Published in final edited form as:

J Child Psychol Psychiatry. 2014 June ; 55(6): 582–610. doi:10.1111/jcpp.12169.

Annual Research Review: The neurobehavioral development of multiple memory systems: implications for childhood and adolescent psychiatric disorders

Jarid Goodman¹, Rachel Marsh², Bradley S. Peterson², and Mark G. Packard¹

¹The Department of Psychology, Texas A&M University, College Station, TX, USA

²The MRI Unit and Division of Child & Adolescent Psychiatry in the Department of Psychiatry, the New York State Psychiatric Institute and the College of Physicians and Surgeons, Columbia University, New York, NY, USA

Abstract

Extensive evidence indicates that mammalian memory is organized into multiple brain systems, including a “cognitive” memory system that depends upon the hippocampus and a stimulus-response “habit” memory system that depends upon the dorsolateral striatum. Dorsal striatal-dependent habit memory may in part influence the development and expression of some human psychopathologies, particularly those characterized by strong habit-like behavioral features. The present review considers this hypothesis as it pertains to psychopathologies that typically emerge during childhood and adolescence. These disorders include Tourette syndrome, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, eating disorders, and autism spectrum disorders. Human and nonhuman animal research shows that the typical development of memory systems comprises the early maturation of striatal-dependent habit memory and the relatively late maturation of hippocampal-dependent cognitive memory. We speculate that the differing rates of development of these memory systems may in part contribute to the early emergence of habit-like symptoms in childhood and adolescence. In addition, abnormalities in hippocampal and striatal brain regions have been observed consistently in youth with these disorders, suggesting that the aberrant development of memory systems may also contribute to the emergence of habit-like symptoms as core pathological features of these illnesses. Considering these disorders within the context of multiple memory systems may help elucidate the pathogenesis of habit-like symptoms in childhood and adolescence, and lead to novel treatments that lessen the habit-like behavioral features of these disorders.

Correspondence: Mark G. Packard, Department of Psychology, Texas A&M University, College Station, TX, 77843-4235, USA; markpackard@tamu.edu.

Conflict of interest statement: No conflicts declared.

This review article was invited by the journal, for which the authors have been offered a small honorarium payment towards personal expenses; it has undergone full, external peer review. The authors have declared that there are no competing or potential conflicts of interest in relation to this article.

Keywords

Learning; Memory; Neuropsychiatry; Psychopathologies; Hippocampus; Striatum; Basal ganglia; Anxiety; Stress

Introduction

Identification of contributing factors in the development of human psychopathologies has often been pursued within the framework of learning theory (e.g. Mowrer, 1939, 1947; Wolpe, 1952; Eysenck, 1976). In this context, some investigators have recently suggested that certain psychopathologies may be characterized by a differential involvement of distinct memory systems (e.g. White, 1996; McDonald, Devan, and Hong, 2004; Marsh et al., 2004, 2005; Packard, 2009; Marsh, Maia, and Peterson, 2009; Goh and Peterson, 2012; Goodman, Leong, and Packard, 2012). Extensive evidence from neurobiological studies indicates that learning and memory processes are organized in multiple systems in the mammalian brain (for reviews see White and McDonald, 2002; Squire, 2004). One prominent view is that the hippocampus and dorsal striatum are critical anatomical components of relatively distinct memory systems (Figure One). According to this idea, the hippocampus mediates a ‘cognitive/relational’ form of memory, whereas the dorsal striatum mediates a “stimulus-response/habit” form of memory. This hypothesis is supported by numerous studies in adult rats that have employed irreversible and reversible brain lesion techniques and localized intracerebral drug injections to dissociate the roles of the hippocampus and dorsal striatum in cognitive and habit memory processes, respectively (Packard, Hirsh, and White, 1989; McDonald and White, 1993; Kesner, Bolland and Dakis, 1993; Packard and McGaugh, 1996; Packard and White, 1991; Packard and Teather, 1997). In rats, early evidence for the multiple memory systems hypothesis was revealed in experiments comparing the effects of manipulations of the hippocampal system and dorsal striatum. In studies using pairs of tasks with similar motivational, sensory, and motoric processes, lesions of the rat hippocampal system and dorsal striatum result in a double dissociation of task acquisition (Packard, Hirsh, and White, 1989; Packard and McGaugh, 1992; McDonald and White, 1993; Kesner, Bolland, and Dakis, 1993). For example, lesions of the hippocampal system impair acquisition of cognitive/spatial learning in the radial maze, a task that requires rats to use spatial information to remember which maze arms have been visited within a daily training session (Packard, Hirsh, and White, 1989). However, lesions of the hippocampal system do not impair acquisition of stimulus-response/habit learning in the radial maze, a task in which maze arms that are baited with food are signaled by a light cue (Packard, Hirsh and White, 1989). In contrast, lesions of the dorsal striatum impair acquisition of stimulus-response learning in the radial maze, but have no effect on acquisition of cognitive radial maze behavior (Packard, Hirsh and White, 1989; McDonald and White, 1993).

A double dissociation between the mnemonic functions of the hippocampal system and dorsal striatum is also revealed in rats trained in different versions of a two-platform water maze task. In this task, two rubber balls protruding above the water serve as cues. One ball (correct) is on a rectangular platform that can be mounted to escape the water, and the other ball (incorrect) is mounted on a thin rod and thus does not provide escape. The two balls

also differ in visual appearance (i.e. vertical versus horizontal black/white stripes). In a cognitive version of the task, the correct platform is located in the same location on every trial, but the visual appearance of the ball varies. Thus, this version of the task requires rats to learn to approach the correct ball on the basis of spatial location, not visual pattern. In the habit version of the task, the correct platform is located in different spatial locations across trials, but the visual pattern is consistent. Thus, this task can be acquired by learning an approach response to the visual cue (i.e. pattern discrimination). Lesions of the hippocampal system, but not the dorsal striatum, impair acquisition of the cognitive task; whereas lesions of the dorsal striatum, and not hippocampus, impair acquisition of the habit task (Packard and McGaugh, 1992).

Double dissociations between the roles of the hippocampus and the dorsal striatum in supporting memory functions have also been observed following post-training intracerebral drug injections (e.g. Packard and White, 1991; Packard, Cahill, and McGaugh, 1994; Packard and Teather, 1997; 1998). Thus, post-training, intra-hippocampal injections of dopaminergic agonists selectively enhance memory in a win-shift radial maze task, while similar injections into the dorsal striatum selectively enhance memory in a win-stay radial maze task (Packard and White, 1991). In addition, post-training, intra-hippocampal injections of the glutamatergic NMDA receptor antagonist AP5 selectively impair memory in a hidden platform water maze task, whereas similar injections into the dorsal striatum selectively impair memory in a visible platform water maze task (Packard and Teather, 1997). More recently, double dissociations between the mnemonic functions of the hippocampus and the dorsal striatum in cognitive and habit memory have also been demonstrated in other mammalian species, including monkeys and humans (for review see Packard, 2010).

Although numerous experiments on memory have emphasized the role of the hippocampus, cognitive memory may also depend on additional regions of the medial temporal lobe. According to one prominent hypothesis (for review see Eichenbaum, 2012), the functional organization of the medial temporal lobe may be divided into two streams, (1) a “what” stream that mediates recognition memory for specific objects and (2) a “where” stream that mediates memory for visuospatial and contextual information. Putatively, the “what” stream originates in cortical sensory areas that project to the perirhinal cortex and by proxy the lateral entorhinal cortex, and the “where” stream originates in parietal and retrosplenial cortices which send afferents to the parahippocampal cortex and subsequently the medial entorhinal cortex. It is hypothesized that the “what” and “where” streams subsequently converge on the hippocampus and encode an “item-in-context” association, a definitive characteristic of episodic memory. This hypothesis is consistent with the observation that recognition memory depends primarily on the perirhinal cortex and not the hippocampus (Zola-Morgan, Squire, Amaral, and Suzuki, 1989; Murray and Mishkin, 1998; Steckler, Drinkenburg, Saghal, and Aggleton, 1998), unless a spatial component is added to the recognition task in which case both perirhinal cortex and hippocampus are required (Barker and Warburton, 2011). The flow of information through the hippocampus itself is classically characterized as a trisynaptic circuit, beginning with entorhinal afferents which through the perforant pathway synapse on the dentate gyrus (synapse 1), through the mossy fiber pathway synapse on the CA3 region (synapse 2), and finally through the Schaffer collateral

pathway synapse on the CA1 region (synapse 3) (Swanson and Cowan, 1977; Amaral and Witter, 1995). In addition, it should be noted that the hippocampus may be divided into a ventral/anterior region that participates in anxiety-related behavior and a dorsal/posterior region that mediates cognitive memory processes (Bannerman et al., 2004).

The present review examines the “multiple memory systems” hypothesis from a developmental perspective and examines how this view may be useful for understanding the pathogenesis of certain psychopathologies in childhood and adolescence. We speculate that during these early stages of development, the hippocampal-dependent memory system has not yet fully matured, whereas the dorsal striatal-dependent memory system is potentially active at adult-like levels of efficiency, and these differing maturational time lines establish the preconditions for emergence of developmental psychopathologies when one or the other of these systems either fails to develop properly or becomes otherwise dysfunctional. First we review briefly what is known of the normal neural development of the hippocampus and the striatum in humans. This is followed by consideration of the rat, monkey, and human behavioral literature, providing evidence for the early maturation of the dorsal striatal-dependent memory system and the relatively slower development of the hippocampal-dependent memory system. The contrasting maturation of these two systems is then considered in the context of various psychopathologies in childhood and adolescence, including Tourette syndrome, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, eating disorders, and autism spectrum disorders. We suggest that key symptoms of these illnesses may reflect the early maturation of a striatal-dependent habit system. If this hypothesis proves correct, then a multiple-memory-systems approach may lead to novel treatments that target the habit-like behavioral features of these disorders.

Normal development of the human hippocampal formation and dorsal striatum

Although much of the overall architecture of the central nervous system is established during prenatal development, many morphological changes can still be observed in the postnatal brain. The hippocampal formation serves as a prime example of this extended development as this brain region shows signs of continued maturation from birth through adolescence and into adulthood (for review see, Seress, 2001). Neuronal development continues through several distinct processes, including cell proliferation, cell migration, and synapse formation, all of which have been observed postnatally in the human hippocampus. Cell proliferation occurs throughout most of the hippocampal formation primarily during pregnancy, with fewer cells being formed after birth, in all mammals, including rodents, nonhuman primates, and humans (for review, see Gould and Gross, 2002). New neurons have been observed in the dentate gyrus and entorhinal cortex of 3–11 month-old human infants (Seress, Ábrahám, Tornóczy, and Kosztolányi, 2001), and proliferating cells have been observed in the postmortem dentate gyrus of children (Seress, 2001) and adults (Eriksson et al., 1998).

Development of hippocampal neurons in humans is protracted. Immature granule cells can be observed from birth to 15 months of age (Seress, 1992). Mossy cells show signs of morphological maturity at 3–7 months of age, but their dendritic and axonal arborizations

take on adult-like appearance only between 3–5 years of age (Seress and Mrzljak, 1992). Human pyramidal cells mature mostly during prenatal development (Purpura, 1975; Ábrahám, Tornóczky, and Kosztolányi, 1999), but visible differences between the pyramidal cells of newborns and adults indicate further dendritic growth in postnatal life (Seress, 2001). Like granule cells and mossy cells, GABAergic interneurons of the hippocampus are poorly developed at birth. Their axonal and dendritic arbors begin branching within the first few postnatal months and become adult-like in their appearance sometime between 2 and 8 years of age (Seress, 2007). Lastly, myelination of axonal fibers throughout the hippocampal formation becomes adult-like in density gradually over the first decade of life, except for the hilus of the dentate gyrus which becomes adult-like in myelin density sometime after 11 years of age (Ábrahám et al., 2010).

Neuroimaging data also indicate substantial postnatal development of the human hippocampus with significant volumetric changes from childhood to adulthood, although specific findings are inconsistent. Hippocampal volume increases with age before puberty in boys and girls; however, during puberty hippocampal volume increases with sexual maturity in girls and decreases with sexual maturity in boys (Hu, Pruessner, Coupé, and Collins, 2013). Another study of male and female subjects reported overall increases of hippocampal grey matter volume between 8–30 years of age (Ostby, Tamnes, Fjell, Westlye, Due-Tønnessen, and Walhovd, 2009). Conversely, other data reported no significant change in overall hippocampal volume between 4–25 years of age, although subregion-specific changes were observed including an age-related volumetric increase of the posterior hippocampus (which is often associated with cognitive memory) and volumetric decrease of the anterior hippocampus (which is more often associated with anxiety-related behaviors; Gogtay et al., 2006).

Relatively fewer data are available on the postnatal development of the human striatum. Data in lower animals, however, indicate that the dorsal striatum also undergoes morphological changes during postnatal life. In rats, medium spiny neurons of the striatum appear functionally and morphologically mature by the end of the first postnatal month (Tepper, Sharpe, Koós, and Trent, 1998; Uryu, Butler, and Chesselet, 1999), and similar observations have been made in monkeys by the fourth postnatal month (DiFiglia, Pasik, and Pasik, 1980). In humans, caudate volumes have been reported to follow an inverted-U shape with advancing age, with peak volumes occurring at 7.5 years in girls and 10 years in boys, then gradually decreasing through adolescence (Lenroot and Giedd, 2006) and adulthood (Raz, Rodrigue, Kennedy, Head, Gunning-Dixon, and Acker, 2003). Putamen volume also decreases linearly between 8–30 years of age in humans (Ostby et al., 2009). Cell proliferation has been observed postnatally in the dorsal striatum of monkeys between the ages of 5 months and 3 years (Stopczynski, Poloskey, and Haber, 2008), with some of the new cells in this portion of the striatum being shown capable of differentiation into neurons in adult monkeys (Bédard, Cossette, Levesque, and Parent, 2002). Postnatal neurogenesis has yet to be observed in the striatum of humans, however.

In sum, both the hippocampus and striatum undergo substantial development in their cellular architectures during postnatal life. Although most of the components of the classical tri-synaptic circuit of the human hippocampus are formed during gestation, hippocampal

neurons generally do not become adult-like in their morphological appearance until 5–8 years of age, proliferation of dentate granule cells occurs even into adulthood (Eriksson et al., 1998), and hippocampal volumes continue to change throughout adolescence and adulthood (e.g. Ostby et al., 2009). The data available specifically for the dorsal striatum are very limited but also suggest protracted postnatal development. Although neuroimaging data show differences in hippocampal and dorsal striatal volumes across the human lifespan, it is not clear how these volumetric changes relate to maturation of learning and memory subserved by each brain region (e.g. Petten, 2004). Therefore, it is difficult to determine the relative maturation of hippocampal- and striatal-dependent memory based solely on current neurobiological findings. In the following sections, we present behavioral evidence suggesting that dorsal striatal-dependent memory is functionally mature earlier than hippocampal-dependent memory. Presumably, the observed differences between learning and memory systems are attributable to variations in the maturational timelines of their respective brain regions. In favor of this hypothesis, there is ample evidence in lower animals linking neurobiological development of the hippocampus to late maturation of cognitive memory (Alvarado and Bachevalier, 2000; Dumas, 2005; Langston et al. 2010; Wills, Cacucci, Burgess, and O'Keefe, 2010; Lavenex and Lavenex, 2013), but no definitive evidence linking neurobiological development of the dorsal striatum to early maturation of habit memory, making this a productive area for future research.

The neurobehavioral development of multiple memory systems

Considering that current neuroimaging and histology data may be too limited to adequately compare the maturational timelines of human hippocampus and dorsal striatum, exploring age-related differences in performance between hippocampal- and dorsal striatal-dependent memory tasks may be more informative. As described previously, our laboratory has used an assortment of maze paradigms to establish operative differences between rodent hippocampal- and dorsal striatal-dependent memory systems, the former mediating spatial/cognitive memory and the latter mediating stimulus-response/habit memory. Other investigators have employed a wider variety of tasks that supports similar distinctions between the two systems in not only rodents, but also monkeys and humans (Packard, 2010). What follows is a review of rodent, monkey, and human studies that have investigated cognitive and habit memory performance as a function of age. A potential confound for any experiment investigating the development of memory is the parallel development of non-mnemonic processes such as perception and motor performance. Therefore, the following review emphasizes studies that have employed pairs of tasks with similar motor, sensory and motivational requirements, but disparate mnemonic principles, one task typically cognitive-based and the other habit-based. We speculate that in this way the development of cognitive and habit memory may be more accurately compared.

Although cognitive and habit memory systems are considered primarily dependent on medial temporal lobe and basal ganglia structures respectively (for reviews see Packard and Knowlton, 2002; White and McDonald, 2002; Squire, 2004), the ostensible development of these memory systems could in part reflect the maturation of other brain regions not classically associated with cognitive or habit memory. For instance, the prefrontal cortex undergoes substantial development between childhood and adulthood (Gogtay et al., 2004),

and various subregions of the prefrontal cortex have been recently implicated in cognitive and habit memory processes in rats. Although not evidently required for the initial acquisition of hippocampal-dependent cognitive or dorsolateral striatal-dependent habit strategies, the infralimbic-prelimbic subregions of the medial prefrontal cortex are required for switching from one strategy to the other (Ragozzino, Detrick, and Kesner, 1999; Ragozzino, Wilcox, Raso, and Kesner, 1999; Rich and Shapiro, 2009). In addition, the infralimbic subregion is selectively involved in the expression of habit behavior (as opposed to goal-directed behavior) in instrumental learning tasks (Killcross and Coutureau, 2003; Coutureau and Killcross, 2003; Haddon and Killcross, 2011; Smith, Virkud, Deisseroth, and Graybiel, 2012). On the other hand, the medial prefrontal cortex is not evidently required for allocentric spatial memory (de Bruin et al., 1994, 2001; Nieto-Escamez, Sanchez-Santed, and de Bruin, 2002; Deacon, Penny, and Rawlins, 2003; Rawson, O’Kane, and Talk, 2010), whereas the orbitofrontal cortex is required for both the acquisition and consolidation of spatial memory (Vafaei and Rashidy-Pour, 2004). How the development of cortical regions may influence the relative maturation of hippocampal- and dorsal striatal-dependent memory is an open question and will require further empirical research to answer definitively.

