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THE FUNCTIONAL NEUROANATOMY OF CLASSIC DELAYED RESPONSE TASKS IN HUMANS AND THE LIMITATIONS OF CROSS-METHOD CONVERGENCE IN PREFRONTAL FUNCTION

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Abstract—Three classic delay tasks: spatial delayed response, delayed spatial alternation and delayed object-alternation are prototypical experimental paradigms for mapping the functional neuroanatomy of prefrontal cortex in animals. These tasks have been applied in human lesion studies, yet there have been very few studies investigating their functional neuroanatomy in healthy human subjects. We used functional magnetic resonance imaging to investigate the functional neuroanatomy of these classic paradigms (and a fourth: object delayed response) in a single sample of healthy human participants. Consistent with previous animal, human lesion, and functional neuroimaging studies, activity was observed in prefrontal and posterior parietal cortices across all three delay tasks. Task-specific activations, however, were not entirely consistent with predictions drawn from animal lesion studies. For example, delayed object-alternation activated dorsolateral prefrontal cortex, a region not generally implicated in animal lesion reports. Spatial delayed response, classically associated with the dorsolateral prefrontal cortex, did not activate this region; it rather activated posterior premotor cortices involved in response preparation, as did spatial alternation. All three tasks activated the frontopolar cortex, a region not considered crucial in animal research but associated with manipulation of internally generated information in recent human research. While cross-method convergence may be attained for lower level perceptual or motor tasks, the results of this study caution against the assumption that lesion-specific effects in animals generalize to human prefrontal cortex function.

Key words: working memory, delayed response, delayed alternation, prefrontal cortex, fMRI.

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Abbreviations: AFNI, Analysis of Functional Neuroimages; aPFC, anterior prefrontal cortex; BA, Brodmann area; BOLD, blood oxygen level dependent; DLPFC, dorsolateral prefrontal cortex; DOA, delayed object alternation; DR-O, object delayed response; DR-S, spatial delayed response; DSA, delayed spatial alternation; fMRI, functional magnetic resonance imaging; FWHM, full-width-half-maximum; PET, positron emission tomography; PFC, prefrontal cortex; VLPFC, ventrolateral prefrontal cortex.

It is common practice in human neuropsychological research and clinical diagnosis to relate test performance to lesion location. This practice rests on the assumption that lesion location and task effects validated in one experimental platform can be transferred to another context. Such cross-method convergence is readily attained in studies of basic perceptual or motor function. Higher-level processes mediated by the prefrontal cortex (PFC) on the other hand, are more variable across species, individuals, and experimental platforms, challenging assumptions of cross-method convergence.

Three classic delayed response tasks: spatial delayed response (DR-S), delayed spatial alternation (DSA) and delayed object alternation (DOA) are among the best localizing tasks in primate lesion studies of the PFC and have been central to theories of prefrontal function, yet few studies have assessed their validity in human samples using lesion and functional neuroimaging (for exceptions, see Freedman and Oscar-Berman, 1986; Freedman et al., 1998; Curtis et al., 2000; Zald et al., 2002, 2005) methods. To our knowledge, their neural correlates have not been explicitly investigated *in vivo* simultaneously in a single sample of healthy human participants. The purpose of this study was to examine the functional neuroanatomy of these tasks, as well as a fourth, object-based delayed response task (DR-O), in healthy adults using functional magnetic resonance imaging (fMRI).

The classic version of the delayed response task (see Fig. 1a) as devised by Hunter (1913), adopted by Jacobsen (1936), and subsequently widely adapted for research in a variety of animal and human populations involves four primary task components: (i) *stimulus-reward placement* in one of two target locations in full view of the participant, (ii) a *delay period* during which the target locations are hidden from the participant's view, (iii) *presentation of target locations* after the delay, and (iv) *motor response* to select the correct location of the stimulus-reward. Starting in the 1950s and 1960s (Pribram et al., 1952; Mishkin and Pribram, 1955, 1956; Pribram and Mishkin, 1956; Mishkin, 1964; Mishkin et al., 1969), investigators began to characterize the role of the PFC in mediating behavior across a brief delay using this simple paradigm. Goldman et al. (1971) reported that deficits on delay tasks following ablations of non-human primate PFC were a function of the delay period and not attributable to primary sensory or motor deficits, demonstrating the *necessity* of PFC in mediating behavior across a delay. Convergent findings from electrophysiological studies of delay-related neuronal activity within the primate PFC (e.g. Fuster and Alexander,

