JOHNS HOPKINS
SCIENCE *of* LEARNING INSTITUTE

Research Award Brief

Does the Brain Learn to Provide Increased Blood Flow to Regions Where and When Neural Activity is Anticipated? (2017-2019)

PI: David Linden, Ph.D.
Professor
Department of Neuroscience
School of Medicine

Co-Investigators: Mikhail Pletnikov, M.D., Ph.D.
Professor
Department of Psychiatry
School of Medicine

Research Question: Does the brain learn to provide increased blood flow to regions where and when neural activity is anticipated?

Interdisciplinary Approach: This project combines high-resolution imaging of blood vessels in the brain of an alert mouse with a careful, parametric approach to simple forms of learning.

Potential Implications of Research: This is basic research that may ultimately have profound implications for learning, memory, and neuropsychiatric disease.

An airpuff delivered to the eye is an unconditioned stimulus (US) that evokes a reflexive eyeblink, an unconditioned response (UR). In classical conditioning, repeated pairing of a neutral conditioned stimulus (CS) like a tone, presented such that its onset precedes and thus predicts the airpuff (US), results in learned production of a conditioned response (CR) - an eyeblink that is carefully timed within the CS-US interval so that the eyelid is already lowered when the airpuff is predicted to arrive. This is a simple and subconscious form of learning that was extensively studied by the pioneering psychologist Ivan Pavlov and his famous dogs.

Increases in blood flow rapidly follow increased neural activity within brain regions in order to increase the delivery of oxygen and nutrients to active brain tissue. This hemodynamic response underlies the widely-used brain activity imaging technique of functional magnetic resonance imaging (fMRI). Recently, it has become clear that, in addition to the hemodynamic response following neural activity, there is a second, stimulus-independent component: after repeated presentation of a cued visual stimulus there are hemodynamic responses in monkey primary visual cortex even on trials where the stimulus is omitted. Importantly, like eyeblink CRs, these responses precede anticipated stimulus arrival. This similarity to classical conditioning led us to hypothesize that stimulus-independent hemodynamic responses are URs that can undergo classical conditioning and thereby come to anticipate and predict localized metabolic demand in the brain.

We propose to test this hypothesis and its applicability to non-visual stimuli using high-resolution imaging of blood vessels in the brains of alert mice. Because the living brain is opaque to conventional optics, these experiments require a special instrument, called a two-photon confocal microscope, that allows us to peer inside the living brain.

We shall perform experiments using tactile whisker stimulation or forced walking as the US and shall image blood flow and record single-unit and local field potential activity in the corresponding regions of the neocortex (whisker barrel, primary motor). We shall use a tone CS and vary CS-US interval to determine whether hemodynamic CRs are well-timed. In trained mice, we shall perform repeated CS-alone trials to determine whether hemodynamic CRs can be extinguished. In all experiments we shall be able to resolve the cellular locus of the anticipatory hemodynamic responses, thereby distinguishing surface arteries from veins, penetrating arterioles and capillaries.