Neurobehavioral development of multiple memory systems in rats

Early research on the ontogenetic development of distinct memory systems in rats focused on spontaneous alternation behavior in a T-maze, a task that typically consists of two trials (e.g. Dember, 1989). In the first trial, a rat is placed in the start arm and given the opportunity to travel up the arm and enter only one of the other two arms of the T-shaped maze before a partition appears and confines the rat to the chosen arm for the remainder of the trial. In the second trial, the same rat is given the choice to enter either of the two arms. Many studies have shown that adult rats typically enter the arm that had not been chosen in the previous trial; in other words, they spontaneously *alternate* arms between the two trials. In contrast, infant rats (between 5–15 days old) fail to show consistent alternation on the second trial, picking either arm at random, suggesting that memory is relatively poor for which arm had initially been selected (Kirkby et al., 1967; Hess and Blozovski, 1987). Rats eventually display significant alternation around postnatal day 17, with the probability of alternation continuing to increase up to postnatal day 100 (Hess and Blozovski, 1987; Egger, Livesey, and Dawson, 1973). Spontaneous alternation is considered to be a hippocampal-dependent task, as bilateral lesions to this area bring the alternation of adult rats to chance levels (Roberts, Dember, and Brodwick, 1962; Kirkby, Stein, Kimble, and Kimble, 1967; Means, Leander, and Isaacson, 1971; Stevens and Cowey, 1973; Johnson, Olton, Gage, and Jenko, 1977). Considering the importance of the hippocampus for cognitive memory in adult rats, a plausible explanation for the delayed onset of spontaneous alternation may be the slow postnatal development of memory structures, such as the hippocampal formation, that support declarative memory functions (for a review of alternative explanations, see Spear and Miller, 1989). In support of this hypothesis, excitatory synaptic transmission in the hippocampus, which is necessary for adult-like synaptic plasticity and memory, begins to mature around the third postnatal week (Dumas, 2005), about the same time young rats begin alternating (Egger et al., 1973). We note, however, that spontaneous alternation does

not depend solely on the hippocampus, but rather on a conglomeration of brain structures, such as the septum, cerebellum, and prefrontal cortex (for review, see Lalonde, 2002). Spontaneous alternation nevertheless is indicative of a late-developing memory system that depends at least in part on a functionally mature hippocampus.

Some studies measuring the development of memory have employed experiments that dissociate the two systems for cognitive and habit learning. The Morris water maze, for instance, remains a popular paradigm for studying hippocampal-dependent spatial memory, yet with minor alterations it can become a task that instead measures dorsal striatal-dependent memory for stimulus-response (S-R) associations. In the spatial version of this task, rats are placed in the water maze at varying starting points and in order to escape must find a hidden platform that remains in the same spatial location across trials. In the S-R version of the task, in contrast, rats are still released at varying starting points, but the platform is signaled by a proximal visual cue and the visibly cued platform is moved to different locations on each trial. This particular procedure requires stimulus-response learning, as the rat must learn to associate the cued platform (the stimulus) with approach behavior (the animal's response) in order to reach the platform quickly. Several studies have shown that the capacity to solve the S-R version of this task emerges around postnatal days 17–18 in rats, whereas the ability to solve the spatial version emerges around postnatal days 20–21 (Rudy, Stadler-Morris, and Albert, 1987; Rudy and Paylor, 1988; Akers and Hamilton, 2007; but see also Brown and Whishaw, 2000). Whether rats in the spatial version actually learn to swim to the same *spatial location* relative to the room's distal cues, or simply learn to swim the correct distance and direction from the pool wall (i.e. directional learning) is controversial. To identify more definitively how rats actually solve the task, 24-day-old rats were trained in the spatial version of the water maze and then subjected to a probe trial in which the pool was shifted to a new position within the room (Akers, Candelaria, and Hamilton, 2007). On the probe trial, 24-day-old rats swam to the same relative location, which—due to the repositioning of the pool—differed from the absolute location to which the rats had swum during training, suggesting that the rats likely solved the task using directional learning rather than spatial learning. Thus, what had initially been conceived as the emergence of spatial learning between postnatal days 20 and 21 (Rudy, Stadler-Morris, and Albert, 1987; Rudy and Paylor, 1988; Akers and Hamilton, 2007) may actually have been the emergence of directional learning. To determine the age at which rats learn the absolute location of the platform, a subsequent study was performed in which the pool was repeatedly repositioned over trials while the hidden platform remained in the same absolute location. The rats were able to solve this task at postnatal days 26–27 (Akers, Candelaria-Cook, Rice, Johnson, and Hamilton, 2009). Taken together, response learning, directional learning, and spatial learning seem to emerge in the young rat at different times, i.e. at postnatal days 17–18, 20–21, and 26–27, respectively. These developmental changes in learning and memory take place during the prepubertal stage of the rat's life cycle, whereas sexual maturity occurs around the fifth postnatal week.

That directional and spatial learning emerge at different ages may be somewhat unexpected, given that both forms of learning are thought to depend primarily on the same brain structure, the hippocampus (Stringer, Martin, and Skinner, 2005). Some have suggested

(Akers et al., 2009) that these differences in development may reflect the differences in maturation of hippocampal place and grid cells, which encode an animal's location in space, and cingulate head direction cells, which encode the direction of the animal's head. Indeed, whereas head direction cells show adult-like activity at postnatal day 16, the proportion and activity of place and grid cells become adult-like between postnatal days 21–28 (Langston et al., 2010; Wills et al., 2010). Thus, subtle changes over the course of maturation for these cell types may underlie the ontogenetic differences between place and directional learning in the water maze.

Ontogenetic disparities between the emergence of different memory systems may also be observed in associative learning paradigms, such as fear conditioning and eyeblink conditioning in rats (for review, see Stanton, 2000). In these experiments, rats are given repeated exposure to a conditioned stimulus (CS; e.g. an auditory tone) that precedes the onset of an unconditioned stimulus (US; shock or air puff), prompting the animal to execute an conditioned response (CR; freeze or blink) whenever it perceives the CS. Although fear conditioning depends primarily on nuclei within the amygdaloid complex (for review, see Maren, 2001), increasing evidence suggests that the dorsal striatum is also required for normal learning in this task (White and Salinas, 2003; Ferreira et al., 2003, 2008). Therefore, the ability for rats at postnatal days 15–17 to display proficient associative learning in fear conditioning (Moye and Rudy, 1987) may be in part attributed to an early-developing striatal-dependent system. Rats at postnatal day 17 also display significant learning in the eyeblink conditioning paradigm, and they require even fewer trials to learn the task at postnatal day 24 (Stanton, Freeman, and Skelton, 1992). However, eyeblink conditioning is thought to arise primarily from cerebellar and brainstem nuclei (Christian and Thompson, 2003), and lesions limited to the dorsal striatum have no effect on simple eyeblink conditioning (Flores and Disterhoft, 2009), indicating the early-developing striatal-dependent memory system may not contribute to the conditioned eyeblink response in young rats.

Altering the parameters of fear and eyeblink conditioning paradigms so that they require “higher order” functioning putatively mediated by the hippocampus reveals a more protracted course of development. In contextual fear conditioning, rats are prompted to associate a specific context with the presence of a foot-shock (the US), a form of learning that depends on the intact hippocampus (Phillips and LeDoux, 1992). Rats at postnatal day 18 display significant contextual freezing, and this conditioned response becomes more adult-like at postnatal day 23 (Pugh and Rudy, 1996). Similarly, the hippocampal-dependent context-preexposure-facilitation effect (Schiffino, Murawski, Rosen, and Stanton, 2011) emerges between postnatal days 23–24, whereas the effect appears completely absent in 19-day-old rats (Jablonski, Schiffino, and Stanton, 2012). In hippocampal-dependent trace fear conditioning, the CS and US are temporally separated by an extended inter-stimulus interval, and the ontogeny of learning in this task depends on the modal properties of the CS, postnatal day 21 for an auditory CS and postnatal day 30 for a visual CS (Moye and Rudy, 1987). Likewise, 30-day-old rats are proficient in hippocampal-dependent trace eyeblink conditioning, relative to 19-day-old rats (Ivkovich, Paczkowski, and Stanton, 2000; Ivkovich and Stanton, 2001).

In sum, converging evidence from rat studies supports the early development of an S-R memory system that is partially mediated by the dorsal striatum, and a relatively late maturing cognitive memory system that is partially mediated by the hippocampus.

Neurobehavioral development of multiple memory systems in monkeys

As in rodents, separate courses of development for distinct memory systems have been observed in monkeys. Some of the early procedures for studying habit or cognitive memory in the monkey included concurrent discrimination and delayed nonmatching-to-sample tasks, respectively. In concurrent discrimination, monkeys are presented with a pair of objects and have the opportunity to displace one of the objects to receive a potential food reward hidden underneath. For each daily session, the same twenty pairs of objects are used, and only one object in each pair is consistently associated with the food reward. Using this task, 3-month old Rhesus monkeys learned to discriminate the correct objects as quickly as 3-year old adults (Bachevalier and Mishkin, 1984), and 1-year old New World capuchin monkeys as quickly as 3 ½-year old adults (Resende, Tavares, and Tomaz, 2003). Although these comparison studies did not test at ages younger than 3 months, earlier studies had shown that monkeys younger than 1 month could also acquire visual discrimination habits (albeit not at adult-like levels of efficiency; Harlow, 1959; Zimmerman and Torrey, 1965), demonstrating the remarkably early development of a habit memory system in the monkey. Several studies have suggested that the dorsal striatum subserves learning of this task. In the adult monkey, for example, lesions of the putamen or caudate nucleus impair both concurrent discrimination and pattern discrimination learning (Divac, Rosvold, and Szwarcbart, 1967; Wang, Aigner, and Mishkin, 1990; Teng, Stefanacci, Squire, and Zola, 2000; Fernandez-Ruiz, Wang, Aigner, and Mishkin, 2001). In addition, monkeys with lesions to the anterior inferotemporal cortex, a region that projects to the caudate nucleus and putamen, are also impaired in both of these forms of discrimination learning (Gross, 1973; Dean, 1976; Phillips, Malamut, Bachevalier, and Mishkin, 1988; Buffalo, Stefanacci, Squire, and Zola, 1998; Buffalo et al., 1999). Importantly and in contrast, monkeys with damage to the hippocampal formation or other regions of the medial temporal lobe acquire both concurrent and pattern discrimination tasks normally (Malamut, Saunders, and Mishkin, 1984; Buffalo et al., 1998; Teng et al., 2000), suggesting that learning of this task does not depend on a functionally mature cognitive memory system. Early maturation of a corticostriatal network may therefore underlie the proficient, adult-like habit learning of young monkeys (Bachevalier and Mishkin, 1984).

In contrast to their performance on discrimination learning tasks, young monkeys are not as proficient as adults in the delayed non-matching to sample task. This task involves an initial acquisition trial in which a monkey is presented with a single object that must be displaced in order to retrieve a food reward hidden underneath. After a brief delay, the monkey is presented with the same object (now unbaited/unrewarded) alongside a new object (baited). Three-year old Rhesus monkeys learn the delayed non-matching to sample task quickly, whereas 3-month old infant monkeys fail to show significant improvement until they reach 4 months of age (Bachevalier and Mishkin, 1984). Even at 4 months, however, Rhesus monkeys fail to perform at adult levels of proficiency, which is finally reached at two years of age. Similarly, 1-year old Capuchin monkeys are deficient in the delayed nonmatching-

to-sample task relative to 3 ½-year-old adults (Resende et al., 2003). Although the role of the hippocampal formation in this task has been debated (Baxter and Murray, 2001a,b; Zola and Squire, 2001), accurate performance may depend largely on other medial temporal lobe structures known to be important for cognitive memory, most notably the perirhinal cortex (Malamut, Saunders, and Mishkin, 1984; Buffalo, Ramus, Clark, Teng, Squire, and Zola, 1999; Alvarado and Bachevalier, 2000; Nemanic, Alvarado, and Bachevalier, 2004), whereas lesions of the dorsal striatum have no effect (Fernandez-Ruiz et al., 2001). We note also that in contrast to their inability to solve the delayed nonmatching-to-sample task, young monkeys can perform some cognitive memory tasks as well as adults. Preferential looking, for example, is a hippocampal-dependent recognition task that measures the amount of time a monkey looks at a novel object, and monkeys show proficient recognition around 1 month of age (Gunderson and Swartz, 1985; Bachevalier, Brickson, and Hagger, 1993), raising the possibility that the delayed nonmatching-to-sample task taps cognitive abilities that are unrelated to recognition memory (Overman, Bachevalier, Sewell, and Drew, 1993; Alvarado and Bachevalier, 2000).

Although the delayed nonmatching-to-sample task has been widely used for studying the development of cognitive memory in the monkey, the uncertainty of what cognitive abilities the task is actually measuring necessitates the use of additional tasks to determine the ontogenetic development of hippocampal-dependent memory. The biconditional discrimination is a task in which a monkey is trained to discriminate four pairs of stimuli, two of them rewarded and the other two unrewarded. For instance, in the paired stimuli AB, AC, CD, and BD, the pairs AB and CD are rewarded, whereas AC and BD are not. Note that A and D are conditional cues that determine whether B or C is correct, and vice versa. Speeding the receipt of reward on repeated trials requires the learning of these conditional cues. Removing both the hippocampal formation and parahippocampal cortical areas bilaterally impairs learning on this task, suggesting its dependence on an intact hippocampal system. Six-month and 1-year old monkeys make significantly more errors on the bidirectional discrimination task than do adults (Killiany and Mahut, 1990), suggesting the protracted development of this memory system. Use of other putative hippocampal-dependent tasks, such as the transverse patterning and oddity tasks (Alvarado, Wright, and Bachevalier, 1995; Alvarado, Mishkin, and Bachevalier, 1998; Alvarado, Kazama, Zeamer, and Bachevalier, 2011), similarly reveal poor performance in young relative to adult monkeys, with achievement of adult levels of proficiency occurring at 2–3 years of age (Harlow, 1959; Málková et al., 1999).

In sum, with the exception of preferential looking, adult-like proficiency in hippocampal-dependent tasks seems to emerge between 2 and 3 years of age in monkeys, whereas striatal-dependent habit memory matures within the first month of life. Thus, both rodent and non-human primate studies indicate that a striatal-dependent habit memory system develops very early in life, whereas a hippocampal-dependent memory system develops later.

Neurobehavioral development of multiple memory systems in humans

Although numerous tasks have been used to investigate the development of memory in human youth, several investigators have suggested that adapting various “animal paradigms”

for use in infants and children may allow experimenters to infer the neural bases of this development (e.g. Diamond, 1990; Overman, Bachevalier, Miller, and Moore, 1996a; Overman, Pate, Moore, and Peuster, 1996b). For instance, the concurrent discrimination and delayed nonmatching-to-sample tasks previously used in monkey studies have been adapted to investigate the development of striatal-dependent habit and medial temporal lobe-dependent cognitive memory systems in human infants (Overman, 1990; Overman et al., 1992, 1993). In the striatal-dependent discrimination task, human adults show significant learning after only a few sessions, whereas children 1–2 years of age require about 8 sessions to show significant learning (Overman et al., 1992), and even then, after 8 sessions, adults solve the task with 87% accuracy and children require about 33 sessions to reach the same level of accuracy. These developmental trajectories in humans stand in contrast to those in monkeys, in that infant monkeys learn the task as rapidly as do adult monkeys (Bachevalier and Mishkin, 1984; for potential reasons regarding this difference between young monkeys and humans, see Overman et al., 1992). Nevertheless, similar to infant monkeys, human infants learn the discrimination task significantly faster than they learn the delayed nonmatching-to-sample task (Overman et al., 1992). As expected, human adults demonstrate significant learning on the delayed nonmatching-to-sample task rapidly, requiring about 2 daily sessions to reach 87% accuracy. Conversely, human infants between 12–15, 18–20, and 22–32 months of age reach the 87% criterion much more slowly, after 69, 24, and 11 daily sessions, respectively. In a two-day version of the task, children 45–81 months of age scored better than the younger groups, but still significantly lower than the adults. Thus, consistent with the monkey studies, human studies demonstrate differing maturational timelines for two relatively independent memory systems: an early-developing, habit memory system, and a later-developing, cognitive-based one.

Although children seem adept at solving the medial temporal lobe-dependent, delayed nonmatching-to-sample task within the first few years of life, more complex cognitive tasks seem to require further maturation of this memory system. The 8-arm radial maze and Morris water maze tasks, which have been used extensively in rodents to study cognitive and habit learning, have been adapted for use in children and reveal a more protracted development of the capacity for cognitive memory, presumably because these more complex tasks provide higher ceiling effects for measures of performance (for other possible explanations, see Discussion). In one version of the 8-arm radial maze task, 4 arms are initially blocked off, allowing the participant to retrieve rewards from only the 4 open arms. In the second trial, all arms are left open, and the participant must remember which arms are still baited with a reward (i.e. those that were blocked off in the previous trial) in order to avoid reentries into the previously-open arms, which would then be scored as errors. Several animal studies have shown that spatial learning in the radial maze that involves remembering which arms of the maze have been previously visited depends on an intact hippocampus (e.g. Olton, 1978; Packard, Hirsh, and White, 1989). Use of the putatively hippocampal-dependent, radial maze task in children demonstrated a developmental progression in which children approximately 6–12 years of age made fewer errors than did children approximately 2–5 years of age, although both groups performed less efficiently than adults (Overman et al., 1996b). A subsequent radial maze study confirmed this developmental progression in more restricted age groupings and in addition documented a

marked acceleration in spatial learning between approximately 5 and 5 ½ years of age (Mandolesi, Petrosini, Menghini, Addona, and Vicari, 2009).

Other hippocampal-dependent tasks that have been adapted for children include the Morris water maze and open-field search tasks. Converging evidence indicates that children can learn these maze paradigms by about the age of 7 years, and they become progressively more adept at solving the tasks through the age of 12 years, whereas when cues signal the correct responses (and thus putatively engage striatal-dependent habit learning), children of all ages tested display adult-like performance (Overman et al., 1996b; Lehnung, Leplow, Friege, Herzog, and Ferstl, 1998; Leplow, Lehnung, Pohl, Herzog, Ferstl, and Mehdorn, 2003; Mandolesi et al., 2009; Bullens, Székely, Vedder, and Postma, 2010; Townsend, Richmond, Vogel-Farley, and Thomas, 2010). These results suggest that the ability to use a striatal-dependent stimulus-response strategy is present much earlier than is the ability to use a hippocampal-dependent spatial strategy.

The early development of striatal-dependent, compared with hippocampal-dependent, memory suggests the hypothesis that, given the opportunity between using a stimulus-response or cognitive strategy, children would be more likely to solve a task using stimulus-response learning. Indeed, when children approximately 3½–4 years of age choose which arms to visit first in the radial maze task, they tend to use an efficient response strategy, oftentimes choosing 4 adjacent arms in perfect succession (Mandolesi et al., 2009). This form of egocentric “response” learning may be considered an exemplar of S-R learning and is known to depend on the dorsal striatum in lower animals (for review see Packard, 2009).

