
Recently, there is a growing interest in surgical variables that are intraoperatively controlled by orthopaedic surgeons, including lower leg alignment, component positioning and soft tissues balancing. Since more tight control over these factors is associated with improved outcomes of unicompartmental knee arthroplasty and total knee arthroplasty (TKA), several computer navigation and robotic-assisted systems have been developed. Although mechanical axis accuracy and component positioning have been shown to improve with computer navigation, no superiority in functional outcomes has yet been shown. This could be explained by the fact that many differences exist between the number and type of surgical variables these systems control. Most systems control lower leg alignment and component positioning, while some in addition control soft tissue balancing. Finally, robotic-assisted systems have the additional advantage of improving surgical precision. A systematic search in PubMed, Embase and Cochrane Library resulted in 40 comparative studies and three registries on computer navigation reporting outcomes of 474,197 patients, and 21 basic science and clinical studies on robotic-assisted knee arthroplasty. Twenty-eight of these comparative computer navigation studies reported Knee Society Total scores in 3504 patients. Stratifying by type of surgical variables, no significant differences were noted in outcomes between surgery with computer-navigated TKA controlling for alignment and component positioning versus conventional TKA (p = 0.63). However, significantly better outcomes were noted following computer-navigated TKA that also controlled for soft tissue balancing versus conventional TKA (mean difference 4.84, 95 % Confidence Interval 1.61, 8.07, p = 0.003). A literature review of robotic systems showed that these systems can, similarly to computer navigation, reliably improve lower leg alignment, component positioning and soft tissues balancing. Furthermore, two studies comparing robotic-assisted with computer-navigated surgery reported superiority of robotic-assisted surgery in controlling these factors. Manually controlling all these surgical variables can be difficult for the orthopaedic surgeon. Findings in this study suggest that computer navigation or robotic assistance may help managing these multiple variables and could improve outcomes.
Future studies assessing the role of soft tissue balancing in knee arthroplasty and long-term follow-up studies assessing the role of computer-navigated and robotic-assisted knee arthroplasty are needed.


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.


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.


The nociceptive noxious heat-activated receptor - TRPV1, conducts calcium and sodium, thus producing a depolarizing receptor potential, leading to activation of nociceptive neurons. TRPV1-mediated calcium and sodium influx is negatively modulated by calcium, via calcium-dependent desensitization of TRPV1 channels. A mitochondrial Ca(2+) uniporter - MCU, controls mitochondrial Ca(2+) entry while a sodium/calcium transporter - NCLX shapes calcium and sodium transients by mediating sodium entry into and removing calcium from the mitochondria. The functional interplay between TRPV1, MCU and NCLX, in controlling the cytosolic and mitochondrial calcium and sodium transients and subsequently the nociceptive excitability, is poorly understood. Here, we used cytosolic and mitochondrial fluorescent calcium and sodium imaging together with electrophysiological recordings of TRPV1-induced currents in HEK293T cells
and nociceptor-like dissociated rat dorsal root ganglion neurons, while modulating NCLX or MCU expression using specific small interfering RNA (siNCLX). We show that the propagation of the TRPV1-induced cytosolic calcium and sodium fluxes into mitochondria is dependent on coordinated activity of NCLX and MCU. Thus, knocking-down of NCLX triggers down regulation of MCU dependent mitochondrial Ca(2+) uptake. This in turn decreases rate and amplitude of TRPV1-mediated cytosolic calcium, which inhibits capsaicin-induced inward current and neuronal firing. TRPV1-mediated currents were fully rescued by intracellular inclusion of the fast calcium chelator BAPTA. Finally, NCLX controls capsaicin-induced cell death, by supporting massive mitochondrial Ca(2+) shuttling. Altogether, our results suggest that NCLX, by regulating cytosolic and mitochondrial ionic transients, modulates calcium-dependent desensitization of TRPV1 channels, thereby, controlling nociceptive signaling.


Computer Aided Orthopaedic Surgery (CAOS) is now about 25 years old. Unlike Neurosurgery, Computer Aided Surgery has not become the standard of care in Orthopaedic Surgery. In this paper, we provide the technical and clinical context raised by this observation in an attempt to elucidate the reasons for this state of affairs. We start with a brief outline of the history of CAOS, review the main CAOS technologies, and describe how they are evaluated. We then identify some of the current publications in the field and present the opposing views on their clinical impact and their acceptance by the orthopaedic community worldwide. We focus on total knee replacement surgery as a case study and present current clinical results and contrasting opinions on CAOS technologies. We then discuss the challenges and opportunities for research in medical image analysis in CAOS and in musculoskeletal radiology. We conclude with a suggestion that while CAOS acceptance may be more moderate than that of other fields in surgery, it still has a place in the arsenal of useful tools available to orthopaedic surgeons.


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.

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.


As part of an effort to improve upon the Snellen chart, we provide a standardized version of the ETDRS chart utilizing five characters in each row. The choice of five characters contradicts the recommended ten characters per row determined by the NAS-NRC, a committee established to provide guidelines for testing visual acuity. We set out to quantify the influence of varying the number of characters per line on the ETDRS chart with respect to the accuracy and reproducibility of visual acuity measurement.

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.


The relatively membrane-impermeable lidocaine derivative QX-314 has been reported to permeate the ion channels transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential cation channel, subfamily A, member 1 (TRPA1) to induce a selective inhibition of sensory neurons. This approach is effective in rodents, but it also seems to be associated with neurotoxicity. The authors examined whether the human isoforms of TRPV1 and TRPA1 allow intracellular entry of QX-314 to mediate sodium channel inhibition and cytotoxicity.


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. Abstract

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.

connectivity in the mouse*. The Journal of comparative neurology. Abstract

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.

Kronman, A, Joskowicz L. 2016*A geometric method for the detection and correction of segmentation
leaks of anatomical structures in volumetric medical images*. International journal of computer
assisted radiology and surgery. 11(3):369-80. Abstract

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.
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