IN BRIEF…

BAC-driven miRNA gene expression knockdown

KA Garbett, S Horvath, PJ Ebert, MJ Schmidt, K Lwin, **A Mitchell**, P Levitt and K Mirnics (2010). Novel animal models for studying complex brain disorders: BAC-driven *mi*RNA-mediated *in vivo* silencing of gene expression. *Mol. Psychiatry*. doi: 10.1038/mp.2010.1

Animal models of disease represent one of the most powerful methods of analyzing the pathophysiological mechanisms of genetic disorders. However, the development of such models is often time-consuming, complex, and carries nonspecific caveats, such as the imprecise deletion of a gene of choice. Using bacterial artificial chromosomes, cell-type specific promoters, a standard reporter, and a microRNA mechanism for gene silencing, Garbett *et al*. present a powerful mechanism to specifically reduce gene expression *in vivo*. As microRNAs are of small size, they anticipate that this new method could simultaneously silence multiple genes in a cell-type specific manner. Accordingly, these transgenic mice would allow exquisite precision in determining the effects of a given set of genes on the presentation of disease.

Pain Pathways: Neuropeptide Y may be targeted to relieve pain

RG Wiley, **LL Lemons** and RH Kline IV (2009). Neuropeptide Y receptor-expressing dorsal horn neurons: role in nocifensive reflex responses to heat and formalin. *Neuroscience*. **161** (1): 139-147.

There is an endless list of reasons why individuals seek treatment for pain, but the molecular mechanisms that underlie pain perception are unclear. Wiley *et al*. demonstrate how Neuropeptide Y (NPY) and its receptor Y1 (Y1R) function in the rodent spinal cord to mediate nociception. After intrathecal injection of saporin toxin conjugated to NPY to selectively kill Y1R-expressing neurons in the dorsal horn of the spinal cord, rats displayed an increased latency to withdraw their paws from noxious hot stimuli. The rodents also had a significant decrease in nocifensive behavior when presented with the hot stimuli or when injected with formalin in the plantar region of the hind paw, as measured by licking and guarding events. This toxin-based approach allows researchers to selectively examine groups of neurons involved in the perception of pain and tease apart each group's contribution. These studies could prove to have a significant impact on the field of pain research and may provide researchers with some insight into alternative approaches to treat pain.

What's unusual about that? Neural substrates for the detection of novel, unusual stimuli

Blackford JU, Buckholtz JW, **Avery SN**, Zald DH (2010). A unique role for the human amygdala in novelty detection. *Neuroimage*. 50(3):1188-93.

Novelty detection is an important trait in perceiving and responding to our environment. In particular novel, yet unusual or uncommon stimuli that are behaviorally salient can engage specific neural mechanisms involved in emotional learning and memory. In this study, the authors used functional magnetic resonance imaging to observe blood oxygen level dependent (BOLD) responses in the human amygdala and hippocampus when they presented participants with novel, common stimuli (e.g., chair, clock, tree) versus novel, unusual stimuli (e.g., Prague Dancing House, futuristic skyscraper, leafy sea dragon). Blackford and colleagues found that novel, common stimuli showed robust BOLD activation in both the amygdala and the hippocampus. However, only the amygdala showed a preferential activation for the novel, unusual stimuli, compared to the novel common stimuli. These results lead the authors to speculate that within the novelty detection circuit, the amygdala plays a distinct role in uniquely responding to a specific category of stimuli, namely those that are novel and unusual.

change or neural reorganization. Powers and colleagues found significant effects in the temporal dynamics of the multisensory binding window after only one day of training, with stable effects observed even after one week. This alludes to the fact that the brain is capable of adapting quickly to new environmental situations and long term memory consolidation may play a role in strengthening learned traits. Thus results from this study would support the idea that the pairing of a sensory stimulus with behavioral salience (like feedback in this study) is crucial for sensory reorganization of adult cortical space.

It is intriguing to consider where and how the plasticity associated with this temporal binding window is modulated. In humans, recent neuroimaging studies reported a large, dynamic network of areas including the insular cortex, posterior parietal and superior temporal cortices, all critically involved in the perception of audiovisual stimuli. The neuronal oscillations among different cortical populations have also been shown to play a potential role in multisensory processing and temporal binding. At a more cellular level, the temporal tuning profile of multisensory neurons has been associated with adult plasticity in various sensory systems, with basal cholinergic signals acting as an instructive cue. This indicates that the synchronous role of both cortical and subcortical mechanisms may be responsible for temporal plasticity in multisensory systems.

The present work by Powers and colleagues and future extensions of similar studies holds particular clinical significance, especially in designing tailored intervention strategies for disorders such as dyslexia, autism and schizophrenia where altered multisensory temporal processes have been observed.

Original Research Article:
AR Powers III, AR Hillock and MT Wallace (2009). Perceptual training narrows the temporal window of multisensory binding. *J Neurosci*. **29** (39): 12265-12274.

Development: birth, life, death, cleanup, repeat.

The development of a nervous system entails several obvious processes such as the proliferation of cells, the elaboration of dendrites, or the wiring of functional axonal circuits, yet it is now becoming clear that the less publicized (and slightly more sinister) mechanisms of programmed cell death and debris clearance are a vital component of nervous growth. For example, in the mouse dorsal root ganglia (DRG) over 50% of sensory neurons undergo

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IN BRIEF…

Manganese, a friend or foe to dopaminergic neurons?

