



Research article

Using pupil size and heart rate to infer affective states during behavioral neurophysiology and neuropsychology experiments



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HIGHLIGHTS

- Heart rate and pupil size can provide information about cognitive and affective states of nonhuman primates.
- Experimental design, data acquisition and data process methods impact successful interpretation of autonomic measures.
- Disruption of autonomic control by amygdala lesion does not necessarily prevent interpretation of pre/post lesion effects.

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ABSTRACT

Background: Nonhuman primates (NHPs) are a valuable research model because of their behavioral, physiological and neuroanatomical similarities to humans. In the absence of language, autonomic activity can provide crucial information about cognitive and affective states during single-unit recording, inactivation and lesion studies. Methods standardized for use in humans are not easily adapted to NHPs and detailed guidance has been lacking.

New method: We provide guidance for monitoring heart rate and pupil size in the behavioral neurophysiology setting by addressing the methodological issues, pitfalls and solutions for NHP studies. The methods are based on comparative physiology to establish a rationale for each solution. We include examples from both electrophysiological and lesion studies.

Results: Single-unit recording, pupil responses and heart rate changes represent a range of decreasing temporal resolution, a characteristic that impacts experimental design and analysis. We demonstrate the unexpected result that autonomic measures acquired before and after amygdala lesions are comparable despite disruption of normal autonomic function.

Comparison with existing methods: Species and study design differences can render standard techniques used in human studies inappropriate for NHP studies. We show how to manage data from small groups typical of NHP studies, data from the short behavioral trials typical of neurophysiological studies, issues associated with longitudinal studies, and differences in anatomy and physiology.

Conclusions: Autonomic measurement to infer cognitive and affective states in NHP is neither off-the-shelf nor onerous. Familiarity with the issues and solutions will broaden the use of autonomic signals in NHP single unit and lesion studies.

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1. Introduction

Autonomic outputs controlled by the central nervous system, like neurosecretory and neuroendocrine outputs, are types of motor output that are often overlooked by behavioral neurophys-

iologists and many other behavioral scientists. Relative to skeletal and oculomotor outputs, which are readily observable, autonomic outputs are largely covert and often occur in the absence of conscious awareness. Because autonomic measures provide information on the internal state of an organism, and can be quantified, they remain valuable tools nearly a century after their initial validation in humans (Larson, 1922). The interpretation of autonomic outputs, however, remains controversial (Committee to Review the Scientific Evidence on the Polygraph (Research Council (U.S.))

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et al., 2003). Inferred internal states and associated behavioral consequences vary among studies and have included veracity (Committee to Review the Scientific Evidence on the Polygraph (Research Council (U.S.)) et al., 2003; Granhag et al., 2015), valence (Bliss-Moreau et al., 2013), reward (Satterthwaite et al., 2007; Varazzani et al., 2015), surprise (Lavin et al., 2014), attention (Iriki et al., 1996), vigilance (Kennerley and Wallis, 2009), arousal (Ebitz and Platt, 2015; Bradley et al., 2008), anxiety (Bertrand et al., 2013; Lader, 1983), impulse control and emotional clarity (Williams et al., 2015), and cognitive performance (Zeki Al Hazzouri et al., 2014; Duschek et al., 2009; Beatty, 1982; Marshall et al., 2004). Some of these states have been grouped into the regulation and expression of emotion (Bauer, 1998; Kreibig, 2010; Lang, 1995). Because they provide a window into emotion regulation and expression, autonomic measures have been an important avenue for understanding cognitive and social aspects of special human populations, e.g., older adults (Allard et al., 2010; van der Kooy et al., 2006), individuals with intellectual disabilities (Chaney et al., 1989; Vos et al., 2013), or autism spectrum disorder (Anderson et al., 2006; Erstenyuk et al., 2014; Farzin et al., 2011; Sepeta et al., 2012), psychiatric populations (Graur and Siegle, 2013), and unresponsive (minimally conscious) patients (O’Kelly et al., 2013).

Despite this interest in the autonomic nervous system as a surrogate for emotion, the primary role of the autonomic nervous system is homeostasis. The mammalian autonomic nervous system is far more complex and dynamic in its architecture by comparison to other vertebrates. Sympathetic and parasympathetic control is antagonistic for some organ functions, for example adjustment of pupil size, vasomotor regulation and heart rate (HR) (Janig and McLachlan, 2013). Yet, these two divisions of the autonomic nervous system can also operate in various coordinated ways (Janig and McLachlan, 2013). The mammalian diving reflex is one example of a complex and coordinated autonomic reflex (Pendergast et al., 2015). Autonomic control is hierarchical in that local reflexes may be modulated by inputs from cortical and brainstem structures, as well as by circulating hormones (Dum et al., 2016). Autonomic activity has numerous physiological effects, many of which, either directly or indirectly, produce effects on the CNS. Thus, autonomic control is bidirectional between the nervous system and organs. The autonomic responses driven by the central nervous system, often termed centrally mediated autonomic responses, form the basis of using autonomic activity to assess affective state (Benarroch, 1993). Although it is generally agreed that autonomic activity is influenced by affective and cognitive behaviors (Benarroch, 1993), there is little consensus over the degree to which autonomic response patterns reflect specific emotional events in humans, if they do so at all (Kreibig, 2010). Studies in nonhuman animals may provide a way to address the central control of patterned responses.