In a nut-gathering task that incorporates elements of both the radial and water maze paradigms (Lehnung et al., 1998), experimenters rotated the proximal cues to determine what strategy children used to solve the task and found that all of the 5-year olds went to the proximal cues to look for the nuts, whereas 10-year olds continued looking for nuts in the same “places” relative to the distal cues. Seven-year olds, however, were split in their use of strategy types, in that some used a cued strategy and others used a place strategy to solve the task. The findings from this experiment, as well as studies employing similar dual-solution paradigms, provide evidence for a gradual shift from the use of striatal-dependent to use of hippocampal-dependent strategies between 5 and 10 years of age (Lehnung et al., 1998; Laurance, Learmonth, and Nadel, 2003; Leplow et al., 2003; Bullens, Igloi, Berthoz, Postma, and Rondi-Reig, 2010). Interestingly, self-report data from children 3–10 years old suggests that this shift may be related to an age-related increase in the number of distal cues children use to navigate a maze (Laurance, Learmonth, and Nadel, 2003).

We should note that some studies have yielded seemingly opposite findings, providing instead evidence for the preferential use of a hippocampal-dependent strategy in younger subjects. In a computerized virtual environment version of the radial maze, for example, 84.4% of the children (8 years old) reported using a place strategy (relative to a response strategy) to solve the task, compared to 46.3% of young adults (19–40 years of age) and 39.3% of older adults (53–85 years of age), suggesting a gradual shift toward striatal-dependent response strategies across the lifespan (Bohbot et al., 2012; Lin et al., 2012). The reasons for these opposing findings are unclear, but some investigators have hypothesized

that younger children may lack a certain degree of experience required to solve complex S-R strategies in a virtual radial arm maze (Bohbot et al., 2012), whereas the cued strategies employed by young participants in previous studies may be simpler to acquire and thus more readily available to younger children. Further studies will be required to test these hypotheses.

Although measures of hippocampal-dependent spatial learning in some cases appears adult-like by age 10 years, the ability to use abstract mental representations of space (e.g. maps) matures much later (Cohen and Schuepfer, 1980; Denckla, Rudel, and Broman, 1980; Pine et al., 2002). For instance, adolescents 12–16 years of age and adults were comparable in performance during memory-guided navigation through a virtual town; but when later prompted to label the goal locations on a two-dimensional representation of that virtual town, adolescents displayed poorer performance relative to adults (Pine et al., 2002). The same study showed that success in the virtual town correlated positively with activation of the medial temporal lobe. Consistent with these findings, 6th graders have been found to be less proficient than college students at reconstructing a route through a two-dimensional map (Cohen and Schuepfer, 1980). The ability to solve some spatial tasks using the hippocampal-dependent memory system therefore seems not to mature fully until adulthood.

Taken together, these human studies suggest that even though children may be able to learn the delayed nonmatching-to-sample test within the first years of life, use of this cognitive learning system in complex spatial tasks doesn't emerge until approximately 7 years of age, and it continues to mature through adolescence and even into adulthood. The late maturation of this cognitive memory system relative to the earlier developing habit memory system, and disturbances in the development of one or the other of these systems, may account for certain features of psychopathologies that affect children and adolescents. For example, aberrant development of the earlier developing, striatal-dependent habit learning system may underlie in part the prominent habit-like symptoms of certain psychopathologies. Conversely, aberrant development of the later maturing, hippocampal-dependent memory system may play a different role in the development of these and other symptoms, especially deficits in higher order cognitive abilities that depend heavily on cognitive/declarative memory capacities. We next explore these possibilities more fully within the context of several psychopathologies that affect children and adolescents, including Tourette syndrome (TS), attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), bulimia (BN) and anorexia nervosa (AN), and autism spectrum disorders (ASD).

Multiple memory systems and developmental psychopathologies

Difficulty controlling thoughts, behaviors, and urges is a common characteristic of many disorders that begin in childhood or adolescence, such as TS, OCD, ADHD, eating disorders (AN and BN), and ASDs. In addition, the impulsive and semi-compulsory thoughts and behavioral symptoms of these disorders tend to be clinically present as “habits” that have escaped regulatory control. Substantial evidence suggests that self-regulatory capacities rely on frontostriatal circuits and that habit learning functions are likely impaired in these disorders due, in part, to core disturbances within the striatum that are released from top-down regulatory control based within projections from cortical regions to the striatum.

Similarly, disturbances in the top-down regulation of medial temporal lobe structures may release disturbances within the hippocampus and related portions of the medial temporal lobe. These functional and anatomical abnormalities in the hippocampus may contribute both to deficits in hippocampal-dependent memory and to the maladaptive and habitual symptoms of these disorders by, for example, contributing to an over-reliance on the habit learning system. Furthermore, the abnormal maturation of these learning and memory systems may contribute to both the development and persistence of these symptoms and, ultimately, the persistence of these illnesses into adulthood.

TS, ADHD, and OCD are three childhood-onset neuropsychiatric disorders that have well-documented anatomical and functional disturbances in striatal circuits. The motor and vocal tics in persons who have TS are typically brief, nonpurposeful or semi-purposeful fragments of motor behaviors elicited in response to stimuli or environmental cues either from within their bodies or from the outside world (Leckman & Riddle, 2000). Sensitivity to these cues is usually experienced as a compulsory urge that is only relieved by performing the tic (Leckman, 2002; Leckman & Riddle, 2000; Peterson & Klein, 1997). Phenomenologically, these urges are similar to the urges that often precede compulsive behaviors. Each is an uncomfortable sensation to perform an action, with discomfort gradually increasing over time until reaching a variable threshold that prompts capitulation to perform the action. Performing the action brings rapid but only temporary relief until the discomfort begins anew. In children with TS, the behaviors and ideational content associated with these conscious urges to action have variable levels of complexity and goal-directed qualities, and are often sufficiently complex and goal-directed to warrant a diagnosis of comorbid OCD (Peterson, Pine, Cohen, & Brook, 2001). ADHD and the eating disorders AN and BN share with TS and OCD the presence of urges to action and abnormal control of them. Youth with ADHD, for example, have great difficulty controlling their urges to action, both for goal-directed and non-goal directed behaviors, manifesting respectively as impulsivity and hyperactivity. Striatal pathology is prominent in persons with ADHD. BN, in contrast, is characterized by recurrent episodes of binge-eating (i.e., the consumption of large amounts of food in a short period of time) followed by compensatory attempts to counteract weight gain, whereas AN is characterized by extreme food restriction in the presence of a pathological preoccupation with a desire for thinness. Whereas behavior in persons with AN is typically hyper-controlled, eating and other behaviors in persons with BN are impulsive, excessive, and poorly controlled (Kaltiala-Heino, Rissanen, Rimpela, & Rantanen, 2003). Functional magnetic resonance imaging (fMRI) findings point to frontostriatal abnormalities in both AN (Wagner et al., 2007) and BN (Marsh et al., 2011; Marsh et al., 2009).

Below we present evidence suggesting that the etiologies of these eating disorders have in common with one another, as well as with TS, ADHD, and OCD, striatal abnormalities that, over time, may allow their disturbed feeding behaviors to crystalize into intractable habits. We also present evidence of anatomical abnormalities in MTL structures in persons with TS and evidence of functional abnormalities in these structures in youth with OCD. Anatomical and functional abnormalities within the striatum likely contribute to the habit-like nature of tics in TS and the impulsive behaviors of ADHD, whereas hypertrophy of hippocampal subregions seems to modulate and attenuate the severity of symptoms in TS and ADHD

(Plessen et al., 2006; Peterson et al., 2007). In contrast, functional abnormalities within the hippocampus likely contribute to an over-reliance on striatal-based systems in OCD, thereby also contributing to the habit-like nature of compulsions. We also present evidence of anatomical abnormalities within hippocampal subregions in individuals with ASDs that likely contribute to their deficits in both episodic and relational memory, as well as evidence of striatal abnormalities that may contribute to the developmental dyspraxia and repetitive behaviors associated with these disorders. Finally, it should be noted that although beyond the scope of this review “higher order” executive functions (e.g. information gathering, organizational skills, attention, etc.) are often impaired in these disorders, which may influence online memory formation and expression (Pennington and Ozonoff, 1996; Seyffert and Castellanos, 2005; Olley, Malhi, and Sachdev, 2007; Ruiz, León, and Díaz, 2008; den Eynde et al., 2011).

Tourette syndrome

The tics of TS are similar in their appearance and subjective experience to habits, and parents of children with tics in fact often describe the behaviors as “habits” or “mannerisms.” Findings from structural imaging studies indicate the presence of smaller caudate volumes in children and adults with TS compared to age-matched comparison participants (Peterson et al., 2003). These documented striatal abnormalities, together with the phenomenological similarity of tics with habits and the role of the striatum in habit learning, prompted us to hypothesize that tics could represent habit learning gone awry. Relative to their healthy counterparts, both children and adults with TS were impaired at habit learning on the weather prediction task (Marsh et al., 2004), a task of probabilistic classification learning that circumvents the use of declarative memory by probabilistically associating cues with specific behavioral responses (outcomes). Participants try to predict rain or sunshine based on the presentation of a varying combination of a set of cards on a computer screen. Each card is independently and probabilistically related to the outcomes (rain or shine), each of which occurs equally often. For example, one card predicts sunshine 25 percent of the time and rain 75 percent of the time, while another card predicts sunshine 57 percent of the time and rain 43 percent of the time. A response is considered correct on a particular trial only if the selected outcome is more strongly associated with the cue combination that appears on that trial. Although participants receive positive or negative feedback after each prediction, they can receive negative feedback even when they think that they have predicted the weather correctly. The cue-outcome associations are not absolute because cue combinations predict different outcomes in differing percentages. Thus, because of the probabilistic nature of the task, participants usually believe that they are simply guessing at the outcome. In the abovementioned study (Marsh et al., 2004), the rate of probabilistic classification learning on the weather prediction task correlated inversely with the severity of tic symptoms in both age groups of TS participants, indicating that the number and severity of tics are a function of the degree to which this learning system is dysfunctional. Measures of declarative learning, in contrast, were normal in the TS groups. Thus, deficient habit learning in persons with TS may contribute to their habit-like, stereotyped behaviors. That is, the tics in TS may be the product of core disturbances in the

structure and function of the striatum that predispose an individual to impairments in habit learning and to the expression of fragmented motor and vocal behaviors.

Impaired habit learning in TS suggests that these behavioral fragments are not concatenated together properly but instead occur in isolation and independently of normal S-R contingencies. Trait-like abnormalities previously documented in the structure and function of the striatum in persons with TS (Peterson et al., 1993; 2001; 2003) may impair the concatenation or chunking of these behavioral fragments into coherent action sequences that are executed smoothly as habits. This interpretation is consistent with findings from electrophysiological studies of animals that have shown how habit learning of complex action sequences is associated with gradual changes in the task-related firing of neural ensembles within the striatum (Matsumoto, Hanakawa, Maki, Graybiel, & Kimura, 1999). The change in firing patterns likely indicates that each of the behavioral fragments comprising the entire action sequence are “chunked” together within the striatum into a single, coherently executed behavior. Once activated, a chunked action sequence tends to execute smoothly and in entirety. Intact dopaminergic innervation seems to be important for these “chunking functions” of the striatum (Matsumoto, et al., 1999). Thus, the long-term acquisition of memories for habit learning tasks, similar to the acquisition of all long-term memories, likely involves the alteration of cellular architecture within the striatum.

Children with TS perform similarly to their healthy counterparts on both the Stroop and Simon tasks, and resolution of cognitive interference on these tasks improves progressively with age, likely reflecting the maturation of the frontostriatal circuits that support response inhibition (Comalli, Wapner, & Werner, 1962; Dash & Dash, 1982; Schiller, 1966). Findings from functional magnetic resonance imaging (fMRI) studies suggest that, compared to healthy individuals and despite their normal behavioral performance, those with TS seem to rely more on exaggerated activation of frontostriatal systems to maintain adequate performance on the Stroop task, perhaps compensating for underlying anatomical disturbances in frontostriatal circuits that may contribute to inefficient processing within these circuits (Marsh, Zhu, Wang, Skudlarski, & Peterson, 2007).

Temporal lobe structures are also likely involved in the pathogenesis of TS in that they are anatomically and functionally related to the basal ganglia. Projections from the hippocampus and amygdala affect activity in the ventromedial striatum (Fudge, Kunishio, Walsh, Richard, & Haber, 2002; Ishikawa & Nakamura, 2003) and modulate dopaminergic input to the ventral striatum (Charara & Grace, 2003). Compared to age-matched controls, adults and children with TS have larger volumes of the hippocampus (3.1% larger in TS group; Peterson et al., 2007), deriving from the head and medial surface of the hippocampus over the length of the dentate gyrus. Volumes of these subregions declined with age in the TS group but not in the controls, such that the subregions were significantly larger in the TS children, but significantly smaller in TS adults compared to controls. In both children and adults with TS, however, volumes of these subregions correlated strongly and inversely with the severity of tic, as well as comorbid OCD, and ADHD symptoms, suggesting that enlargement of these subregions may have a compensatory and neuromodulatory influence over these symptoms. Similarly, the enlargement of these hippocampal subregions in TS children may have a compensatory influence over the learning and memory functions that

the hippocampus subserves. fMRI studies of these functions have not yet been reported in children with TS, and most neuropsychological studies have focused on frontostriatal executive functions. One study, however, reported deficits in visual memory (Rasmussen, Soleimani, Carroll, & Hodlevsky, 2009), whereas other studies have reported no memory deficits in TS children (Channon, Pratt, & Robertson, 2003; Crawford, Channon, & Robertson, 2005) without comorbid OCD or ADHD. These neuropsychological findings highlight the importance of assessing the effects of comorbid conditions on the functioning of learning and memory systems in TS. Nevertheless, the presence of habit learning deficits and smaller caudate volumes in children with TS indicates that the habit learning system is both functionally and anatomically impaired early in the course of the disorder while enlargement of hippocampal subregions may have an attenuating effect on tic symptoms throughout adolescence.

Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is defined by the presence of inattention, hyperactivity, and impulsivity to a degree that is inconsistent with the affected person's age and developmental level. In addition to commonly reported disturbances in frontal and other cortical regions (Castellanos et al., 2002; Sowell et al., 2003; Shaw et al., 2007), the pathogenesis of ADHD is thought to involve anatomical and functional alterations of the basal ganglia and hippocampus, including the learning and memory functions that those regions support.

Morphological features and functional activation of the basal ganglia nuclei are prominently altered in youth with ADHD relative to typically developing controls. The overall volumes of each of the basal ganglia nuclei (caudate, putamen, and globus pallidus), for example, are reduced relative to healthy comparison youth, but volumes of the putamen are particularly small (Sobel et al., 2010; Qiu et al., 2008). The volume reductions are scattered throughout the spatial extent of each of the three basal ganglia nuclei, but they most prominently affect the ventral portions of these nuclei (Sobel et al., 2010), regions that anatomically connect and functionally interact with the limbic system, including the orbitofrontal cortex, amygdala, and nucleus accumbens (Nakano, Kayahara, Tsutsumi, and Ushiro, 2000). Presumably striatal connections to these limbic regions help guide reinforcement-based learning (Pasupathy and Miller, 2005), and therefore striatal disturbances could account for the difficulties that ADHD youth have with delaying gratification and with selecting inappropriate behaviors for a given environmental context. Additional reductions in volume are located in the anterodorsal portions of these nuclei, portions that support habit learning and that connect with association cortices, including frontal cortex, to support executive functioning. A greater magnitude of volume reduction generally accompanies more severe symptoms, whereas the local volume disturbances are markedly attenuated in ADHD youth who are taking stimulant medications, to the extent that their basal ganglia are morphologically nearly normal. These normalizing effects of stimulant medications on basal ganglia morphology may derive from the dopaminergic actions of stimulant medications, which animal studies have shown induce changes in gene expression and increases in dendritic arborization within basal ganglia nuclei (Li, Kolb, and Robinson, 2003). These cellular changes could in turn support improved learning and memory capacities based

within the striatum. Caudate volumes in ADHD may also normalize with advancing age, and some investigators have speculated this normalization of caudate volume may be associated with age-related decreases in hyperactivity/impulsivity in ADHD (Castellanos et al., 2002; Nakao, Radua, Rubia, and Mataix-Cols, 2011); however, relatively modest (yet significant) reductions in caudate volume may still be observed in adults with ADHD (Montes et al., 2010; Proal et al., 2011; Seidman et al., 2011). In addition, accompanying smaller basal ganglia volumes is reduced activation of the basal ganglia in individuals with ADHD across a wide range of tasks (Cubillo, Halari, Smith, Taylor, and Rubia, 2012; Hart, Radua, Nakao, Mataix-Cols, and Rubia, 2007; Scheres, Milham, Knutson, and Castellanos, 2007) and across all ages, from early childhood to adulthood.

Although two studies reported normal hippocampus volumes in children and adolescents with ADHD (Filipek et al., 1997; Castellanos et al., 2001), a more recent and more detailed study reported larger hippocampus volumes bilaterally, especially in more anterior portions of the hippocampus, in children and adolescents with ADHD (Plessen et al., 2006). Further, larger volumes in these same subregions of the hippocampus correlated inversely with the severity of symptoms of ADHD, suggesting that the larger volumes were compensatory in nature. Based on its location and the known functions of that portion of the hippocampus, the regional hypertrophy was hypothesized to compensate for deficits of temporal perception and temporal sequencing in ADHD. Findings of normal hippocampus volumes in a smaller sample of adults with ADHD relative to healthy controls (Perlov et al., 2008) could suggest that failure of adults to generate a compensatory hypertrophy of the hippocampus may contribute to persistence of symptoms in to adulthood.

Although studies of striatal- and hippocampal-based learning in ADHD are few and somewhat inconclusive, the balance of available evidence thus far suggests that striatal-based learning is likely impaired in both children and adults with ADHD (Adi-Japha, Fox, and Karni, 2011; Fabio and Antoniette, 2012; Pederson and Ohrmann, 2012), whereas findings in regards to medial temporal lobe-based learning are mixed, showing either impaired or normal cognitive memory in youth with ADHD. Two SRT studies of procedural learning reported fewer oculomotor anticipations and a more inconsistent progression of learning in children with ADHD compared with control children (Karatekin, White, and Bingham, 2009; Barnes, Howard, Howard, Kenealy, and Vaidya, 2010; but see also, Vloet, Marx, Kahraman-Lanzerath, Zepf, Herpertz-Dahlmann, and Konrad, 2010), and one of these studies reported normal medial temporal lobe-based spatial learning functions in the same sample of youth who were impaired in striatal-based learning (Barnes et al., 2010). In contrast to this study and other research suggesting normal cognitive memory functions (e.g. Kaplan, Dewey, Crawford, and Fisher, 1998; Skowronek, Leichtman, and Pillemer, 2008), impairments have also been reported in boys with ADHD using recognition memory tasks, such as delayed matching-to-sample and spatial recognition (Rhodes, Coghill, and Matthews, 2004; Rhodes, Park, Seth, and Coghill, 2012), and some evidence indicates these memory deficits in ADHD cannot be entirely attributed to the frontal lobe dysfunction or executive impairments commonly observed in this disorder (Rhodes, Coghill, and Matthews, 2004, 2005, 2006; Coghill, Rhodes, and Matthews, 2007).