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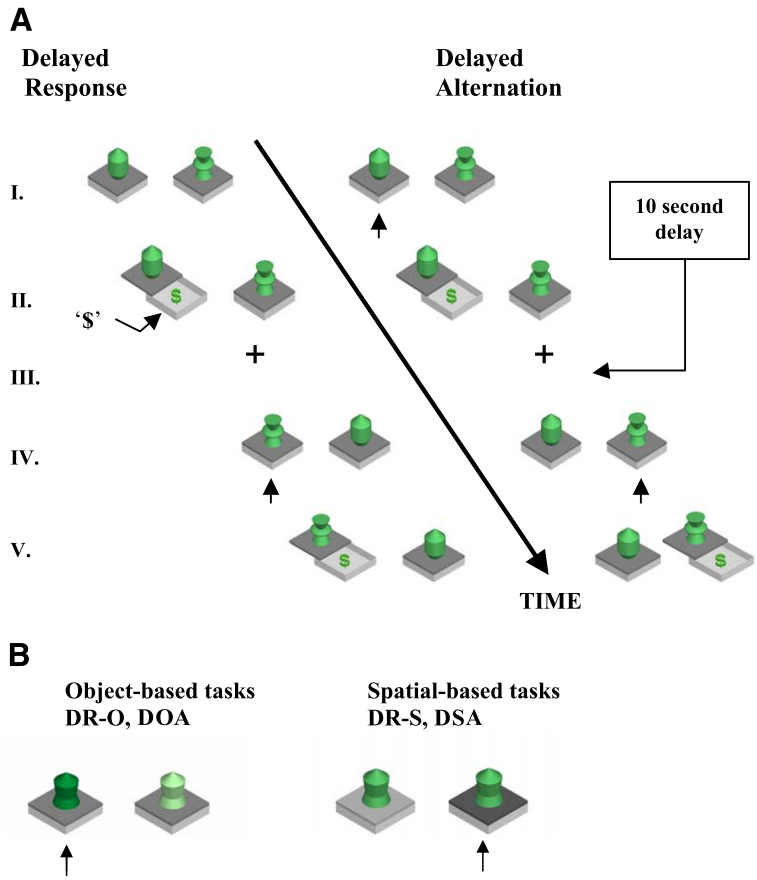

Fig. 1. (A) Phases of delayed response tasks: I. Stimulus presentation. II. 'Baiting' of target (in 'alternation' tasks, this depends on accuracy of previous response). III. Delay. IV. Probe stimulus. V. Feedback. The vertical arrow signifies participant response. Feedback provided by appearance of either a happy or sad face between and just above the two wells. During 'spatial' tasks, objects are uninformative (they are placed randomly across locations). During 'object' tasks, location is uninformative. Thus for delayed response (left side of figure) the bait remains in the left well, even though the object switches. For delayed object response (DR-O, not pictured), the bait would remain under the same object, although the location would switch at random. For DSA (right side of figure), the bait is found on the opposite side as on the previous trial, irrespective of object. The alternation trial depicted here would also hold for object alternation (DOA), in which the bait is found under the opposite object as on the previous trial, irrespective of side. Note that the visual stimuli remain constant for all tasks, eliminating variance due to perceptual processing. Total trial length: 17.5 s (DR-S, DR-O); 15 s (DSA, DOA). (B) Left: perceptuomotor control tasks for DR-O/DOA. Participants were instructed to always choose the darker green object (correct response signified by the arrow in this diagram). Right: perceptuomotor tasks for DR-S/DSA. Participants were instructed to always select the side with the darker lid. Feedback as in panel A.

1973), and reports of delayed response deficits in persons with frontal brain disease (e.g. Oscar-Berman and Zola-Morgan, 1980) defined a central role for PFC in what is currently labeled as working (Baddeley, 1986) or representational (Goldman-Rakic, 1987) memory. Moreover, delayed response deficits were sensitive to topographically distributed lesions within PFC depending upon subtle manipulations of the original task (see Mishkin, 1964, for an early review), further enhancing the importance of this delay paradigm as a tool for studying structure–function relationships within PFC.

Early investigators altered the nature of the pre-delay cue (e.g. Mishkin and Pribram, 1955; Goldman et al., 1971; Passingham, 1975), demonstrating that lesions to the principal sulcus in the monkey impacted performance primarily on spatial delay tasks, while inferior frontal convexity lesions in the monkey led to deficits on a non-spatial (i.e. color-matching) delay task (Passingham, 1975). More recent reports have questioned this functional division of the PFC based solely on mnemonic domain. They suggest other factors, including the need to inhibit prepotent responses (Mishkin and Manning, 1978), monitoring/manipulation demands (Petrides, 1996) or attention to and selection from items held on line (Rushworth et al., 1997; Rowe et al., 2000), more than the nature of the stimulus cue, might better characterize regional PFC contributions to delay task performance. Indeed, a second classic manipulation of the delay task paradigm involved reversing the reward contingencies after each correct trial (i.e. delayed alternation). Deficits on these alternation tasks appeared to be disrupted by lesions to ventral regions of PFC, irrespective of the type of pre-delay cue (Mishkin et al., 1969).

Relatively less work has been done using these paradigms in humans. A series of 'comparative neuropsychology' studies has sought to transfer the classic delay tasks