## EVOKED POTENTIALS

# Motivation: The Driving Force in All We Do

In our February issue of CLINICAL NEUROLOGY NEWS, we are inspired by the enormous effort represented by all of the research trials, new legislation, and progress leading our field forward. It is a fitting backdrop for our discussion of human creativity that we now continue by delving into some of the amazing work that has illuminated our understanding of motivation.

Creativity requires motivation; it does not happen passively. Our lives begin with biologic appetitive and aversive drives, such as the need to feed or avoid the cold. They are the roots of motivation. In the 1950s, James Olds, Ph.D., showed that appetitive and aversive behaviors were controlled by distinct brain regions (J. Comp. Physiol. Psychol. 1954;47:419-27). He implanted electrodes into rat brains and placed the rats in a cage containing a foot switch that, when pressed, delivered an electrical shock to the brain region in which the electrode was implanted. By varying the location of the electrodes and the conditions under which rats were tested, Dr. Olds found that some regions and situations led to self-stimulation rates as high as 7,000 shocks per hour, and others led the rats to avoid self-stimulation. The size of the shock, fatigue, hunger, pain, hormonal levels, and drugs all influenced response rates.

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Three brain regions, or systems, involved in motivation are the hypothalamus; the mesolimbic dopaminergic system (comprised of the ventral tegmental area [VTA], the nucleus accumbens/ventral striatum, and the orbitofrontal cortex [OFC], all linked together by the median forebrain bundle); and the amygdala. The hypothalamus maintains set points for different aspects of the "internal milieu," such as body weight and fluid balance. As our body strays from a set point, we are driven by hunger or thirst to alter our behavior and restore the set point. Returning our body to an established set point is powerfully rewarding. Within the mesolimbic system, VTA neurons generate a reward signal by comparing what occurs with what was expected (J. Neurophysiol. 1998;80:1-27). VTA dopaminergic reward neurons are most strongly activated by rewarding events that are better than expected.

The basolateral amygdala forms associations between sensory cues and rewarding or aversive stimuli, and acts as a "fear center" (J. Neurosci. 1995;15:5879-91). It is interconnected with sensory cortices and the hippocampus, forming associations with emotionally salient aspects of a stimulus that influence our perception and memory encoding of the stimulus (Curr. Opin. Neurobiol. 2004;14:198-202). Reward centers also modulate activity of the hypothalamus and locus ceruleus, thereby influencing endocrine and noradrenergic feedback to cortical regions.

The interplay of appetitive and aversive signals define a predicted, most rewarding (or least punishing) goal. Neurologists typically awaken early and perform a variety of duties over a long day (plus hospital call). Some appetitive signals include helping patients, research discoveries, educating students, pay, and benefits. Some aversive signals are the stresses of sick or otherwise difficult patients, research failures, underperforming students, and long hours. On balance, however, the net result is a greater feeling of reward than punishment so we keep doing it. But our behavior will change if discrepancies arise between the predicted and realized reward. If my health coverage were discontinued or my pay cut in half, I would seek a different position. The activity of anterior cingulate neurons – the earliest anatomical stage of action planning and movement – is influenced by reward signals from the orbitofrontal cortex. If a goal is made less rewarding, OFC neuronal activity declines as then does OFC stimulation of anterior cingulate neurons. The less rewarding activity stops and is replaced by a more rewarding one. Immediately preceding the change in behavior, specific neurons in the anterior cingulate fire, marking the first step that results in the altered response to the reduced reward (Science 1998;282:1335-8; Proc. Natl. Acad. Sci. U.S.A. 2002;99:523-8).

*This is the second installment of Dr. Caselli's 10-part series on creativity.*

Our reward system has many targets defining our wants. These include biologic stimuli such as food when we are hungry; aesthetic stimuli such as humor, paintings, music, and sports cars; and money (Neuron 2001;30:619-39). Reward centers also are activated by socially relevant behaviors, such as the decision to enact justice-related punishment and social comparisons in which we may perceive ourselves as better off than our neighbor. The developing relationship between two people learning the degree to which they can trust one another also causes changes in reward center activity (detected by fMRI) in an interpersonally synchronized fashion (Science 2005;308:78-83).