Obsessive-compulsive disorder

OCD is characterized by intrusive thoughts, images, or impulses (i.e., obsessions) and repetitive actions (i.e., compulsions) that are performed to prevent or reduce distress. Despite overlapping symptoms in early- and late-onset OCD, early-onset (i.e., pediatric) OCD is often considered a distinct subtype of OCD, given its greater familiarity (Pauls, Alsobrook, Goodman, Rasmussen, & Leckman, 1995), genetic underpinnings (Walitza et al., 2010), phenomenology, comorbidity with tic disorders and ADHD, male preponderance (Marsh, Leckman, Bloch, Yazgan, & Peterson, 2008), and treatment responsiveness (Walsh & McDougle, 2011). Because childhood-onset OCD most commonly occurs in the context of a family or personal history of a tic disorder, it is often referred to as “tic-related” OCD (Eichstedt & Arnold, 2001).

Neuropsychological findings suggest that visuo-spatial and fine-motor skill deficits are trait-related (Grisham et al., 2009) and predictive of poor long-term outcome in pediatric OCD (Bloch et al., 2011). In the latter study, visuo-spatial skills were assessed with the block design subtest of the Wechsler Intelligence Scale for Children (Wechsler, 1991) and fine-motor skills with the Purdue Pegboard test, a timed test that requires participants to place pins into small holes on a board. Because fine motor skills rely on intact functioning of the striatum and cerebellum, these neuropsychological findings may suggest striatal deficits in pediatric OCD. Although data from adults with OCD suggest that declarative memory functions are intact (Roth, Baribeau, Milovan, O'Connor, & Todorov, 2004), neuropsychological studies of pediatric patients suggest deficits in verbal learning and memory (Ornstein, Arnold, Manassis, Mendlowitz, & Schachar, 2010), especially when under time pressure (Shin et al., 2008), as well as deficits in spatial attention (Chang, McCracken, & Piacentini, 2007) that are generally consistent with reported findings of deficits in spatial memory in OCD adults (Savage et al., 1999).

Findings of structural abnormalities in orbitofrontal and anterior cingulate cortices, as well as striatum vary across pediatric (Rosenberg & Keshavan, 1998; Szeszko et al., 2008; Szeszko, MacMillan, McMeniman, Chen, et al., 2004; Zarei et al., 2011) and adult studies (Atmaca, Yildirim, Ozdemir, Tezcan, & Poyraz, 2007; Pujol et al., 2004; Rosenberg & Keshavan, 1998; Rotge et al., 2009). Findings of striatal abnormalities among studies of childhood-onset OCD are themselves inconsistent, reporting decreased putamen but not caudate volumes (Rosenberg et al., 1997), decreased globus pallidus but not caudate or putamen volumes (Szeszko, MacMillan, McMeniman, Chen, et al., 2004), and, more recently, increased grey matter bilaterally in the putamen (Szeszko, et al., 2008) in children with OCD compared to age-matched controls. These discrepancies across studies likely derive in part from differences in image quality and the different methods used to measure brain structure in each study (i.e., region of interest or voxel-based morphometry). In addition, differences in sample ascertainment and participant characteristics have likely contributed to variability in findings, as the presence of undiagnosed comorbid tic disorders could account for the stronger findings of striatal abnormalities in children with OCD, as well as in studies of adults who have childhood-onset OCD, presumably representing a shared neural substrate with TS and other tic disorders.

Two fMRI studies of implicit (habit) learning (using the Serial Reaction Time Task) reported that healthy adults recruit the dorsal striatum, whereas adults with OCD recruit the hippocampus, despite having similar behavioral performance on the task (Rauch et al., 1997; Rauch et al., 2001). These findings suggest that adults with OCD might use the hippocampus-dependent (declarative) learning system as a strategy to compensate for abnormalities in the striatal-dependent (habit) learning system, leading to the prevailing habit hypothesis of OCD (Graybiel & Rauch, 2000). This hypothesis has since been tested further in behavioral studies using goal devaluation procedures in adults with OCD (Gillan et al., 2013; Gillan et al., 2011) showing an overreliance on both appetitive and avoidant habits. However, no studies have yet investigated directly the functioning of the habit learning system in children or adolescents with OCD.

One anatomical study of the hippocampus and amygdala in pediatric OCD reported a significant inverse association of symptom severity with grey matter volumes in the hippocampus bilaterally (Carmona, 2007), and another reported asymmetry of the amygdala in drug-naïve pediatric OCD patients but not in age-matched controls (Szeszko, MacMillan, McMeniman, Lorch, et al., 2004). Compared to controls, OCD children and adolescents may less strongly activate the amygdala/hippocampus during emotional face discrimination (Britton et al., 2010) and have increased diffusivity of white matter tracts throughout corticolimbic circuits (Jayarajan et al., 2012). These findings are not sufficient, however, to determine whether the declarative memory system is impaired in pediatric-onset OCD. However, the abovementioned verbal and spatial memory deficits in pediatric samples may arise, in part, due to the hypothesized engagement of the hippocampus to compensate for primary disturbances in the striatum in OCD. These primary disturbances are likely due to the abnormal maturation of the striatum that typically develops earlier than the declarative memory system in healthy individuals. The compensatory engagement of the hippocampus may exceed its processing resources, also leaving some declarative memory functions impaired. Future research with animal models should test whether enhanced habit memory and impaired cognitive memory are perhaps modulated by frontal disturbances and, together, contribute to the compulsive behaviors of persons with OCD.

Bulimia nervosa

Bulimia nervosa (BN) is characterized by the presence of recurrent episodes of binge-eating (the consumption of an excessive amount of food in a short period of time) that are followed by self-induced vomiting or other compensatory behaviors to counteract weight gain. BN typically arises during adolescence and typically affects females. Approximately 2% to 3% of adolescents have clinically significant BN symptoms but binge-eat and purge less frequently than the DSM-IV criteria requires for a diagnosis of BN (Van Hoeken, Seidell, & Hoek, 2004). Thus, the lower and more developmentally sensitive thresholds in the DSM-5 proposed diagnostic criteria for BN (American Psychiatric Association, 2013) are more appropriate for adolescents (Bravender et al., 2010). Both DSM versions require that episodes of binge-eating are accompanied by a sense of loss of control. Thus, deficient self-regulation may contribute to binge-eating in BN by releasing feeding behaviors from regulatory control. Over time, these behaviors likely become maladaptive habits.

Cognitive deficits on neuropsychological measures are reported in BN (Lena, Fiocco, and Leyenaar, 2004). Compared to healthy controls, participants with BN tend to complete neuropsychological tests with more errors, using relatively deficient problem-solving strategies (Ferraro, Wonderlich, and Jolic, 1997). Tests used in studies of individuals with BN have required attention, short-term memory, forming abstract concepts, and visuo-spatial processing. Recent findings suggested that children of women with a lifetime history of BN, who are therefore at high risk for developing BN, have poorer visuo-spatial functioning than children who are not at high risk (Kothari, Solmi, Treasure, Micali, 2013). These findings suggest that visuo-spatial deficits may be a trait marker for the development of BN. However, the general consensus in the literature is that the trade-off in speed-accuracy that individuals with BN tend to display on various neuropsychological tests of cognitive and motor functions suggests that they are cognitively impulsive.

fMRI findings suggest that both adult (Marsh et al., 2009) and adolescent (Marsh et al., 2011) females with BN fail to activate striatum and portions of the frontal cortex that project to it appropriately during performance of the Simon task, a task that is similar to the Stroop in that it requires control of automatic behavioral responses to simple stimuli in favor of the performance of a competing, less automatic response. The Simon task specifically requires ignoring a task-irrelevant feature of a stimulus (the side of the screen on which an arrow appears) when it conflicts with a more task-relevant one (the direction the arrow points). The abovementioned fMRI findings suggest that the inability of persons with BN to engage striatal-based circuits may contribute to their binge-eating and possibly other impulsive behaviors, such as shop-lifting, drug abuse, and cutting, that are especially common in adolescents with BN (Boisseau, Thompson-Brenner, Eddy, and Satir, 2009).

Although frontostriatal circuits are implicated in the pathophysiology of BN, the specific role of the striatum in the pathogenesis of BN is unknown. One fMRI study using the weather prediction task that requires striatal-based probabilistic learning, reported that young women with subthreshold BN (those who performed recurrent binge-eating and compensatory behaviors at a lower frequency than three times each month for three consecutive months) performed similarly to matched controls on the task but nevertheless demonstrated increased activation of the caudate and dorsolateral prefrontal cortex while learning the probabilistic associations (Celone, Thompson-Brenner, Ross, Pratt, and Stern, 2011). These findings suggest that women with subthreshold BN compensate for their inefficient processing within frontostriatal circuits by relying more on these regions in the service of learning probabilistic associations. Perhaps increased activation of frontostriatal circuits during learning on the weather prediction task represents poor efficiency of striatal-dependent learning systems and a need to activate this tissue more to generate a normal performance level on the task. The poor efficiency of processing in this system, like that hypothesized for persons with TS based on their poor performance on this same task (Marsh, et al., 2004), could represent a propensity to manifest maladaptive habits and fragments of normal behavioral repertoires, that manifest as binge-eating behaviors rather than normal, nutritive feeding in persons with BN. Unpublished data from our laboratory suggests that both adult and adolescent females with BN (a combined sample of full syndrome and subthreshold BN participants) perform normally on a version of the weather prediction task performed outside of the scanner, consistent with the aforementioned findings of normal

behavioral performance on this task despite increased neural activation of the striatum in women with subthreshold BN (Celone, et al., 2011). To our knowledge, the functioning of the hippocampal-dependent memory system has not been assessed with fMRI in BN. Neuropsychological findings suggest impaired conditional-associative learning in adults with AN and OCD, but not in those with BN (Murphy, Nutzinger, Paul, & Leplow, 2004), and some data suggest BN-specific deficits in both immediate and delayed verbal memory (Murphy, et al., 2004). Anatomical data from individuals with BN is also lacking. Thus, future studies are needed to determine whether structural or functional abnormalities in either the striatal- or hippocampal-dependent systems exist in BN, both earlier and later in the course of the illness. Nevertheless, increased striatal activation during habit learning may suggest that this system is deficient in BN and may lead to fragmented behaviors similar to TS, but in the feeding domain and without hippocampal compensation.

Anorexia nervosa

AN is characterized by the maintenance of an abnormally low body weight, a relentless preoccupation with concerns about body shape and weight, and repetitive, ritualized behaviors to control eating and weight. Individuals with AN exhibit persistent, perfectionist, and obsessive temperament traits (Halmi et al., 2005) that persist after recovery from the eating disorder. Moreover, individuals with AN, while ill, manifest remarkably rigid control over their eating behaviors. These characteristics suggest that persons with AN excessively mobilize regulatory control over their feeding-related thoughts, emotions, and behaviors (Marsh, Steinglass, Graziano, Walsh, & Peterson, 2007).

Neuropsychological findings suggest that adults with AN have deficits in set-shifting (Steinglass, Stern, and Walsh, in press) and cognitive flexibility (Tchanturia, Morris, Anderluh, Collier, Nikolaou, and Treasure, 2004) that persist after weight gain. They also perform poorly on the Iowa Gambling Task (Tchanturia, Liao, Uher, Campbell, and Treasure, 2004), a frontally mediated task that assesses the ability to sacrifice immediate rewards in favor of long-term gains by requiring participants to choose cards from high- or low-risk decks. These deficits in set-shifting, cognitive flexibility, and in changing responses in accord with changing reward and environmental contingencies are consistent with the perseverative obsessions with food and body shape, and the persistent dieting behaviors of patients with AN.

Although the behavioral manifestations of AN, like those of BN, typically emerge during adolescence (Klein and Walsh, 2004), imaging data from ill adolescents are sparse likely because malnutrition confounds findings from underweight patients, making those findings difficult to interpret. Nevertheless, evidence suggests the presence of structural disturbances within striatum and portions of the prefrontal cortex that project to the striatum in adolescents with AN, both in the ill and recovered states (Castro-Fornieles et al., 2009). Other evidence, however, suggests that reduced grey matter volumes in frontal regions in adolescents with AN are reversible after weight gain (Mainz, Schulte-Ruther, Fink, Herpertz-Dahlmann, & Konrad, 2012).

Similar to symptom provocation studies of individuals with OCD (Adler et al., 2000), findings of functional disturbances in frontal regions from these studies likely represent attempts of the patients to inhibit their anxiety and preoccupation with food and body shape stimuli, consistent with the role of the frontal cortex in self-regulation (Miller & Cohen, 2001). In addition, these fMRI studies do not inform us of the role of striatal circuits in adolescent AN, regardless of age and duration of illness. fMRI studies of reward processing in recovered adults (Wagner, et al., 2007) and ill adolescents (Bischoff-Grethe et al., under review) with AN suggest the presence of functional abnormalities in the striatum. Compared to control participants, recovered AN adults showed excessive activation of the caudate, regardless of trial type, and abnormal activation of the ventral striatum during negative feedback on a guessing game. Together with PET evidence indicating increased D2/D3 receptor binding in the ventral striatum in both ill and recovered adults with AN (Frank et al., 2005), these findings suggest that impaired reward processing within the ventral striatum may contribute to the diminished motivation to eat, as food may not be as rewarding to these individuals as it is to others. Although interesting, these data do not inform us about habit learning capabilities within the dorsolateral striatum in persons with AN. Clinically, however, the formulation of dieting behavior as an entrenched habit in AN may allow us to understand the remarkable persistence of this disorder.

As in BN, little is known about the structure or functioning of the hippocampal-dependent memory system in AN. One study reported bilateral reductions in hippocampal volume in women with AN compared to controls, but no deficits on a test of hippocampal-dependent memory (Connan et al., 2006). In contrast, other neuropsychological findings suggest impaired memory performance in adults with AN (Nikendei et al., 2011). A recent study of children and adolescents with restricting type AN, however, reported superior performance in verbal fluency and memory compared to age- and body mass index-matched (but not IQ-matched) control participants on the NEPSY-II, a developmental neuropsychological assessment (Calderoni et al., 2013). These findings, however, were likely attributable to the presence of an associated mood disorder in the AN group. Nevertheless, hippocampal-dependent memory may be spared early in the course of the illness and degrade with age, or be impaired in those whose illness persists into adulthood, consistent with recent findings suggesting that gray matter volumes increase in adolescents with AN after weight gain (Mainz et al., 2012). We suspect that in contrast to TS, OCD, and BN, striatal pathology likely contributes to the heightened habit formation of overly rigid and organized feeding behaviors in AN. The late maturation of the conscious cognitive functions supported by the hippocampal-dependent system likely serves to reinforce the rigidity of that behavioral profile in AN and may account for its typical persistence into adulthood. However, future longitudinal studies are needed to identify the developmental trajectory of both memory systems in AN.

Autism spectrum disorders

The earliest descriptions of children with ASD emphasized the presence of behavioral disturbances that included “obsessive repetitiousness” (Kanner, 1943). In one of the first published case studies of a child with autism, the behavioral disturbances were described as “repetitions carried out in exactly the same way in which they had been performed

originally” (Kanner, 1943, pg. 219). The same patient also was preoccupied with the spinning of various objects and performing various highly stereotyped movements, such as shaking his head side to side and crossing his fingers in the air. So common are these types of behaviors in ASD that they have become a central part of the diagnostic criteria for the disorders (American Psychiatric Association, 2000). Numerous investigators have speculated that, given their typically rigid and invariant qualities, these behaviors may arise in part from aberrant striatal-dependent habit memory (for review see Goh & Peterson, 2012).

Consistent with this hypothesis, several neuroimaging studies have associated repetitive and stereotyped behaviors (RSB) with activation or morphological abnormalities of striatal subregions in subjects with ASD. For instance, a relatively common finding among ASD participants of all ages is increased volume of the caudate nucleus (Langen, Durston, Staal, Palmen, and van Engeland, 2007), with the volume usually correlating with quantitative measures of RSB (Sears, Vest, Mohamed, Bailey, Ranson and Piven, 1999; Hollander et al., 2005; Langen et al., 2009; Rojas, Peterson, Winterrowd, Reite, Rogers, and Tregellas, 2006). Another study correlated the degree of deformation of the caudate nucleus with social and communicative impairments in boys with ASD (Qiu, Adler, Crocetti, Miller, and Mostofsky, 2010). The volume of the putamen, another portion of the human striatum, has been reported to correlate with measures of RSB in children and adults with ASD (Hollander et al., 2005; Estes et al., 2011). Moreover, deformation of the putamen has been reported to correlate with poor praxis and motor skills in young boys with ASD (Qiu et al., 2010). Fractional anisotropy of white matter tracts connecting the putamen to frontal cortical areas was lower in adult subjects with ASD, and the magnitude of this abnormality correlated with poor inhibitory control as measured by the go/no go task (Langen et al., 2012). Similarly, reduced volumes of gray matter in fronto-striatal circuits have been reported in adults with Asperger’s syndrome (McAlonan et al., 2002). Thus, striatal abnormalities seem to be relatively common in persons of all ages with ASD, and the magnitude of those abnormalities correlate with the severity of symptoms, such as RSBs, in specific domains that the striatum is thought to subserve.

Several studies suggest that the development of striatal abnormalities in ASD may be an ongoing process that begins in childhood and continues to magnify through adulthood. In typically developing persons, caudate volume decreases with age (Raz et al., 2003; Lenroot and Giedd, 2006), whereas caudate volume increases between 6–25 years of age in persons with ASD (Langen et al., 2009). In a separate study, the caudate volume of persons with Asperger’s syndrome did not vary with age throughout adulthood, whereas it decreased with advancing age in typically developing participants (McAlonan et al., 2002). An aberrant developmental trajectory of the caudate nucleus in ASD may explain the early and continued presence of RSBs across the lifespan in this population (Langen et al., 2009).