GD Stanwood, **DB Leitch**, V Savchenko, J Wu, VA Fitsanakis, DJ Anderson, **JN Stankowski**, M Aschner, B McLaughlin (2009). Manganese exposure is cytotoxic and alters dopaminergic and GABAergic neurons within the basal ganglia. *J Neurochem*. **110** (1): 378-89.

Manganese is a naturally occurring element essential for the proper metabolism of amino acids, protein and lipids. It is crucial for maintaining proper cellular functioning including maintenance of redox states, facilitating protein conformation, modulating ion and energy homeostasis and overall signal transduction in neurons. Over exposure to manganese can result in various irreversible neurological phenomenon such as motor symptoms similar to that of Parkinsons, dystonia and gastrointestinal tract dysfunction. In this study, the authors explored the neurotxic potential of manganese in dopaminergic neurons *in vivo* in mice, looking especially at the vulnerability of nigrostrial pathways. They found that manganese chloride exposure, even at subtoxic doses changed the neuronal cytoskeleton of dopaminergic neurons. When the manganese treatment was extended to a period of 30days, a 20% reduction in TH-posiive neurons was observed in the substantia nigra pars compacta (SNpc), quantified by a widespread reduction in SNpc cell numbers through Nissil body staining. Parts of the basal ganglia including the striatum were also affected during treatment, showing sensitivity to nigrostriatal pathways. This study provides chronicles the timely repercussions of acute and chronic manganese exposure and provides an explanation for the motor manifestations observed from manganese intoxification.

How quickly can you detect a face? Temporal dynamics within neural constructs involved in the detection of familiar and novel faces

Blackford JU, **Avery SN**, Shelton RC, Zald DH. (2009). Amygdala temporal dynamics: temperamental differences in the timing of amygdala response to familiar and novel faces. *BMC Neurosci*. 10:145.

Inhibited temperament involves a predisposition of individuals to respond to new people, places or things with wariness or avoidance behavior, a characteristic trait known to be associated with increased risk for social anxiety disorder and major depression. Within the human brain, functional magnetic resonance imaging (fMRI) has shown the magnitude of blood oxygen level dependent (BOLD) responses in the amygdala for novel stimuli to be associated with inhibited temperament. The authors in this study used an event related fMRI paradigm to investigate the temporal dynamics (latency, duration and peak) of the BOLD response to novel stimuli within the amygdala. They presented both novel and familiar faces to both inhibited and uninhibited temperament populations. Results indicated that the amygdala in inhibited participants responded faster to novel faces than familiar faces. In addition, they found that the inhibited participants showed both a longer and greater amygdala response to all faces in comparison to the uninhibited population, even though there were no differences in the peak BOLD response. Blackford and colleagues speculate that this temporal computational bias for novel stimuli within the amygdala may lead to greater neophobic responses and could allude to a plausible mechanism for the development of social anxiety.

apoptosis during embryogenesis. The rapid and controlled clearance of these dead cells is vital, as non-ingested cells can generate inflammation and detrimental immune responses.

In a recent *Nature Neuroscience* article, a team led by Bruce Carter recognizes a specialized glial cell, satellite glial cell precursors (SGC), in the clearance of dead neurons in the dorsal root ganglia of embryonic mice. Previously, it was unclear which cells were responsible for apoptotic clearance, with default responsibility handed to macrophages. However, through confocal and electron microscopy and *in vitro* assays, the group demonstrates that the vast majority of apoptotic neurons are associated or engulfed within SGC's, highlighting an unrecognized role for glial cells in phagocytosis.

In addition, the group provided a potential molecular mechanism for engulfment of dead cells. Jedi-1 and MEGF10, homologues of known *c. elegans* and *Drosophila* proteins, are expressed in the brain and specifically within SGCs in the DRG. Transient expression of the either protein in cultured HEK cells led to binding of neuronal corpses, and overexpression of the proteins in glial cells leads to increased engulfment of dead cells, suggesting a clear role for Jedi-1 and MEGF10 as engulfment receptors. Through their research, Wu et al establish satellite glial cell precursors as members of the 'clean-up' crew in the peripheral nervous system, performing a similar role as microglia in the brain, and importantly implicate two receptors as crucial sensors in the proper clearance of apoptotic cells.

Original Research Article:
HH Wu, E Bellmunt, **JL Scheib**, V Venegas, C Burkert, LF Reichardt, Z Zhou, I Fariñas, BD Carter (2009). Glial precursors clear sensory neuron corpses during development via Jedi-1, an engulfment receptor. *Nat Neurosci.* **12** (12): 1534-1541.

Bad huntingtin, protective effect

Huntington's disease (HD) is a unique neurodegenerative disorder in that it has been mapped to a single locus, the *huntingtin* gene. In the disease, huntingtin protein progressively undergoes an expansion of a polyglutamate region. Onset of symptoms correlates with a specific number of polyglutamate repeats, such that the disease progressively worsens with age. Thus far, research has been unable to explain how mutant huntingtin leads to a remarkably specific loss of medium spiny neurons in the striatum, a primary cause of the motor deficits seen in patients. One hypothesis is that striatal neurons are situated in an environment that may uniquely impact their vulnerability to mutant HTT; a

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