Surrogate measures of attention, emotion and decision making have enormous importance to basic and translational research. These measures provide opportunities to use animal models, especially nonhuman primates (NHPs), to dissect neuronal mechanisms of emotion and investigate potential therapeutics. Genetic (Rhesus Macaque Genome et al., 2007), anatomical (Crawford, 1977; Van Essen, 2002) and physiological (Clarke et al., 2003; Gamlin et al., 1998; Amiez et al., 2003; Jansen and Dellinger, 1988) similarities between humans and NHPs offer strong evidence that similar mechanisms are at play. In NHPs, autonomic measures additionally provide a useful means to understand the animal’s state beyond overt skeletomotor responses, such as button presses or licking behavior (Paton et al., 2006). Indeed, when verbal, declarative responses and self-reports are unavailable, as is the case in animals and some patient groups, autonomic measures are all the more valuable as an index of internal state.

Differences in anatomy, behavior, and experimental design pose unique challenges for the acquisition and analysis of autonomic data from NHPs. Two autonomic measures, pupil size and HR, are being used increasingly in NHP studies as indicators of affective responses (Kennerley and Wallis, 2009; Ebitz and Platt, 2015; Braesicke et al., 2005). Based on our experience using these techniques, our objective here is to provide background and guidance for researchers planning to use these measures in NHPs in the context of controlled neuropsychological and behavioral neurophysiological experiments. Software based tools for the methods we describe are open-access and available at: <ftp://helix.nih.gov/lsn/autonomics/>.

2. Animal procedures

The experimental aims, methods, and results of our original studies have been described in detail elsewhere (Rudebeck et al., 2014; Rudebeck et al., 2013a). Here we present unpublished data from these same studies to provide guidance for acquisition of autonomic measures in NHP. All experimental procedures were performed in accordance with the ILR Guide for the Care and Use of Laboratory Animals and were approved by the Animal Care and Use Committee of the National Institute of Mental Health. Procedures adhered to applicable United States federal and local laws, regulations and standards, including the Animal Welfare Act (AWA 1990) and Regulations (PL 89-544; USDA 1985) and Public Health Service (PHS) Policy (PHS 2002).

3. Measuring affective influences on pupil size

3.1. Physiology

Pupil size is regulated by the opposing musculature of the iris: the sphincter and the dilator. The sphincter constricts the pupil under tonic parasympathetic control and the dilator enlarges the pupil under sympathetic control. Changes in pupil diameter are dominated by a short-latency pupillary light reflex (PLR). Light-driven neural activity is transmitted through the optic nerve to the Edinger-Westphal nuclei, which supply the parasympathetic component of the oculomotor nerve bilaterally. Brighter environmental conditions drive consensual constriction of the pupils through oculomotor nerve control of the pupillary sphincters. Pupil size is logarithmically related to the intensity of the photic stimulus. Reflex latency is variable from subject-to-subject, and is limited primarily by sphincter muscle mechanics. The temporal characteristics of the response are species dependent; rhesus monkeys (*Macaca mulatta*) generally have faster dynamics than humans (Gamlin et al., 1998). In either species, any change in lighting, including those produced by eye movements, will require hundreds of milliseconds to settle. The impact of stabilization of the PLR on experimental design will be discussed in more detail in Section 3.3. The dynamic sensitivity of the PLR change depends upon pupil size over a wide range of pupil sizes, which reflects the physiology and mechanics of the opposing pupillary muscles (Usui and Stark, 1982). Spontaneous pupil size changes (called “hippus”) are the result of essentially Gaussian neuronal noise shaped by the muscle mechanics (Usui and Stark, 1982). Although the mechanics are pupil size dependent, hippus occurs even under isoluminant conditions. The PLR can also be unstable, showing a rise in either phase sensitivity or amplitude sensitivity near onset of oscillation (Longtin et al., 1990).

When driven by emotional or cognitive stimuli, the amount and direction of pupil size change depend on context. For example, dilation can occur with pleasure and constriction with displeasure

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