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## REVIEW

# THE NEURAL BASIS OF REVERSAL LEARNING: AN UPDATED PERSPECTIVE

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Cortical regions	00	23
Striatal and amygdalar regions	00	24
Neurochemical modulation of reversal	00	25
Serotonin	00	26
Dopamine	00	27
Glutamate: N-methyl-D-aspartate receptors (NMDAR)	00	28
Concluding remarks	00	29
Conflict of interest	00	30
Acknowledgments	00	31
References	00	32

**Abstract**—Reversal learning paradigms are among the most widely used tests of cognitive flexibility and have been used as assays, across species, for altered cognitive processes in a host of neuropsychiatric conditions. Based on recent studies in humans, non-human primates, and rodents, the notion that reversal learning tasks primarily measure response inhibition, has been revised. In this review, we describe how cognitive flexibility is measured by reversal learning and discuss new definitions of the construct validity of the task that are serving as a heuristic to guide future research in this field. We also provide an update on the available evidence implicating certain cortical and subcortical brain regions in the mediation of reversal learning, and an overview of the principal neurotransmitter systems involved.

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**Key words:** frontal cortex, striatum, amygdala, dopamine, serotonin, glutamate.

## INTRODUCTION

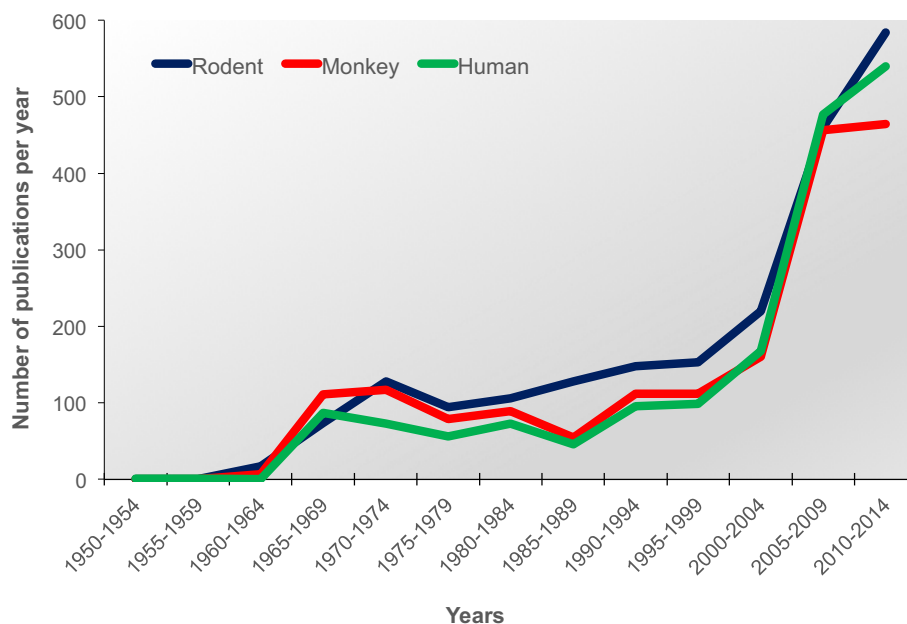
Cognitive flexibility, the ability to rapidly change behavior in the face of changing circumstances, is disrupted in many psychiatric and neurological disorders. Determining the neural basis of cognitive flexibility is therefore important for understanding the pathophysiology of these disorders and potentially developing treatments. To study the neural substrates of cognitive flexibility in rodents, nonhuman primates, and humans, researchers have often used a set of paradigms collectively referred to as reversal learning. Across species, these paradigms are subtly different, but importantly they all assess cognitive flexibility by evaluating adaptive responding in the face of changing stimulus-outcome (S-O) or response-outcome (R-O) contingencies.

Over the years, reversal learning has become a pre-eminent test of cognitive flexibility and has been used to characterize altered cognitive processes in a host of neuropsychiatric disorders, including substance abuse, obsessive compulsive disorder, psychopathy, Parkinson's disease, schizophrenia, and to assess cognition at certain developmental time periods such as adolescence (Swainson et al., 2000; Remijne et al., 2006; Finger et al., 2008; Brigman et al., 2009; Leeson et al., 2009; van der Schaaf et al., 2011; Izquierdo and Jentsch, 2012). Despite its long history of use, reversal learning continues to be an essential experimental paradigm for assessing cognitive function. Indeed, recent years have seen a precipitous rise in the number of published studies using reversal learning, with almost equal focus on rodent, monkey and human subjects (Fig. 1).