Aversive stimuli, such as pain or the loss of money, activate similar brain regions, although specific areas differ from those activated by reward (Nat. Neurosci. 2001;4:95-102). Motivation is also attenuated by diminished reward, and by nonescalating, static reward. We quickly accommodate to any improvement in our life circumstances (for example a higher income) so that initially heightened satisfaction rapidly recalibrates to baseline (the hedonic treadmill) (Science 2004;306:1776-80).

These examples illustrate that there is a final common reward pathway. All appetitive and aversive stimuli are translated into a common biologically relevant motivational signal that tells us whether something will enhance or diminish our survival or quality of life. The perceived difference in reward value between *what is* and *what should be* generates the motivational voltage that drives creativity. In our next issue, we will consider perception and mental imagery as the steps that create, in our mind's eye and imagination, *what is* and *what should be*, or the generation of ideas. ■

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# Plasmapheresis Guidelines Revised for Neurologic Diseases

BY MITCHEL L. ZOLER

FROM NEUROLOGY

Despite widespread use of plasmapheresis for treating several different neurologic diseases, it has clearly proven efficacy for only acute inflammatory demyelinating polyneuropathy and chronic inflammatory demyelinating polyneuropathy, according to revised guidelines released by the American Academy of Neurology.

An expert subcommittee of the academy also determined that plasmapheresis is probably effective for two other indications: polyneuropathy associated with immunoglobulin A and immunoglobulin G, and for managing exacerbations in relapsing forms of multiple sclerosis. The treatment also might be effective for fulminant demyelinating central nervous system disease (Neurology 2011;76:294-300).

"Plasmapheresis is one of the key, major treatments used in a variety of neurologic diseases, but it is relatively expensive, labor intensive, and intrusive with some risk to patients. That's why it needs to be fully evaluated in a critical way," said Dr. Alexander Rae-Grant, a neurologist at the Mellen Center for Multiple Sclerosis of the Cleveland Clinic and a member of the AAN Therapeutics and Technology Assessment subcommittee that wrote the new guidelines.

**There was insufficient evidence to support or refute the use of plasma exchange for myasthenia gravis.**

DR. RAE-GRANT

The subcommittee's recommendations form the AAN's first revision of its plasmapheresis recommendations since 1996 (Neurology 1996;47:840-3). For certain indications the intervening years produced new data, and in other cases the subcommittee produced a more contemporary assessment of the existing data.

Despite this, "not many differences exist" between the new revision and the prior guidelines, he noted. In particular, the two most well-documented applications of plasmapheresis in neurology remain the same as 15 years ago: treatment of acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome), and short-term treatment of chronic inflammatory demyelinating neuropathy.

However, for all other current neurologic applications of plasmapheresis, the committee determined that either the evidence base was insufficient to judge its efficacy or the treatment is probably ineffective or proven ineffective. These conditions included Sydenham chorea; acute obsessive-compulsive disorder and tics in patients with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS); polyneuropathy associated with immunoglobulin M, a monoclonal gammopathy of undetermined significance; chronic progressive or secondary progressive multiple sclerosis; and myasthenia gravis.

Perhaps the most controversial application of plasmapheresis in neurology is for myasthenia gravis, an indication that the subcommittee judged had insufficient evidence to either support or refute its efficacy when used for myasthenic crisis or myasthenia gravis prethymectomy. Despite the equivocal evidence base, "plasmapheresis is used at many medical centers for this indication," the guidelines noted.

"Experts in myasthenia gravis feel there are anecdotal data [in favor of its efficacy]. We tried to balance the expert concept and what the data show. Because our assessment was not in line with active practice, we tried to show [in the wording of the guidelines] that we were aware of this and thought about it," Dr. Rae-Grant said in an interview.

Dr. Rae-Grant said that he has received speaker honoraria from Biogen Idec, Teva, and EMG Serono. He receives publishing royalties for "Handbook of Multiple Sclerosis" and has served on the speaker's bureau for Biogen Idec. ■