Although the existence of anatomical abnormalities in the striatum and their correlation with RSBs leads immediately to the hypothesis that striatal-dependent memory is impaired in persons with ASD, studies of striatal-dependent learning and memory in this population are too few and small to provide conclusive evidence to support or reject that hypothesis. The serial reaction time (SRT) test is considered a valid measure of procedural sequence learning

and has been used previously to measure implicit learning in youth with ASD (Eigsti and Mayo, 2011). When performing the SRT test, a computer screen displays a sequence of items that predicts the presence of a pre-specified target. When the participant sees the target, he or she must either tap the target on the screen or press a button associated with the target. In general, reaction time decreases after the participant learns that the sequence reliably predicts the target. This learning is assumed to be implicit, because the sequence of items is usually too long for the participant to be consciously aware that the sequence predicts the target. Several studies have shown that children with ASD are impaired in the SRT task, displaying little to no improvement in reaction time across multiple trials (Mostofsky, Goldberg, Landa, and Denckla, 2000; Gordon and Stark, 2007), whereas other studies have shown that persons with ASD perform just as well as healthy controls (Barnes et al., 2008; Wallace, Happé, and Giedd, 2009). In attempting to explain this inconsistency, investigators have suggested that ASD participants may learn the SRT task faster when the number of items is relatively low, and that performance deficits emerge only when the number of items is large (Eigsti and Mayo, 2011), a possibility that will require further research to address definitively. Other tasks that measure implicit, procedural, or sequence learning, however, have not revealed deficits in habit learning in persons with ASD (for review, see Boucher, Mayes, and Bigham, 2012), although some have argued that the motor skill deficits commonly observed in ASD may represent poor procedural learning (Walenski, Tager-Flusberg, and Ullman, 2006; Romero-Munúí, 2008).

Deficits in declarative memory have also been observed in persons with ASD and have attributed to possible abnormalities of the hippocampal system (Rimland, 1964; Hauser, DeLong, and Rosman, 1975; Boucher and Warrington, 1976; DeLong, 1978). Several neuroimaging studies have consistently reported differences in the morphology of the hippocampus in persons with ASD compared with typically developing controls. Although one meta-analysis found no difference in overall hippocampal volume (Stanfield et al., 2008), more recent meta-analyses have shown reduced hippocampal volumes in ASD relative to healthy controls (Via, Radua, Cardoner, Happé, and Mataix-Cols, 2011; Yu, Cheung, Chua, and McAlonan, 2011). In addition to decreased volumes, increases in hippocampal volumes have also been reported in youth with ASD, likely as a consequence of differing methods for region definition and correction for individual differences in overall brain size (Rojas et al., 2006; Groen, Teluij, Buitelaar, and Tendolkar, 2010).

Although behavioral performance on hippocampal-dependent memory tasks have been studied extensively in ASD (for review, see Boucher, Mayes, and Bigham, 2012), attempts to associate declarative learning deficits with the magnitude of morphological abnormalities of the hippocampus have yielded inconsistent results (Goh and Peterson, 2012). Children with ASD, for instance, performed worse than typically developing children in several cognitive memory tasks, including the delayed non-matching to sample task, and the magnitude of behavioral impairments correlated with the degree of hippocampal abnormality (Dager et al., 2007). Another study using the Rivermead Behavioural Memory Test reported impaired episodic memory and increased hippocampal gray matter density in adolescents with ASD, but no significant correlation was detected between hippocampal gray matter density and episodic memory scores (Salmond, Ashburner, Connelly, Friston, Gadian, and Vargha-Khadem, 2005). A study of adults with high-functioning autism found

no impairment in episodic memory or correlation of hippocampal volume with memory performance (Boucher et al., 2005). Some have suggested that a more detailed analysis of hippocampal structures (such as those conducted by Dager et al., 2007) may yield more concordant findings for the relationship of hippocampal abnormalities with learning deficits in ASD (Goh and Peterson, 2012).

Despite some inconsistencies in findings across studies, research in young and adult persons with ASD have revealed deficits in both striatal-dependent and hippocampal-dependent memory systems, and in some cases these deficits have been correlated with abnormalities in the brain structures that mediate that particular memory system. As suggested before by others (Langen et al., 2009; Goh and Peterson, 2012), abnormal development of hippocampal and dorsal striatal structures may underlie some of the core symptoms of ASD, in particular deficits in learning and memory, as well as the presence of RSBs.

Discussion

Although developmental changes in multiple memory systems may be observed throughout the human lifespan, changes in dorsal striatal- and hippocampal-dependent memory systems that occur during middle childhood (i.e. between 5 and 12 years of age) may be relevant for understanding the early emergence of various psychopathologies. Within this period of development, the hippocampal system and dorsal striatum show signs of adult-like maturation. Nonprincipal and principal cells of the dentate gyrus appear morphologically mature by age 8, whereas the dorsal striatum undergoes a turning point in its developmental trajectory between 5 and 10 years of age, when striatum begins to decline in volume with advancing age. These maturational changes in morphology correlate roughly with important developments in hippocampal-dependent learning and memory. Although children as young as 3 years can solve striatal-dependent, cued mazes with adult-like proficiency, the ability to solve hippocampal-dependent spatial mazes as efficiently as adults emerges at approximately 7 years. Likewise, in dual solution tasks that can be solved adequately with either memory system, several studies indicate a gradual shift from use of striatal-dependent to hippocampal-dependent strategy between 5 and 10 years of age.

Interestingly, a particular memory system may first appear adult-like at different ages depending in part on how the memory system is behaviorally assessed. For instance, cognitive/declarative memory appears adult-like earlier when measured by delayed-nonmatching to-sample, but later when measured by spatial tasks. Such observations underscore the importance of comparing the development of different memory systems using pairs of tasks with similar behavioral requirements in order to rule out the parallel development of non-mnemonic processes. An alternative, yet perhaps more complex, approach is to include the various non-mnemonic parameters across experiments as additional variables in comparing the development between memory systems. Previously this approach has been employed for assessing the relative maturation of memory systems implicated in Pavlovian conditioning paradigms, revealing complex interactions among age, type of conditioning (fear vs. eyeblink), mode of the CS (auditory vs. visual), the behavioral response being measured (e.g. freezing vs. potentiated startle), and whether a hippocampal-dependent process was engaged through trace conditioning (for review see Stanton, 2000).

In short, the development of a particular memory system may depend on its developing capacity to use different sensory and behavioral systems to drive or express the memory, which could explain how a memory system appears adult-like relatively early in life when measured by one behavioral task and later when measured by another (Stanton, 2000). An additional explanation is that a particular memory system can be divided into distinct sub-systems (e.g. hippocampal-dependent memory may be subdivided into recognition memory, relational memory, spatial memory, etc.), each of which could mature at different ages. In the case of hippocampal-dependent memory, the development of different sub-systems may depend on differential maturation of distinct hippocampal modules (Alvarado and Bachevalier, 2000), cell types (e.g. head direction cells vs. place and grid cells; Dumas, 2005; Wills et al., 2010; Langston et al., 2010), or associated medial temporal lobe structures (Alvarado and Bachevalier, 2000; Lavenex and Lavenex, 2013). The incremental development of hippocampal sub-systems should in the future be investigated in children with psychiatric disorders, as each hippocampal sub-system may show a different capacity to offset the dominance of early-developing habit-like symptoms.

One important question is whether the early emergence of habit-like behaviors in the disorders discussed may be attributed to *typical* or *aberrant* development of memory systems. The typical early development of striatal-dependent memory may allow children to solve problems using habit learning mechanisms. This reliance on habit strategies in children as opposed to cognitive-based strategies may reflect the fact that hippocampal-dependent memory is typically less-developed early in life. This idea may be similar to a finding in adults, showing that poor episodic memory is associated with the use of a striatal-dependent procedural strategy in a dual solution virtual maze (Bohbot, Gupta, Banner, and Dahmani, 2011). As young children are also relatively deficient in hippocampal-dependent memory tasks, they may be more inclined to use striatal-dependent strategies, and this propensity may contribute to the early emergence of habit-like behaviors. For instance, it may be speculated that a child with OCD relieves an obsession about germs through habitual hand-washing due in part to the relative maturation of these memory systems in *typical* childhood development. On the other hand, extensive evidence comprising behavioral and neuroimaging data reveal hippocampal and striatal abnormalities in children not only with OCD, but TS and ADHD either alone or in co-occurring combination, suggesting that *aberrant* development of memory systems may in part underlie the habit-like symptoms as well. The role of aberrant development is further substantiated by the correlations drawn between brain abnormalities and habit-like behaviors in children and adolescents with these disorders. In ASD, brain abnormalities include smaller hippocampal volumes and larger dorsal striatal volumes as compared to healthy controls, a pattern that has been associated with the spontaneous use of a procedural strategy in healthy adults (Bohbot, Lerch, Thorndyck, Iaria, and Zijdenbos, 2007). Such developmental abnormalities of the dorsal striatum may increase habit-like symptoms in several ways. For instance, aberrant development may increase excitability of striatal medium spiny neurons, thus enhancing the consolidation of habit memories. Also, as discussed specifically within the context TS, ADHD, and OCD, abnormal development may impair the striatum's ability to concatenate motor sub-units into smooth procedural behaviors, thus contributing to the rigid and fragmentary nature of tic-like symptoms. Lastly, we speculate that the dysfunction in

frontostriatal circuits observed in these disorders may also contribute to habit-like symptoms by releasing the dorsal striatum from regulatory control, thus increasing the expression (as opposed to formation) of aberrant habit-like symptoms. Taken together, both typical and aberrant development of memory systems may have a role in the pathogenesis and phenotypic expression of childhood onset psychiatric disorders.

Limited data suggest that the directions of abnormality (e.g. an impairment or enhancement) in memory systems may vary across disorders and therefore may contribute uniquely to the pathogenesis of each disorder (Table 1). We speculate that, in all of the disorders we have discussed, the early-emerging striatal-dependent system may contribute to the early onset or exacerbation of habit-like symptoms. In TS, habit learning appears to be impaired, whereas hippocampal-dependent learning remains unimpaired. Symptom severity often declines through adolescence in TS and ADHD, and we speculate this attenuation may be attributed to the later-maturing hippocampal-dependent system, which may compensate for the inadequacies of an impaired striatal-dependent system. The putative compensatory role of the hippocampus in TS and ADHD is somewhat substantiated by lower volume of basal ganglia regions and greater volume of the hippocampus, and particularly the association of hippocampal enlargement with less severe symptoms, in youth who have TS or ADHD. OCD, in contrast, is partly characterized by impaired hippocampal-dependent memory and an overreliance on habit learning (relative to goal-directed learning), two factors that we suggest may contribute to the formation or expression of compulsions. Youth with BN display an abnormal increase in striatal activation when performing habit learning tasks, which may lead to manifestations of fragmented behaviors similar to TS, but expressed instead in the feeding domain. Also unlike TS and ADHD, some data suggest the presence of impaired hippocampal-dependent memory in BN, which may preclude the hippocampus' potential to compensate for impaired habit memory and allow habit-like symptoms to persist through adolescence and adulthood. In youth with AN, limited data suggest the presence of increased activity of striatal regions and impaired hippocampal-dependent memory, which in combination may contribute the rigid, habit-like refusal to eat. In ASD, increased volume and activation of striatal regions is coupled with decreased hippocampal volume and impaired hippocampal-dependent memory, perhaps enhancing the formation or expression of repetitive and stereotyped behaviors. We note that these specific hypotheses remain speculative and require more rigorous testing. In particular, many of our hypotheses may be tested by examining the relative maturation/impairment of hippocampal- and striatal-dependent memory in children with these disorders using pairs of tasks (one habit-based and the other cognitive-based) like those previously employed in studies with lower animals and typically developing children (e.g. cued vs. spatial versions of the radial maze task).

Another important consideration in the pathogenesis of these disorders is the prominent role that stress or anxiety plays in the functioning of multiple memory systems and in each of these disorders. Research in human and nonhuman animals indicates that stress and anxiety enhances use of striatal-dependent, habit memory systems and biases persons to use of stimulus-response strategies in dual-solution tasks (For reviews see Packard, 2009; Packard and Goodman, 2012). Stressful life events or anxiety early in life may also enhance habit formation, contribute to the use of developmentally less mature or more regressive forms of problem-solving, and thereby contribute to the pathogenesis of psychiatric disorders in

childhood and adolescence. Consistent with this idea, stressful life events have been associated with the onset or exacerbation of symptoms in all the disorders that we have discussed in connection with multiple memory systems (Hoekstra, Steenhuis, Kallenberg, and Minderaa, 2004; Lin et al., 2007; Conelea and Woods, 2008; Sauro, Ravaldi, Cabras, Faravelli, and Ricca, 2008; Rodgers, Glod, Connolly, and McConachie, 2012; Rodgers, Riby, Janes, Connolly, and McConachie, 2012). Similar hypotheses have been proposed regarding stress and psychiatric disorders that typically emerge during adulthood, including posttraumatic stress disorder (Goodman, Leong, and Packard, 2012) and drug addiction and relapse (Schwabe et al., 2011).

In sum, the relative maturation of hippocampal- and striatal-dependent memory systems may prove relevant to understanding the nature, timing of emergence, and persistence or resolution of various psychopathologies that emerge during childhood or adolescence. The rigid and invariant characteristics of habit-like symptoms may be likened to stimulus-response learning mediated by the dorsolateral striatum, and abnormalities in the dorsal striatum and hippocampus have been associated with habit-like symptoms in children and adolescents. Memory systems other than those based on hippocampal or striatal brain systems should also be considered within the context of these disorders. For instance, disruptions of a cerebellar-dependent conditioned motor learning or an amygdala-dependent affective memory system may contribute to the presence or severity of habit symptoms. Future research should investigate more precisely the roles of striatal- and hippocampal-dependent memory, as well as memory systems arising from other brain regions, in the pathogenesis of childhood and adolescent psychiatric disorders.

Acknowledgments

Work supported in part by NSF grant IBN-0312212 (M. P.), and NIMH grants MH093677, MH089582, MH36197, MH090966, NIDA grants DA027100, NIEHS grant ES015579, the Suzanne Crosby Murphy endowment at Columbia University, and the Tom Klingenstein and Nancy Perlman Family Fund (B. P.).

References

- Ábrahám H, Tornóczy T, Kosztolányi GY, Seress L. Peri- and postnatal cell formation in the human brain. *Society for Neuroscience Abstracts*. 1999; 25:2267.
- Ábrahám H, Vincze A, Jewgenow I, Veszpremi B, Kravjak A, Gógori E, et al. Myelination in the human hippocampal formation from midgestation to adulthood. *International Journal of Developmental Neuroscience*. 2010; 28:401–410. [PubMed: 20417266]
- Adi-Japha E, Fox O, Karni A. Atypical acquisition and atypical expression of memory consolidation gains in a motor skill in young female adults with ADHD. *Research in Developmental Disabilities*. 2011; 32:1011–1020. [PubMed: 21349685]
- Adler CM, McDonough-Ryan P, Sax KW, Holland SK, Arndt S, Strakowski SM. FMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive disorder. *J Psychiatric Res*. 2000; 34:317–324.
- Akers KG, Candelaria FT, Hamilton DA. Prewaning rats solve the Morris task via directional navigation. *Behavioral Neuroscience*. 2007; 121:1426–1430. [PubMed: 18085897]
- Akers KG, Candelaria-Cook FT, Rice JP, Johnson TE, Hamilton DA. Delayed development of place navigation compared to directional responding in young rats. *Behavioral Neuroscience*. 2009; 123:267–275. [PubMed: 19331450]
- Akers KG, Hamilton DA. Comparison of developmental trajectories for place and cued navigation in the Morris water task. *Developmental Psychobiology*. 2007; 49:553–564. [PubMed: 17680604]

- Alvarado MC, Bachevalier J. Revisiting the maturation of medial temporal lobe memory functions in primates. *Learning and Memory*. 2000; 7:244–256. [PubMed: 11040255]
- Alvarado MC, Kazama A, Zeamer A, Bachevalier J. The effects of selective hippocampal damage on tests of oddity in rhesus monkeys. *Hippocampus*. 2011; 21:1137–1146. [PubMed: 20882541]
- Alvarado MC, Mishkin M, Bachevalier J. Neurotoxic lesions of the hippocampal formation impair monkeys' acquisition of the transverse patterning problem. *Society for Neuroscience Abstracts*. 1998; 24:928.
- Alvarado MC, Wright AA, Bachevalier J. Monkeys with early hippocampal formation lesions are impaired on the transverse patterning problem. *Society for Neuroscience Abstracts*. 1995; 21:1494.
- Amaral, DG.; Witter, MP. Hippocampal formation. In: Paxinos, G.; Watson, C., editors. *The Rat Brain in Stereotaxic Coordinates*. 3. San Diego: Academic Press; 1995.
- American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. 4. Washington, DC, USA: American Psychiatric Association; 2000. text revision
- American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders, DSM-5*. 5. Arlington, VA: American Psychiatric Publishing; 2013.
- Atmaca M, Yildirim H, Ozdemir H, Tezcan E, Poyraz AK. Volumetric MRI study of key brain regions implicated in obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007; 31(1):46–52. [PubMed: 16859819]
- Bachevalier J, Brickson M, Hagger C. Limbic-dependent recognition memory in monkeys develops early in infancy. *Neuroreport*. 1993; 4:77–80. [PubMed: 8453042]
- Bachevalier J, Mishkin M. An early and a late developing system for learning and retention in infant monkeys. *Behavioral Neuroscience*. 1984; 98:770–778. [PubMed: 6541498]
- Bannerman DM, Rawlins JNP, McHugh SB, Deacon RMJ, Yee BK, Bast T, et al. Regional dissociations within the hippocampus – memory and anxiety. *Neuroscience and Biobehavioral Reviews*. 2004; 28:273–283. [PubMed: 15225971]
- Barker GRI, Warburton EC. When is the hippocampus involved in recognition memory? *Journal of Neuroscience*. 2011; 31:10721–10731. [PubMed: 21775615]
- Barnes KA, Howard J, Howard DV, Kenealy L, Vaidya CJ. Two forms of implicit learning in childhood ADHD. *Developmental Neuropsychopathology*. 2010; 35:494–505.
- Barnes KA, Howard JH, Howard DV, Gilotty L, Kenworthy L, Gaillard WD, et al. Intact implicit learning of spatial context and temporal sequences in childhood autism spectrum disorder. *Neuropsychology*. 2008; 22:563–570. [PubMed: 18763876]
- Baxter MG, Murray EA. Opposite relationship of hippocampal and rhinal cortex damage to delayed nonmatching-to-sample deficit in monkeys. *Hippocampus*. 2001a; 11:61–71. [PubMed: 11261774]
- Baxter MG, Murray EA. Effects of hippocampal lesions on delayed nonmatching-to-sample in monkeys: a reply to Zola and Squire (2001). *Hippocampus*. 2001b; 11:201–203. [PubMed: 11769304]
- Bédard A, Cossette M, Lévesque M, Parent A. Proliferating cells can differentiate into neurons in the striatum of normal adult monkey. *Neuroscience Letters*. 2002; 328:213–216. [PubMed: 12147309]
- Bischoff-Grethe A, McCurdy D, Gerenesko-Stevens E, Irvine LE, Wagner A, Yau WW, Kaye WH. Altered Brain Response to Positive and Negative Feedback in Adolescents with Anorexia Nervosa. under review.
- Bloch MH, Sukhodolsky DG, Dombrowski PA, Panza KE, Craiglow BG, Landeros-Weisenberger A, et al. Poor fine-motor and visuospatial skills predict persistence of pediatric-onset obsessive-compulsive disorder into adulthood. *Journal of Child Psychology and Psychiatry*. 2011; 52:974–983. [PubMed: 21244423]
- Bohbot VD, Gupta M, Banner H, Dahmani L. Caudate nucleus-dependent response strategies in a virtual navigation task are associated with lower basal cortisol and impaired episodic memory. *Neurobiology of Learning and Memory*. 2011; 96:173–180. [PubMed: 21539927]
- Bohbot VD, Lerch J, Thorndyck B, Iaria G, Zijdenbos AP. Gray matter differences correlate with spontaneous strategies in a human virtual navigation task. *Journal of Neuroscience*. 2007; 27:10078–10083. [PubMed: 17881514]