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**Abbreviations:** DMS, dorsomedial striatum; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; NMDAR, N-methyl-D-aspartate receptors; OFC, orbitofrontal cortex; PCP, phencyclidine; PCPA, parachlorophenylalanine; RL, reinforcement learning; R-O, response-outcome; S-O, stimulus-outcome; WGTA, Wisconsin General Testing Apparatus.



**Fig. 1.** Publications of reports on reversal learning in rodent, monkey, and human subjects. Pubmed search terms “reversal learning” from 1950 to 2014. The early-to-mid 2000’s witnessed the steepest rise in the number of publications on reversal learning. Reversal learning continues to be a widely used paradigm for assessing cognitive function, with an almost equal focus on rodent, monkey and human subjects.

68 While the literature on the neural basis of reversal and  
69 the interpretation of findings using this task have been  
70 reviewed elsewhere (Clark et al., 2004; Izquierdo and  
71 Jentsch, 2012; Costa et al., 2015; Hamilton and  
72 Brigman, 2015; Wassum and Izquierdo, 2015), our aim  
73 here is to: (1) consider how reversal can be measured  
74 and compare different versions of the paradigm across  
75 species; (2) provide an updated perspective on the con-  
76 struct validity of reversal learning paradigms; (3) discuss  
77 current thinking on the major neural circuits mediating  
78 the ability to flexibly change behavior; and (4) review the  
79 neurochemical modulation of the cognitive processes  
80 engaged during reversal learning.

## 81 REVERSAL LEARNING PARADIGMS ACROSS 82 SPECIES

83 In the classic reversal learning paradigm used in humans  
84 (Fellows and Farah, 2003a), monkeys (Butter, 1969) and  
85 rodents (Schoenbaum et al., 2000), subjects are trained  
86 to discriminate between two visual stimuli or spatial loca-  
87 tions, one of which is rewarded every time it is chosen and  
88 the other which is not. After successful discrimination  
89 learning has been demonstrated by reaching a criterion  
90 level of performance, the outcomes associated with the  
91 two stimuli are reversed and subjects are again trained  
92 until they meet a performance criterion. Note, that while  
93 in this review we focus on instrumental, appetitive forms  
94 of reversal learning, Pavlovian associations can also be  
95 reversed and outcomes can also be aversive (Morris  
96 and Dolan, 2004; Burke et al., 2009).

97 An advantage of reversal learning paradigms is that  
98 they can be employed in multiple species and, as such,  
99 can have significant translational value for  
100 understanding the neural bases of cognitive flexibility.  
101 Reflecting this, many of the key findings concerning the

neural mechanisms of reversal learning have been  
102 replicated across rodent, non-human primate and  
103 human subjects, as discussed later in this review. We  
104 briefly review some of the common procedures  
105 employed to test reversal learning in different species  
106 noting the differences in paradigms, but also their  
107 similarities.  
108

109 For reversal learning tasks in rodents, behavioral  
110 apparatus are often outfitted with either two levers,  
111 nosepoke portals or a touch-sensitive screen. Mazes  
112 are also commonly used to test spatial discriminations  
113 and reversals (Jentsch and Taylor, 2001; Bannerman  
114 et al., 2003; Palencia and Ragozzino, 2004). With mazes,  
115 levers and portals, reversal may be performed solely  
116 using information about spatial location or incorporate  
117 the use of visual or auditory cues (Neill et al., 2001;  
118 Widholm et al., 2003; Boulougouris et al., 2007;  
119 Castañé et al., 2010). When a touchscreen is used, a  
120 wider variety of visual stimuli become available and spa-  
121 tial and egocentric strategies better controlled for  
122 (Izquierdo et al., 2006; Mar et al., 2013; Graybeal et al.,  
123 2014). In nonhuman primates, modified versions of the  
124 Wisconsin General Testing Apparatus (WGTA) have  
125 been used to test reversal learning (Jones and Mishkin,  
126 1972; Stern and Passingham, 1995; Izquierdo et al.,  
127 2004a). In one paradigm, an opaque screen is lowered  
128 while one of two food wells is baited with a reward. When  
129 the screen is raised the monkey is tasked with displacing  
130 one of the objects to reveal the reward. Alternatively, ani-  
131 mals can be presented with visual stimuli on cards or a  
132 touchscreen (Crofts et al., 1999; Clarke et al., 2005;  
133 Walker et al., 2009). With either method, selection of  
134 the correct stimulus results in delivery or access to a  
135 reward. Thus, the paradigms used in both rodents and  
136 monkeys are very similar. However, where reversal learn-  
137 ing tasks differ between species is in the number of rever-

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