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Somatic and neuroendocrine responses to standard and biologically salient acoustic startle stimuli in monkeys

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Summary The startle response, a simple defensive response to a sudden stimulus signaling proximal threat, has been well studied in rodents and humans, but has been rarely examined in monkeys. The first goal of the present studies was to develop a minimally immobilizing startle measurement paradigm and validate its usefulness by testing two core features of the startle response (habituation and graded responsivity) in squirrel monkey subjects. Two different types of startle stimuli were used: standard broad-band noise bursts, and species-specific alarm vocalizations (''yaps'') which are elicited in response to threat in both wild and captive animals. The second goal of the present studies was to test whether yaps produce enhanced startle responsivity due to their increased biological salience compared to simple, non-biologically relevant noise bursts. The third goal of the present studies was to evaluate the hypothalamic-pituitary-adrenal (HPA) axis response to startle stimuli, as little is known about the stress-activating role of startle stimuli in any species. These experiments determined that the whole-body startle response in relatively unrestrained squirrel monkeys habituates across repeated stimulus presentations and is proportional to stimulus intensity. In addition, differential habituation was observed across biologically salient vs. standard acoustic startle stimuli. Responses to ''yaps'' were larger initially but attenuated more rapidly over trials. Responses to ''yaps'' were also larger in the early subepochs of the response window but then achieved a lower level than responses to noise bursts in the later subepochs. Finally, adrenocorticotropic hormone and cortisol concentrations were significantly elevated above baseline after startle stimuli presen-

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tation, though monkeys did not exhibit differential HPA axis responses to the two types of startle stimuli. The development of monkey startle methodology may further enhance the utility of this paradigm in translational studies of human stress-related psychiatric disorders.

1. Introduction

The startle response is a simple defensive response to a sudden acoustic, tactile, or visual stimulus signaling proximal threat (Landis and Hunt, 1939). Startle responses habituate rapidly and response magnitude is a monotonic function of stimulus intensity (Davis and File, 1984; Pilz and Schnitzler, 1996; Pilz et al., 1987). The neural circuitry of the startle response and its primary modulating inputs have been described in detail (Davis et al., 1982, 1997). In animals, the startle response is typically measured by the magnitude of whole-body movement. In humans, the most common response channel has been contraction of the *orbicularis oculi* muscle, though cardiac acceleration and scalp electroencephalographic potential are also used (Blumenthal et al., 2005). Across species, the startle response can be potentiated or attenuated by a variety of factors (Bradley et al., 2006; Lang and Davis, 2006), in particular, fear and stress (Brown et al., 1951; Davis, 1984). Startle is enhanced in people with anxiety disorders (Grillon and Baas, 2003; Stam, 2007), and can be attenuated by anxiolytic medications (Bitsios et al., 1999). For these reasons, the startle response is a leading tool in translational research into human psychopathology.

There have been few attempts to develop startle paradigms in monkeys with a few important exceptions (Davis et al., 2008; Linn and Javitt, 2001; Winslow et al., 2002). Monkey models are important because corticolimbic brain substrates involved in complex cognition and emotion regulation differ significantly in rats and mice compared to human and non-human primates (Ongur and Price, 2000; Preuss, 1995). Because functional abnormalities in these brain regions are thought to underlie stress-related psychiatric disorders characterized by enhanced startle responsivity, and neurobiological assessments can be made readily in monkeys but not in humans, monkey models bridge a critical gap between existing rodent and human research paradigms.

The first goal of the present studies was to develop an acoustic startle paradigm for use in squirrel monkeys that was minimally immobilizing and therefore did not require extensive acclimation prior to experimental initiation. The specific details of this startle paradigm are described below. Our studies sought to evaluate two core features of the startle response: habituation to repeated stimulus presentations and monotonically increasing response magnitudes to stimuli of increasing intensity.

The second goal of these studies was to examine whether the biological salience of acoustic stimuli alters the two core features of the startle response evaluated in these experiments. In view of the fact that broad-band noise bursts are rare under free-living conditions in nature, we chose to employ a second type of stimulus, a biologically salient one, which could be expected to elicit abrupt imperative interruptions of on-going activity. Squirrel monkeys utilize a relatively large corpus of species-specific vocalizations (Jurgens, 1998). Among them, "yap" alarm vocalizations are typically elicited in response to threats (e.g., terrestrial carnivores), and serve to orient other troop members to them (Newman, 1985). It is noteworthy that "yaps" are otherwise physically divergent from classic broad-band noise burst startle stimuli especially in having long rise-times (see Fig. 1). Because yaps are typically elicited in response to threatening circumstances (Newman, 1985), we hypothesized that yaps would produce enhanced startle responsivity due to their increased biological salience compared to simple, non-biologically relevant noise bursts.

The third goal of these studies was to examine the hypothalamic-pituitary-adrenal (HPA) axis response to startle stimuli in monkeys. There is considerable evidence that the HPA axis impacts startle responsivity in rodents and humans. Pharmacological pretreatment with drugs that either increase HPA axis drive [e.g., corticotropin-releasing hormone (CRH) agonists or metyrapone] or block negative feedback (e.g., glucocortiocoid receptor antagonists)

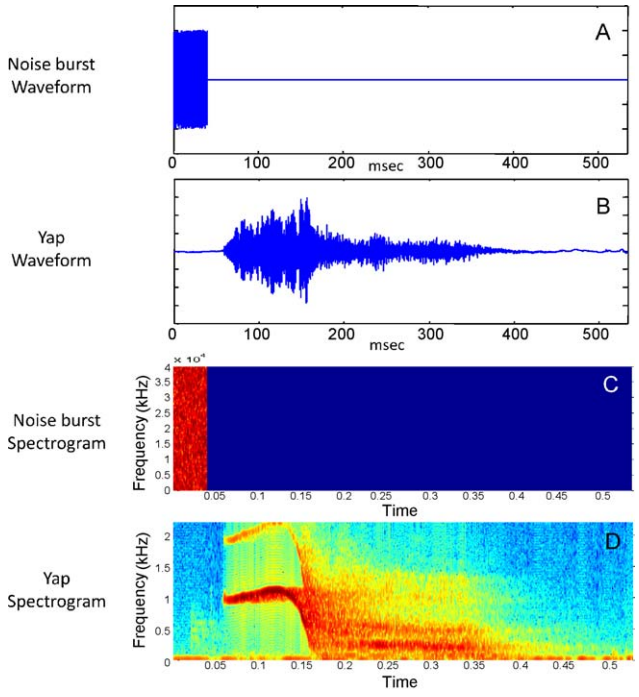

Figure 1 Comparative time-domain and spectrographic representations of the standard noise burst (panels A and C) and biologically salient yap (panels B and D) startle stimuli. It is evident that these are highly contrastive physical stimuli. The noise burst offsets precede the onsets of the energetic portion of the yaps. Yap onsets are relatively graded in comparison to noise bursts. Yaps are also harmonically complex (possess distinct formants), segment, and extend in time.