- Bohbot VD, McKenzie S, Konishi K, Fouquet C, Kurdi V, Schachar R, et al. Virtual navigation strategies from childhood to senescence, evidence for changes across the life span. *Frontiers in Aging Neuroscience*. 2012;4.10.3389/fnagi.2012.00028 [PubMed: 22536185]
- Boisseau CL, Thompson-Brenner H, Eddy KT, Satir DA. Impulsivity and personality variables in adolescents with eating disorders. [Comparative Study Research Support, Non-U.S. Gov't]. *The Journal of nervous and mental disease*. 2009; 197(4):251–259.10.1097/NMD.0b013e31819d96c0 [PubMed: 19363381]
- Boucher J, Cowell P, Howard M, Broks P, Farrant A, Roberts N, et al. A combined clinical, neuropsychological, and neuroanatomical study of adults with high functioning autism. *Cognitive Neuropsychiatry*. 2005; 10:165–213. [PubMed: 16571459]
- Boucher J, Mayes A, Bigham S. Memory in autistic spectrum disorder. *Psychological Bulletin*. 2012; 138:458–496. [PubMed: 22409507]
- Boucher J, Warrington EK. Memory deficits in early infantile autism – some similarities to amnesic syndrome. *British Journal of Psychology*. 1976; 67:73–87. [PubMed: 1268453]
- Bravender T, Bryant-Waugh R, Herzog D, Katzman D, Kriepe RD, Lask B, Zucker N. Classification of eating disturbance in children and adolescents: proposed changes for the DSM-V. *European Eating Disorders Review*. 2010; 18(2):79–89.10.1002/erv.994 [PubMed: 20151366]
- Britton JC, Stewart SE, Killgore WD, Rosso IM, Price LM, Gold AL, Rauch SL. Amygdala activation in response to facial expressions in pediatric obsessive-compulsive disorder. [Research Support, N.I.H., Intramural Research Support, Non-U.S. Gov't]. *Depression and anxiety*. 2010; 27(7):643–651.10.1002/da.20718 [PubMed: 20602430]
- Brown RW, Whishaw IQ. Similarities in the development of place and cue navigation by rats in a swimming pool. *Developmental Psychobiology*. 2000; 37:238–245. [PubMed: 11084605]
- de Bruin JPC, Moita MP, de Brabander HM, Joosten RNJMA. Place and response learning of rats in a Morris water maze: differential effects of fimbria fornix and medial prefrontal cortex lesions. *Neurobiology of Learning and Memory*. 2001; 75:164–178. [PubMed: 11222058]
- de Bruin JPC, Sánchez-Santed F, Heinsbroek RPW, Donker A, Postmes P. A behavioural analysis of rats with damage to the medial prefrontal cortex using the Morris water maze: evidence for behavioural flexibility, but not for impaired spatial navigation. *Brain Research*. 1994; 652:323–333. [PubMed: 7953746]
- Buffalo EA, Ramus SJ, Clark RE, Teng E, Squire LR, Zola SM. Dissociation between the effects of damage to the perirhinal cortex and area TE. *Learning and Memory*. 1999; 6:572–599. [PubMed: 10641763]
- Buffalo EA, Stefanacci L, Squire LR, Zola SM. A reexamination of the concurrent discrimination learning task, the importance of anterior inferotemporal cortex, area TE. *Behavioral Neuroscience*. 1998; 112:3–14. [PubMed: 9517811]
- Bullens J, Igloi K, Berthoz A, Postma A, Rondi-Reig L. Developmental time course of the acquisition of sequential egocentric and allocentric navigation strategies. *Journal of Experimental Child Psychology*. 2010; 107:337–350. [PubMed: 20598705]
- Bullens J, Székely E, Vedder A, Postma A. The effect of experience on children's ability to show response and place learning. *British Journal of Developmental Psychology*. 2010; 28:909–920. [PubMed: 21121474]
- Calderoni S, Muratori F, Leggero C, Narzisi A, Apicella F, Balottin U, Urgesi C. Neuropsychological functioning in children and adolescents with restrictive-type anorexia nervosa: An in-depth investigation with NEPSY-II. *Journal of clinical and experimental neuropsychology*. 2013; 35(2): 167–179.10.1080/13803395.2012.760536 [PubMed: 23351019]
- Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Medical Association*. 2002; 288:1740–1748. [PubMed: 12365958]
- Castro-Fornieles J, Bargallo N, Lazaro L, Andres S, Falcon C, Plana MT, Junque C. A cross-sectional and follow-up voxel-based morphometric MRI study in adolescent anorexia nervosa. [Clinical Trial Research Support, Non-U.S. Gov't]. *Journal of psychiatric research*. 2009; 43(3):331–340.10.1016/j.jpsychires.2008.03.013 [PubMed: 18486147]

- Celone KA, Thompson-Brenner H, Ross RS, Pratt EM, Stern CE. An fMRI investigation of the fronto-striatal learning system in women who exhibit eating disorder behaviors. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *NeuroImage*. 2011; 56(3):1749–1757.10.1016/j.neuroimage.2011.03.026 [PubMed: 21419229]
- Chang SW, McCracken JT, Piacentini JC. Neurocognitive correlates of child obsessive compulsive disorder and Tourette syndrome. [Research Support, N.I.H., Extramural]. *Journal of clinical and experimental neuropsychology*. 2007; 29(7):724–733.10.1080/13825580600966383 [PubMed: 17896198]
- Channon S, Pratt P, Robertson MM. Executive function, memory, and learning in Tourette's syndrome. *Neuropsychology*. 2003; 17(2):247–254. [PubMed: 12803430]
- Charara A, Grace AA. Dopamine receptor subtypes selectively modulate excitatory afferents from the hippocampus and amygdala to rat nucleus accumbens neurons. *Neuropsychopharmacology*. 2003; 28(8):1412–1421. [PubMed: 12799620]
- Christian KM, Thompson RF. Neural substrates of eyeblink conditioning: acquisition and retention. *Learning & Memory*. 2003; 10:427–455. [PubMed: 14657256]
- Coghill DR, Rhodes SM, Matthews K. The neuropsychological effects of chronic methylphenidate on drug-naïve boys with attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2007; 62:954–962. [PubMed: 17543895]
- Cohen R, Schuepfer T. The representation of landmarks and routes. *Child Development*. 1980; 51:1065–1071.
- Comalli PE Jr, Wapner S, Werner H. Interference effects of Stroop color-word test in childhood, adulthood, and aging. *J Genet Psychol*. 1962; 100:47–53. [PubMed: 13880724]
- Conelea CA, Woods DW. The influence of contextual factors on tic expression in Tourette's syndrome: A review. *Journal of Psychosomatic Research*. 2008; 65:487–496. [PubMed: 18940379]
- Connan F, Murphy F, Connor SE, Rich P, Murphy T, Bara-Carill N, Treasure J. Hippocampal volume and cognitive function in anorexia nervosa. [Research Support, Non-U.S. Gov't]. *Psychiatry research*. 2006; 146(2):117–125.10.1016/j.psychres.2005.10.006 [PubMed: 16510268]
- Coutureau E, Killcross S. Inactivation of the infralimbic prefrontal cortex reinstates goal-directed responding in overtrained rats. *Behavioural Brain Research*. 2003; 146:167–174. [PubMed: 14643469]
- Crawford S, Channon S, Robertson MM. Tourette's syndrome: performance on tests of behavioural inhibition, working memory and gambling. *J Child Psychol Psychiatry*. 2005; 46(12):1327–1336. [PubMed: 16313433]
- Cubillo A, Halari R, Smith A, Taylor E, Rubia K. A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. *Cortex*. 2012; 48:194–215. [PubMed: 21575934]
- Dager SR, Wang L, Friedman SD, Shaw DW, Constantino JN, Artru AA. Shape mapping of the hippocampus in young children with autism spectrum disorder. *American Journal of Neuroradiology*. 2007; 28:672–677. [PubMed: 17416819]
- Dash X, Dash AS. Cognitive developmental studies of the Stroop phenomena: Cross-sectional and longitudinal data. *Indian Psychologist*. 1982; 1:24–33.
- Deacon RMJ, Penny C, Rawlins JNP. Effects of medial prefrontal cortex cytotoxic lesions in mice. *Behavioural Brain Research*. 2003; 139:139–155. [PubMed: 12642185]
- Dean P. Effects of inferotemporal lesions on behavior of monkeys. *Psychological Bulletin*. 1976; 83:41–71. [PubMed: 828276]
- DeLong, GR. A neuropsychological interpretation of infantile autism. In: Rutter, M.; Schopler, E., editors. *Autism*. New York: Plenum; 1978. p. 207-218.
- Dember, WN. Historical overview. In: Dember, WN.; Richman, CL., editors. *Spontaneous Alternation Behavior*. New York: Springer-Verlag; 1989. p. 1-17.
- Denckla, MB.; Rudel, RG.; Broman, M. The development of spatial orientation skill in normal, learning-disabled, and neurologically impaired children. In: Caplan, D., editor. *Biological Studies of Mental Processes*. Cambridge, England: MIT Press; 1980. p. 45-60.

- Dennis NA, Cabeza R. Age-related dedifferentiation of learning systems, an fMRI study of implicit and explicit learning. *Neurobiology of Aging*. 2011; 32:2318.e17–2318.e30. [PubMed: 20471139]
- Diamond A. The Development and Neural Bases of Higher Cognitive Functions. *Annals of the New York Academy of Sciences*. 1990:608. entire issue.
- DiFiglia M, Pasik P, Pasik T. Early postnatal-development of the monkey neostriatum – a golgi and ultrastructural study. *Journal of Comparative Neurology*. 1980; 190:303–331. [PubMed: 6769982]
- Divac I, Rosvold E, Szwedart MK. Behavioral effects of selective ablation of caudate nucleus. *Journal of Comparative and Physiological Psychology*. 1967; 63:184–190.
- Dumas TC. Late postnatal maturation of excitatory synaptic transmission permits adult-like expression of hippocampal-dependent behaviors. *Hippocampus*. 2005; 15:562–578. [PubMed: 15884034]
- Egger GJ, Livesey PJ, Dawson RG. Ontogenetic aspects of central cholinergic involvement in spontaneous alternation behavior. *Developmental Psychobiology*. 1973; 6:289–299. [PubMed: 4793359]
- Eichenbaum H, Sauvage M, Fortin N, Komorowski R, Lipton P. Towards a functional organization of episodic memory in the medial temporal lobe. *Neuroscience and Biobehavioral Reviews*. 2012; 36:1597–1608. [PubMed: 21810443]
- Eichstedt JA, Arnold SL. Childhood-onset obsessive-compulsive disorder: a tic-related subtype of OCD? *Clin Psychol Rev*. 2001; 21(1):137–157. [PubMed: 11148894]
- Eigsti, IM.; Mayo, J. Implicit Learning in ASD. In: Fein, DA., editor. *The Neuropsychology of Autism*. 2011. p. 267-279.
- Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, et al. Neurogenesis in the adult human hippocampus. *Nature Medicine*. 1998; 11:1313–1317.
- Estes A, Shaw DWW, Sparks BF, Friedman S, Giedd JN, Dawson G, et al. Basal ganglia morphometry and repetitive behavior in young children with autism spectrum disorder. *Autism Research*. 2011; 4:212–220. [PubMed: 21480545]
- van den Eynde F, Guillaume S, Broadbent H, Stahl D, Campbell IC, Schmidt U, et al. Neurocognition in bulimic eating disorders: a systemic review. *Acta Psychiatrica Scandinavica*. 2011; 124:120–140. [PubMed: 21477100]
- Eysenck HJ. Learning-theory model of neurosis – new approach. *Behaviour Research and Therapy*. 1976; 14:251–267. [PubMed: 962779]
- Fabio RA, Antonietti A. Effects of hypermedia instruction on declarative, conditional and procedural knowledge in ADHD students. *Res Dev Disabil*. 2012; 33:2028–2039. [PubMed: 22750359]
- Fernandez-Ruiz J, Wang J, Aigner TG, Mishkin N. Visual habit formation in monkeys with neurotoxic lesions of the ventrocaudal neostriatum. *Proceedings of the National Academy of Science of the United States of America*. 2001; 98:4196–4201.
- Ferraro FR, Wonderlich S, Jovic Z. Performance variability as a new theoretical mechanism regarding eating disorders and cognitive processing. *Journal of Clinical Psychology*. 1997; 53:117–121. [PubMed: 9029341]
- Ferreira TL, Moreira KM, Ikeda DC, Bueno OFA, Oliveira MGM. Effects of dorsal striatum lesions in tone fear conditioning and contextual fear conditioning. *Brain Res*. 2003; 987:17–24. [PubMed: 14499941]
- Ferreira TL, Shammah-Lagnado SJ, Bueno OFA, Moreira KM, Fornari RV, Oliveira MGM. The indirect amygdala-dorsal striatum pathway mediates conditioned freezing: insights on emotional memory networks. *Neuroscience*. 2008; 153:84–94. [PubMed: 18367339]
- Frank GK, Bailer UF, Henry SE, Drevets W, Meltzer CC, Price JC, Kaye WH. Increased dopamine D2/D3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [¹¹C]raclopride. *Biol Psychiatry*. 2005; 58(11):908–912. [PubMed: 15992780]
- Fudge JL, Kunishio K, Walsh P, Richard C, Haber SN. Amygdaloid projections to ventromedial striatal subterritories in the primate. *Neuroscience*. 2002; 110(2):257–275. [PubMed: 11958868]
- Gillan CM, Morein-Zamir S, Urcelay GP, Sule A, Voon V, Apergis-Schoute AM, Robbins TW. Enhanced Avoidance Habits in Obsessive-Compulsive Disorder. *Biological psychiatry*. 2013; 10.1016/j.biopsych.2013.02.002
- Gillan CM, Papmeyer M, Morein-Zamir S, Sahakian BJ, Fineberg NA, Robbins TW, de Wit S. Disruption in the balance between goal-directed behavior and habit learning in obsessive-

- compulsive disorder. [Comparative Study Research Support, Non-U.S. Gov't]. The American journal of psychiatry. 2011; 168(7):718–726.10.1176/appi.ajp.2011.10071062 [PubMed: 21572165]
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101:8174–8179. [PubMed: 15148381]
- Gogtay N, Nugent TF, Herman DH, Ordonez A, Greenstein D, Hayashi KM, et al. Dynamic mapping of normal human hippocampal development. Hippocampus. 2006; 16:664–672. [PubMed: 16826559]
- Goh S, Peterson BS. Imaging evidence for disturbances in multiple learning and memory systems in persons with autism spectrum disorders. Developmental Medicine and Child Neurology. 2012; 54:208–213. [PubMed: 22269006]
- Goodman J, Leong KC, Packard MG. Emotional modulation of multiple memory systems, implications for the neurobiology of post-traumatic stress disorder. Reviews in the Neurosciences. 2012; 23:627–643. [PubMed: 23001314]
- Gordon B, Stark S. Procedural learning of a visual sequence in individuals with autism. Focus on Autism and Other Developmental Disabilities. 2007; 22:14–22.
- Gould E, Gross CG. Neurogenesis in adult mammals, some progress and problems. Journal of Neuroscience. 2002; 22:619–623. [PubMed: 11826089]
- Graybiel AM, Rauch SL. Toward a neurobiology of obsessive-compulsive disorder. Neuron. 2000; 28(2):343–347. [PubMed: 11144344]
- Grisham JR, Anderson TM, Poulton R, Moffitt TE, Andrews G. Childhood neuropsychological deficits associated with adult obsessive-compulsive disorder. British Journal of Psychiatry. 2009; 195:138–141. [PubMed: 19648544]
- Groen W, Teluij M, Buitelaar J, Tendolkar I. Amygdala and hippocampus enlargement during adolescence in autism. Journal of the American Academy of Child and Adolescent Psychiatry. 2010; 49:552–560. [PubMed: 20494265]
- Gross, CG. Visual functions of inferotemporal cortex. In: Autrum, H.; Jung, R.; Lowenstein, WR.; McKay, DM.; Teuner, HL., editors. Handbook of Sensory Physiology. Berlin: Springer; 1973. p. 451–482.
- Gunderson VM, Swartz KB. Visual recognition in infant pigtailed macaques after a 24-hour delay. American Journal of Primatology. 1985; 8:259–264.
- Haddon JE, Killcross S. Inactivation of the infralimbic prefrontal cortex in rats reduces the influence of inappropriate habitual responding in a response-conflict task. Neuroscience. 2011; 199:205–212. [PubMed: 22015928]
- Halmi KA, Tozzi F, Thornton LM, Crow S, Fichter MM, Kaplan AS, Bulik CM. The relation among perfectionism, obsessive-compulsive personality disorder and obsessive-compulsive disorder in individuals with eating disorders. Int J Eat Disord. 2005; 38(4):371–374. [PubMed: 16231356]
- Harlow HF. The development of learning in the rhesus monkey. American Scientist. 1959; 47:458–479.
- Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. JAMA Psychiatry. 2013; 70:185–198. [PubMed: 23247506]
- Hauser S, DeLong GR, Rosman N. Pneumographic findings in the infantile autism syndrome, a correlation with temporal lobe disease. Brain. 1975; 98:667–688. [PubMed: 1218372]
- Hess C, Blozovski D. Hippocampal muscarinic cholinergic mediation of spontaneous alternation and fear in the developing rat. Behavioural Brain Research. 1987; 24:203–214. [PubMed: 3606803]
- Hoekstra PJ, Steenhuis MP, Kallenberg CGM, Minderaa RB. Association of small life events with self reports of tic severity in pediatric and adult tic disorder patients: a prospective longitudinal study. Journal of Clinical Psychiatry. 2004; 65:426–431. [PubMed: 15096084]

