. 2016 Hierarchies of Attention and Experimental Designs: Effects of Spatial and Intermodal Attention Revisited. Journal of cognitive neuroscience. 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. 43(10):1284-5.


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.
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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