- Hollander E, Anagnostou E, Chaplin W, Esposito K, Haznedar MM, Licalzi E, et al. Striatal volume on magnetic resonance imaging and repetitive behaviors in autism. *Biological Psychiatry*. 2005; 58:226–232. [PubMed: 15939406]
- Hu SY, Pruessner JC, Coupé Collins DL. Volumetric analysis of medial temporal lobe structures in brain development from childhood to adolescence. *Neuroimage*. 2013; 74:276–287. [PubMed: 23485848]
- Ishikawa A, Nakamura S. Convergence and interaction of hippocampal and amygdalar projections within the prefrontal cortex in the rat. *J Neurosci*. 2003; 23(31):9987–9995. [PubMed: 14602812]
- Ivkovich D, Paczkowski CM, Stanton ME. Ontogeny of delay versus trace eyeblink conditioning in the rat. *Developmental Psychobiology*. 2000; 36:148–160. [PubMed: 10689285]
- Ivkovich D, Stanton ME. Effects of early hippocampal lesions on trace, delay, and long-delay eyeblink conditioning in developing rats. *Neurobiology of Learning and Memory*. 2001; 76:426–446. [PubMed: 11726246]
- Jablonski SA, Schiffrino FL, Stanton ME. Role of age, post-training consolidation, and conjunctive associations in the ontogeny of the context preexposure facilitation effect. *Developmental Psychobiology*. 2012; 54:714–722. [PubMed: 22127879]
- Jayarajan RN, Venkatasubramanian G, Viswanath B, Reddy YC, Srinath S, Vasudev MK, Chandrashekar CR. White matter abnormalities in children and adolescents with obsessive-compulsive disorder: a diffusion tensor imaging study. *Depression and anxiety*. 2012; 29(9):780–788.10.1002/da.21890 [PubMed: 22323419]
- Johnson CT, Olton DS, Gage FH, Jenko PG. Damage to hippocampus and hippocampal connections – effects on DRL and spontaneous alternation. *Journal of Comparative and Physiological Psychology*. 1977; 91:508–522. [PubMed: 874119]
- Kanner L. Autistic disturbances of affective contact. *Nervous Child*. 1943; 2:217–250.
- Kaltiala-Heino R, Rissanen A, Rimpela M, Rantanen P. Bulimia and impulsive behaviour in middle adolescence. *Psychotherapy & Psychosomatics*. 2003; 72(1):26–33. [PubMed: 12466635]
- Kaplan BBJ, Dewey DD, Crawford SSG, Fisher GGC. Deficits in long-term memory are not characteristic of ADHD. *Journal of Clinical and Experimental Neuropsychology*. 1998; 20:518–528. [PubMed: 9892055]
- Karatekin C, White T, Bingham C. Incidental and intentional sequence learning in youth-onset psychosis and attention-deficit/hyperactivity disorder (ADHD). *Neuropsychology*. 2009; 23:445–459. [PubMed: 19586209]
- Kesner RP, Bolland BL, Dakis M. Memory for spatial locations, motor-responses, and objects – triple dissociation among the hippocampus, caudate-nucleus, and extrastriate visual-cortex. *Experimental Brain Research*. 1993; 93:462–470. [PubMed: 8519335]
- Killcross S, Coutureau E. Coordination of actions and habits in the medial prefrontal cortex of rats. *Cerebral Cortex*. 2003; 13:400–408. [PubMed: 12631569]
- Killiany R, Mahut H. Hippocampectomy in infant rhesus monkeys facilitates object-reward association learning but not memory for conditional object-object associations. *Society for Neuroscience Abstracts*. 1990; 16:847.
- Kirkby RJ. A maturation factor in spontaneous alternation. *Nature*. 1967; 215:784. [PubMed: 6059563]
- Kirkby RJ, Stein DG, Kimble RJ, Kimble DP. Effects of hippocampal lesions and duration of sensory input on spontaneous alternation. *Journal of Comparative and Physiological Psychology*. 1967; 64:342–345. [PubMed: 6050582]
- Klein DA, Walsh BT. Eating disorders: clinical features and pathophysiology. *Physiol Behav*. 2004; 81(2):359–374. [PubMed: 15159176]
- Kothari R, Solmi F, Treasure J, Micali N. The neuropsychological profile of children at high risk of developing an eating disorder. *Psychological Medicine*. 2013; 43:1543–1554. [PubMed: 23021014]
- Lalonde R. The neurobiological basis of spontaneous alternation. *Neuroscience and Biobehavioral Reviews*. 2002; 26:91–104. [PubMed: 11835987]

- Langen M, Durston S, Staal WG, Palmen SJMC, van Engeland H. Caudate nucleus is enlarged in high-functioning medication-naïve subjects with autism. *Biological Psychiatry*. 2007; 62:262–266. [PubMed: 17224135]
- Langen M, Leemans A, Johnston P, Ecker C, Daly E, Murphy CM. Fronto-striatal circuitry and inhibitory control in autism, findings from diffusion tensor imaging tractography. *Cortex*. 2012; 48:183–193. [PubMed: 21718979]
- Langen M, Schnack HG, Nederveen H, Bos D, Lahuis BE, de Jonge MV, et al. Changes in the developmental trajectories of striatum in autism. *Biological Psychiatry*. 2009; 66:327–333. [PubMed: 19423078]
- Langston RF, Ainge JA, Couey JJ, Canto CB, Bjerknes TL, Witter MP, et al. Development of the spatial representation in the rat. *Science*. 2010;1576–1580. [PubMed: 20558721]
- Laurance HE, Learmonth AE, Nadel L. Maturation of spatial navigation strategies: convergent findings from computerized spatial environments and self-report. *Journal of Cognition and Development*. 2003; 4:211–238.
- Lavenex, P.; Lavenex, PB. Building hippocampal circuits to learn and remember: insights into the development of human memory. *Behavioral Brain Research*. 2013. <http://dx.doi.org/10.1016/j.bbr.2013.02.007>
- Lehning M, Leplow B, Friege L, Herzog A, Ferstl R, Mehdorn M. Development of spatial memory and spatial orientation in preschoolers and primary school children. *British Journal of Psychology*. 1998; 89:463–480. [PubMed: 9734301]
- Leckman JF. Tourette's syndrome. *Lancet*. 2002; 360(9345):1577–1586. [PubMed: 12443611]
- Leckman JF, Riddle MA. Tourette's Syndrome: When habit-forming systems form habits of their own? *Neuron*. 2000; 28:349–354. [PubMed: 11144345]
- Lena SM, Fiocco AJ, Leyenaar JK. The role of cognitive deficits in the development of eating disorders. *Neuropsychology Review*. 2004; 14:99–113. [PubMed: 15264711]
- Lenroot RK, Giedd JN. Brain development in children and adolescents, insights from anatomical magnetic resonance imaging. *Neuroscience and Biobehavioral Reviews*. 2006; 30:718–729. [PubMed: 16887188]
- Leplow B, Lehning M, Pohl J, Herzog A, Ferstl R, Mehdorn M. Navigational place learning in children and young adults as assessed with a standardized locomotor search task. *British Journal of Psychology*. 2003; 94:299–317. [PubMed: 14511545]
- Li Y, Kolb B, Robinson TE. The location of persistent amphetamine-induced changes in the density of dendritic spines on medium spiny neurons in the nucleus accumbens and caudate-putamen. *Neuropsychopharmacology*. 2003; 28:1082–1085. [PubMed: 12700699]
- Lin, SY.; Calcott, A.; Germann, J.; Konishi, K.; Bohbot, VD.; Lerch, JP. Society for Neuroscience 2012 Abstracts. New Orleans, LA: 2012. Decreased use of hippocampus-dependent spatial strategy in favor caudate nucleus-dependent response strategy from childhood to adolescence.
- Lin HQ, Katsoyich L, Ghebremichael M, Findley DB, Grantz H, Lomroso PJ, et al. Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. *Journal of Child Psychology and Psychiatry*. 2007; 48:157–166. [PubMed: 17300554]
- Mainz V, Schulte-Ruther M, Fink GR, Herpertz-Dahlmann B, Konrad K. Structural brain abnormalities in adolescent anorexia nervosa before and after weight recovery and associated hormonal changes. [Research Support, Non-U.S. Gov't]. *Psychosomatic medicine*. 2012; 74(6): 574–582.10.1097/PSY.0b013e31824ef10e [PubMed: 22511729]
- Malamut BL, Saunders RC, Mishkin M. Monkeys with combined amygdalo-hippocampal lesions succeed in object discrimination-learning despite 24-hour intertrial intervals. *Behavioral Neuroscience*. 1984; 98:759–769. [PubMed: 6487412]
- Málková L, Alvarado MC, Pixley EL, Belcher AM, Mishkin M, Bachevalier J. Maturation of relational memory processes in monkeys. *Society for Neuroscience Abstracts*. 1999; 25:1892.
- Mandolesi L, Petrosini L, Menghini D, Addona F, Vicari S. Children's radial arm maze performance as a function of age and sex. *International Journal of Developmental Neuroscience*. 2009; 27:789–797. [PubMed: 19716409]

- Maren S. Neurobiology of pavlovian fear conditioning. *Ann Rev Neurosci.* 2001; 24:897–931. [PubMed: 11520922]
- Marsh R, Alexander GM, Packard MG, Zhu HT, Peterson BS. Perceptual-motor skill learning in Gilles de la Tourette syndrome Evidence for multiple procedural learning and memory systems. *Neuropsychologia.* 2005; 43:1456–1465. [PubMed: 15989936]
- Marsh R, Alexander GM, Packard MG, Zhu HT, Wingard JC, Quackenbush G, et al. Habit learning in Tourette syndrome – a translational neuroscience approach to a developmental psychopathology. *Archives of General Psychiatry.* 2004; 61:1259–1268. [PubMed: 15583117]
- Marsh R, Horga G, Wang Z, Wang P, Klahr KW, Berner LA, Peterson BS. An fMRI study of self-regulatory control and conflict resolution in adolescents with bulimia nervosa. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *The American journal of psychiatry.* 2011; 168(11):1210–1220.10.1176/appi.ajp.2011.11010094 [PubMed: 21676991]
- Marsh, R.; Leckman, JF.; Bloch, MH.; Yazgan, Y.; Peterson, BS. Tics and Compulsions: Disturbances of Self-Regulatory Control in the Development of Habitual Behaviors. In: Nelson, CA.; Luciana, M., editors. *Handbook of Developmental Cognitive Neuroscience.* 2. Cambridge MA: Massachusetts Institute of Technology; 2008. p. 717-737.
- Marsh R, Maia TV, Peterson BS. Functional disturbances within frontostriatal circuits across multiple childhood psychopathologies. *American Journal of Psychiatry.* 2009; 166:664–674. [PubMed: 19448188]
- Marsh R, Steinglass JE, Gerber AJ, O'Leary KG, Walsh BT, Peterson BS. Deficient Activity in the Neural Systems that Mediate Self-Regulatory Control in Bulimia Nervosa. *Arch Gen Psychiatry.* 2009; 66(1):1–13.
- Marsh R, Steinglass JE, Graziano K, Walsh BT, Peterson BS. Self-regulatory control and habit learning in the development of eating disorders. *Current Psychiatry Reviews.* 2007; 3:73–83.
- Marsh R, Zhu H, Wang Z, Skudlarski P, Peterson BS. A Developmental fMRI Study of Self-Regulatory Control in Tourette's Syndrome. *Am J Psychiatry.* 2007; 164(6):955–966. [PubMed: 17541057]
- Martin PD, Berthoz A. Development of spatial firing in the hippocampus of young rats. *Hippocampus.* 2002; 12:465–480. [PubMed: 12201631]
- Matsumoto N, Hanakawa T, Maki S, Graybiel AM, Kimura M. Role of [corrected] nigrostriatal dopamine system in learning to perform sequential motor tasks in a predictive manner. *J Neurophysiol.* 1999; 82(2):978–998. [PubMed: 10444692]
- McAlonan GM, Daly E, Kumari V, Critchley HD, van Amelsvoort T, Suckling J, et al. Brain anatomy and sensorimotor gating in Asperger's syndrome. *Brain.* 2002; 125:1594–1606. [PubMed: 12077008]
- McDonald RJ, Devan B, Hong NS. Multiple memory systems, the power of interactions. *Neurobiology of Learning and Memory.* 2004; 82:333–346. [PubMed: 15464414]
- McDonald RJ, White NM. A triple dissociation of memory-systems – hippocampus, amygdala, and dorsal striatum. *Behavioral Neuroscience.* 1993; 107:3–22. [PubMed: 8447956]
- Means LW, Leander JD, Isaacson RL. Effects of hippocampectomy on alternation behavior and response to novelty. *Physiology and Behavior.* 1971; 6:17–22. [PubMed: 5125451]
- Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci.* 2001; 24:167–202. [PubMed: 11283309]
- Miyake Y, Okamoto Y, Onoda K, Kurosaki M, Shirao N, Yamawaki S. Brain activation during the perception of distorted body images in eating disorders. [Research Support, Non-U.S. Gov't]. *Psychiatry research.* 2010; 181(3):183–192.10.1016/j.psychres.2009.09.001 [PubMed: 20153150]
- Miyake Y, Okamoto Y, Onoda K, Shirao N, Otagaki Y, Yamawaki S. Neural processing of negative word stimuli concerning body image in patients with eating disorders: an fMRI study. [Research Support, Non-U.S. Gov't]. *NeuroImage.* 2010; 50(3):1333–1339.10.1016/j.neuroimage.2009.12.095 [PubMed: 20045473]
- Montes LGA, Ricardo-Garcell J, De la Torre LB, Alcantara HP, Garcia RBM, Fernandez-Bouzas A, et al. Clinical correlations of grey matter reductions in the caudate nucleus of adults with attention

- deficit hyperactivity disorder. *Journal of Psychiatry and Neuroscience*. 2010; 35:238–246. [PubMed: 20569650]
- Mostofsky SH, Goldberg MC, Landa RJ, Denckla MB. Evidence for a deficit in procedural learning in children and adolescents with autism, implications for cerebellar contribution. *Journal of the International Neuropsychological Society*. 2000; 6:752–759. [PubMed: 11105465]
- Mowrer OH. A stimulus-response analysis of anxiety and its role as a reinforcing agent. *Psychological Review*. 1939; 46:553–565.
- Mowrer OH. On the dual nature of learning – a re-interpretation of “conditioning” and “problem-solving”. *Harvard Educational Review*. 1947; 17:102–148.
- Murphy R, Nutzinger DO, Paul T, Leprow B. Conditional-associative learning in eating disorders: a comparison with OCD. [Comparative Study]. *Journal of clinical and experimental neuropsychology*. 2004; 26(2):190–199.10.1076/jcen.26.2.190.28091 [PubMed: 15202539]
- Murray EA, Mishkin M. Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. *Journal of Neuroscience*. 1998; 18:6568–6582. [PubMed: 9698344]
- Nakano K, Kayahara T, Tsutsumi T, Ushiro H. Neural circuits and functional organization of the striatum. *J Neurol*. 2000; 247(Suppl 5):V1–V15. [PubMed: 11081799]
- Nakao T, Radua J, Rubia K, Mataix-Cols D. Gray matter volume abnormalities in ADHD: Voxel-based meta-analysis exploring the effects of age and stimulant medication. *American Journal of Psychiatry*. 2011; 168:1154–1163. [PubMed: 21865529]
- Nemanic S, Alvarado MC, Bachevalier J. The hippocampal/parahippocampal regions and recognition memory: insights from visual paired comparison versus object-delayed nonmatching in monkeys. *Journal of Neuroscience*. 2004; 24:2013–2026. [PubMed: 14985444]
- Nieto-Escámez FA, Sánchez-Santed F, de Bruin JPC. Cholinergic receptor blockade in prefrontal cortex and lesions of the nucleus basalis: implications for allocentric and egocentric spatial memory in rats. *Behavioural Brain Research*. 2002; 134:93–112. [PubMed: 12191796]
- Nikendei C, Funiok C, Pfüller U, Zastrow A, Aschenbrenner S, Weisbrod M, Friederich HC. Memory performance in acute and weight-restored anorexia nervosa patients. *Psychological medicine*. 2011; 41(4):829–838.10.1017/S0033291710001121 [PubMed: 20529417]
- Olley A, Malhi G, Sachdev P. Memory and executive functioning in obsessive-compulsive disorder: a selective review. *Journal of Affective Disorders*. 2007; 104:15–23. [PubMed: 17442402]
- Olton, DS. The Function of Septo-Hippocampal Connections in Spatially Organized Behaviour. In: Elliot, K.; Whelan, J., editors. *Ciba Foundation Symposium 58 – Functions of the Septo-Hippocampal System*. 1978.
- Ornstein TJ, Arnold P, Manassis K, Mendlowitz S, Schachar R. Neuropsychological performance in childhood OCD: a preliminary study. [Research Support, Non-U.S. Gov't]. *Depression and anxiety*. 2010; 27(4):372–380.10.1002/da.20638 [PubMed: 19960527]
- Ostby Y, Tamnes CK, Fjell AM, Westlye LT, Due-Tønnessen P, Walhovd KB. Heterogeneity in subcortical brain development: a structural magnetic resonance imaging study of brain maturation from 8 to 30 years. *Journal of Neuroscience*. 2009; 29:11772–11782. [PubMed: 19776264]
- Overman WH. Performance on traditional match-to-sample, non-match to sample, and aobject discrimination tasks by 12–32-month-old children, a developmental progression. *Annals of the New York Academy of Sciences, The development and neural basis of higher cognitive functions*. 1990; 608:365–383.
- Overman WH, Bachevalier J, Miller M, Moore K. Children’s performance on “animal tests” of oddity, implications for cognitive processes required for tests of oddity and delayed nonmatch to sample. *Journal of Experimental Child Psychology*. 1996a; 62:223–242. [PubMed: 8683187]
- Overman WH, Bachevalier J, Sewell F, Drew J. A comparison of children’s performance on 2 recognition memory tasks – a delayed nonmatch-to-sample versus visual paired-comparison. *Developmental Psychobiology*. 1993; 26:345–357. [PubMed: 8119484]
- Overman WH, Bachevalier J, Turner M, Peuster A. Object recognition versus object discrimination, comparison between human infants and infant monkeys. *Behavioral Neuroscience*. 1992; 106:15–29. [PubMed: 1554428]

- Overman WH, Pate BJ, Moore K, Peuster A. Ontogeny of place learning in children as measured in the radial arm maze, Morris search task, and open field task. *Behavioral Neuroscience*. 1996b; 110:1205–1228. [PubMed: 8986326]
- Packard MG. Anxiety, cognition, and habit, a multiple memory systems perspective. *Brain Research*. 2009; 1293:121–128. [PubMed: 19328775]
- Packard, MG. Role of basal ganglia in habit learning and memory, Rats, monkeys, and humans. In: Steiner, H.; Tseng, KY., editors. *Handbook of Basal Ganglia Structure and Function*. Elsevier/Academic Press; 2010. p. 561-567.
- Packard MG, Goodman J. Emotional arousal and multiple memory systems in the mammalian brain. *Frontiers in Behavioral Neuroscience*. 2012; 6:14. [PubMed: 22470324]
- Packard MG, Hirsh R, White NM. Differential effects of fornix and caudate-nucleus lesions on 2 radial maze tasks – evidence for multiple memory-systems. *Journal of Neuroscience*. 1989; 9:1465–1472. [PubMed: 2723738]
- Packard MG, Knowlton BJ. Learning and memory functions of the basal ganglia. *Annual Review of Neuroscience*. 2002; 25:563–593.
- Packard MG, McGaugh JL. Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiology of Learning and Memory*. 1996; 65:65–72. [PubMed: 8673408]
- Packard MG, Teather LA. Double dissociation of hippocampal and dorsal-striatal memory systems by posttraining intracerebral injections of 2-amino-5-phosphonopentanoic acid. *Behavioral Neuroscience*. 1997; 111:543–551. [PubMed: 9189269]
- Packard MG, White NM. Dissociation of hippocampus and caudate-nucleus memory-systems by posttraining intracerebral injection of dopamine agonists. *Behavioral Neuroscience*. 1991; 105:295–306. [PubMed: 1675062]
- Pasupathy A, Miller EK. Different time courses of learning-related activity in the prefrontal cortex and striatum. *Nature*. 2005; 433:873–876. [PubMed: 15729344]
- Pauls DL, Alsobrook JP 2nd, Goodman W, Rasmussen S, Leckman JF. A family study of obsessive-compulsive disorder. *Am J Psychiatry*. 1995; 152(1):76–84. [PubMed: 7802125]
- Pederson A, Ohrmann P. Impaired behavioral inhibition in implicit sequence learning in adults ADHD. *J Atten Disord*. 2012; 10.1177/1087054712464392
- Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry*. 1996; 37:51–87. [PubMed: 8655658]
- Perlov E, Philipsen A, Tebartz van Elst L, Ebert D, Henning J, Maier S, et al. Hippocampus and amygdala morphology in adults with attention-deficit hyperactivity disorder. *J Psychiatry Neurosci*. 2008; 33:509–515.
- Peterson B, Riddle MA, Cohen DJ, Katz LD, Smith JC, Hardin MT, Leckman JF. Reduced basal ganglia volumes in Tourette's syndrome using three-dimensional reconstruction techniques from magnetic resonance images. [see comments]. *Neurology*. 1993; 43(5):941–949. [PubMed: 8492950]
- Peterson BS, Choi HA, Hao X, Amat JA, Zhu H, Whiteman R, Bansal R. Morphologic features of the amygdala and hippocampus in children and adults with Tourette syndrome. *Arch Gen Psychiatry*. 2007; 64(11):1281–1291. [PubMed: 17984397]
- Peterson BS, Pine DS, Cohen P, Brook J. A prospective, longitudinal study of tic, obsessive-compulsive, and attention deficit-hyperactivity disorders in an epidemiological sample. *J Am Acad Child Adolesc Psychiatry*. 2001; 40:685–695. [PubMed: 11392347]
- Peterson BS, Staib L, Scahill L, Zhang H, Anderson C, Leckman JF, Webster R. Regional brain and ventricular volumes in Tourette syndrome. *Arch Gen Psychiatry*. 2001; 58:427–440. [PubMed: 11343521]
- Peterson BS, Thomas P, Kane MJ, Scahill L, Zhang Z, Bronen R, Staib L. Basal ganglia volumes in patients with Gilles de la Tourette syndrome. *Arch Gen Psychiatry*. 2003; 60:415–424. [PubMed: 12695320]
- Peterson, BS.; Klein, J. Neuroimaging of Tourette's syndrome neurobiologic substrate. In: Peterson, BS., editor. *Child Psychiatry Clinics of North America: Neuroimaging*. Vol. 6. Philadelphia, PN: W. B. Saunders; 1997. p. 343-364.

- van Petten C. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia*. 2004; 42:1394–1413. [PubMed: 15193947]
- Phillips RR, Malamut BL, Bachevalier J, Mishkin M. Dissociation of the effects of inferior temporal and limbic lesions on object discrimination-learning with 24-H intertrial intervals. *Behavioral Brain Research*. 1988; 27:99–107.
- Pine DS, Grun J, Maguire EA, Burgess N, Zarahn E, Koda V, et al. Neurodevelopmental aspects of spatial navigation, a virtual reality fMRI study. *Neuroimage*. 2002; 15:396–406. [PubMed: 11798274]
- Plessen KJ, Bansal R, Zhu H, Whiteman R, Amat J, Quackenbush, et al. Hippocampus and amygdala morphology in Attention-Deficit/Hyperactivity Disorder. *Arch Gen Psychiatry*. 2006; 63:2006.
- Proal E, Reiss PT, Klein RG, Mannuzza S, Gotimer K, Ramos-Olazagasti MA, et al. Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. *Archives of General Psychiatry*. 2011; 68:1122–1134. [PubMed: 22065528]
- Pujol J, Soriano-Mas C, Alonso P, Cardoner N, Menchon JM, Deus J, Vallejo J. Mapping structural brain alterations in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2004; 61(7):720–730. [PubMed: 15237084]
- Pugh CR, Rudy JW. A developmental analysis of contextual fear conditioning. *Developmental Psychobiology*. 1996; 29:87–100. [PubMed: 8919089]
- Purpura, DS. *Brain Mechanisms in Mental Retardation*. New York: Academic Press; 1975. Normal and aberrant neuronal development in the cerebral cortex of human fetus and young infant; p. 141-169.
- Qiu A, Crocetti D, Adler M, Mahone MB, Denckla MI, Miller, Mostofsky SH. Basal Ganglia Volume and Shape in Children with Attention Deficit Hyperactivity Disorder. *Am J Psychiatry*. 2008; 166:74–82. [PubMed: 19015232]
- Qiu AQ, Adler M, Crocetti D, Miller MI, Mostofsky SH. Basal ganglia shapes predict social, communication, and motor dysfunctions in boys with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49:539–551. [PubMed: 20494264]
- Ragozzino ME, Detrick S, Kesner RP. Involvement of the prelimbic-infralimbic areas of the rodent prefrontal cortex in behavioral flexibility for place and response learning. *Journal of Neuroscience*. 1999; 19:4585–4594. [PubMed: 10341256]
- Ragozzino ME, Wilcox C, Raso M, Kesner RP. Involvement of rodent prefrontal cortex subregions in strategy switching. *Behavioral Neuroscience*. 1999; 113:32–41. [PubMed: 10197904]
- Rawson T, O’Kane M, Talk A. The medial prefrontal cortex and memory of cue location in the rat. *Neurobiology of Learning and Memory*. 2010; 93:132–136. [PubMed: 19761860]
- Rasmussen C, Soleimani M, Carroll A, Hodlevsky O. Neuropsychological functioning in children with Tourette syndrome (TS). *Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l’Academie canadienne de psychiatrie de l’enfant et de l’adolescent*. 2009; 18(4):307–315.
- Rauch SL, Savage CR, Alpert NM, Dougherty D, Kendrick A, Curran T, Jenike MA. Probing striatal function in obsessive-compulsive disorder: a PET study of implicit sequence learning. *J Neuropsychiatry Clin Neurosci*. 1997; 9(4):568–573. [PubMed: 9447498]
- Rauch SL, Whalen PJ, Curran T, Shin LM, Coffey BJ, Savage CR, Jenike MA. Probing striato-thalamic function in obsessive-compulsive disorder and Tourette syndrome using neuroimaging methods. *Adv Neurol*. 2001; 85:207–224. [PubMed: 11530429]
- Raz N, Rodrigue KM, Kennedy KM, Head D, Gunning-Dixon F, Acker JD. Differential aging of the human striatum, longitudinal evidence. *American Journal of Neuroradiology*. 2003; 24:1849–1856. [PubMed: 14561615]
- Resende MC, Tavares MCH, Tomaz C. Ontogenetic dissociation between habit learning and recognition memory in capuchin monkeys (*Cebus apella*). *Neurobiology of Learning and Memory*. 2003; 79:19–24. [PubMed: 12482675]

- Rhodes SM, Coghill DR, Matthews K. Methylphenidate restores visual memory, but not working memory function in attention deficit-hyperkinetic disorder. *Psychopharmacology*. 2004; 175:319–330. [PubMed: 15138760]
- Rhodes SM, Coghill DR, Matthews K. Neuropsychological functioning in stimulant-naïve boys with hyperkinetic disorder. *Psychological Medicine*. 2005; 35:1109–1120. [PubMed: 16116937]
- Rhodes SM, Coghill DR, Matthews K. Acute neuropsychological effects of methylphenidate in stimulant drug-naïve boys with ADHD II – broader executive and non-executive domains. *Journal of Child Psychology and Psychiatry*. 2006; 47:118–1194.
- Rhodes SM, Park J, Seth S, Coghill DR. A comprehensive investigation of memory impairment in attention deficit hyperactivity disorder and oppositional defiant disorder. *Journal of Child Psychology and Psychiatry*. 2012; 53:128–137. [PubMed: 21770938]
- Rich EL, Shapiro M. Rat prefrontal cortical neurons selectively code strategy switches. *Journal of Neuroscience*. 2009; 29:7208–7219. [PubMed: 19494143]
- Rimland, B. *Infantile Amnesia*. New York: Appleton-Century-Crofts; 1964.
- Roberts WW, Dember WN, Brodwick M. Alternation and exploration in rats with hippocampal lesions. *Journal of Comparative and Physiological Psychology*. 1962; 55:695–700. [PubMed: 13974341]
- Rodgers J, Glod M, Connolly B, McConachie H. The relationship between anxiety and repetitive behaviours in autism spectrum disorder. *Journal of Autism and Developmental Disorders*. 2012; 42:2404–2409. [PubMed: 22527704]
- Rodgers J, Riby DM, Janes E, Connolly B, McConachie H. Anxiety and repetitive behaviours in autism spectrum disorders and Williams syndrome: a cross-syndrome comparison. *Journal of Autism and Developmental Disorders*. 2012; 42:175–180. [PubMed: 21424863]
- Rojas DC, Peterson E, Winterrowd E, Reite ML, Rogers SJ, Tregellas JR. Regional gray matter volumetric changes in autism associated social and repetitive behaviors symptoms. *BMC Psychiatry*. 2006; 6:56. [PubMed: 17166273]
- Romero-Munúfía MA. Mnesic imbalance, a cognitive theory about autism spectrum disorders. *Annals of General Psychiatry*. 2008; 7:20. [PubMed: 18925971]
- Rosenberg DR, Keshavan MS. Toward a neurodevelopmental model of of obsessive--compulsive disorder. *biol Psychiatry*. 1998; 43(9):623–640. [PubMed: 9582996]
- Rosenberg DR, Keshavan MS, O'Hearn KM, Dick EL, Bagwell WW, Seymour AB, Birmaher B. Frontostriatal measurement in treatment-naïve children with Obsessive-Compulsive Disorder. *Arch Gen Psychiatry*. 1997; 54:824–830. [PubMed: 9294373]
- Rotge JY, Guehl D, Dilharreguy B, Tignol J, Bioulac B, Allard M, Auouizerate B. Meta-analysis of brain volume changes in obsessive-compulsive disorder. *Biol Psychiatry*. 2009; 65(1):75–83. [PubMed: 18718575]
- Roth RM, Baribeau J, Milovan D, O'Connor K, Todorov C. Procedural and declarative memory in obsessive-compulsive disorder. *Journal of the International Neuropsychological Society*. 2004; 10:647–654. [PubMed: 15327712]
- Rudy JW, Paylor R. Reducing the temporal demands of the morris place-learning task fails to ameliorate the place-learning impairment of preweanling rats. *Psychobiology*. 1988; 16:152–156.
- Rudy JW, Stadler-Morris S, Albert P. Ontogeny of spatial navigation behaviors in the rat – dissociation of proximal-cue and distal-cue-based behaviors. *Behavioral Neuroscience*. 1987; 101:62–73. [PubMed: 3828056]
- Ruiz EJC, de León MDEP, Días JMM. Neuropsychological evaluation in patients with eating disorders. *Salud Mental*. 2008; 31:441–446.
- Salmond CH, Ashburner J, Connelly A, Friston KJ, Gadian DG, Vargha-Khadem F. The role of the medial temporal lobe in autistic spectrum disorders. *European Journal of Neuroscience*. 2005; 22:764–772. [PubMed: 16101758]
- Sauro CL, Raval di C, Cabras PL, Faravelli C, Ricca V. Stress, hypothalamic-pituitary-adrenal axis and eating disorders. *Neuropsychobiology*. 2008; 57:95–115. [PubMed: 18552511]
- Savage CR, Baer L, Keuthen NJ, Brown HD, Rauch SL, Jenike MA. Organizational strategies mediate nonverbal memory impairment in obsessive-compulsive disorder. [Research Support, Non-U.S. Gov't]. *Biological psychiatry*. 1999; 45(7):905–916. [PubMed: 10202579]

- Scheres A, Milham MP, Knutson B, Castellanos FX. Ventral striatal hypo-responsiveness during reward anticipation in attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2007; 61:720–724. [PubMed: 16950228]
- Schiffino FL, Murawski NJ, Rosen JB, Stanton ME. Ontogeny and neural substrates of the context preexposure facilitation effect. *Neurobiology of Learning and Memory*. 2011; 95:190–198. [PubMed: 21129493]
- Schiller PH. Developmental study of color-word interference. *J Exp Psychol*. 1966; 72(1):105–108. [PubMed: 5967713]
- Schwabe L, Dickinson A, Wolf OT. Stress, habits, and drug addiction: a psychoneuroendocrinological perspective. *Experimental and Clinical Psychopharmacology*. 2011; 19:53–63. [PubMed: 21341923]
- Sears LL, Vest C, Mohamed S, Bailey J, Ranson BJ, Piven J. An MRI study of the basal ganglia in autism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 1999; 23:613–624. [PubMed: 10390720]
- Seidman LJ, Biederman J, Liang LC, Valera EM, Monuteaux MC, Brown A, et al. Gray matter alterations in adults with attention-deficit/hyperactivity disorder identified by voxel based morphometry. *Biological Psychiatry*. 2011; 69:857–866. [PubMed: 21183160]
- Seress L. Morphological variability and developmental aspects of monkey and human granule cells, differences between the rodent and primate dentate gyrus. *Epilepsy Research Suppl*. 1992; 7:3–28.
- Seress, L. Morphological changes of the human hippocampal formation from midgestation to early childhood. In: Nelson, CA.; Luciana, M., editors. *Handbook of Developmental Cognitive Neuroscience*. Cambridge, MA: The MIT Press; 2001. p. 45-58.
- Seress L. Comparative anatomy of the hippocampal dentate gyrus in adult and developing rodents, non-human primates and humans. *Progress in Brain Research*. 2007; 163:23–41. [PubMed: 17765710]
- Seress L, Abraham H, Tornoczky T, Kosztolanyi G. Cell formation in the human hippocampal formation from mid-gestation to the late postnatal period. *Neuroscience*. 2001; 105:831–843. [PubMed: 11530221]
- Seress L, Mrzljak L. Postnatal-development of mossy cells in the human dentate gyrus – a light microscopic golgi-study. *Hippocampus*. 1992; 2:127–142. [PubMed: 1308178]
- Seyffert M, Castellanos FX. Functional MRI in pediatric neurobehavioral disorders. *Neuroimaging*. 2005; 67:239–284.
- Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci USA*. 2007; 104:19649–19654. [PubMed: 18024590]
- Shin MS, Choi H, Kim H, Hwang JW, Kim BN, Cho SC. A study of neuropsychological deficit in children with obsessive-compulsive disorder. [Research Support, Non-U.S. Gov't]. *European psychiatry : the journal of the Association of European Psychiatrists*. 2008; 23(7):512–520.10.1016/j.eurpsy.2008.03.010 [PubMed: 18514491]
- Skowronek JS, Leichtman MD, Pillemer DB. Long-term episodic memory in children with attention-deficit/hyperactivity disorder. *Learning Disabilities Research and Practice*. 2008; 23:25–35.
- Smith KS, Virkud A, Deisseroth K, Graybiel AM. Reversible online control of habitual behavior by optogenetic perturbation of medial prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*. 2012; 109:18932–18937.
- Sobel LJ, Bansal R, Maia TV, Sanchez J, Mazzone L, Durkin K, et al. Surface morphology of the basal ganglia and the effects of stimulant medications in children with Attention-Deficit/Hyperactivity Disorder. *Am J Psychiatry*. 2010; 167:977–986. [PubMed: 20595414]
- Sowell ER, Thompson PM, Welcome SE, Henkenius AL, Toga AW, Peterson BS. Cortical abnormalities in children and adolescents with Attention Deficit Hyperactivity Disorder. *Lancet*. 2003; 362:1699–1707. [PubMed: 14643117]
- Spear, NE.; Miller, JS. Ontogeny of spontaneous alternation behavior. In: Dember, WN.; Richman, CL., editors. *Spontaneous Alternation Behavior*. New York: Springer-Verlag; 1989. p. 131-144.

- Squire LR. Memory systems of the brain, a brief history and current perspective. *Neurobiology of Learning and Memory*. 2004; 82:171–177. [PubMed: 15464402]
- Stanfield AC, McIntosh AM, Spencer MD, Philip R, Gaur S, Lawrie SM. Towards a neuroanatomy of autism, a systematic review and meta-analysis of structural magnetic resonance imaging studies. *European Psychiatry*. 2008; 23:289–299. [PubMed: 17765485]
- Stanton ME. Multiple memory systems, development and conditioning. *Behavioural Brain Research*. 2000; 110:25–37. [PubMed: 10802301]
- Steckler T, Drinkenburg WHIM, Sahgal A, Aggleton JP. Recognition memory in rats – II. Neuroanatomical substrates. *Progress in Neurobiology*. 1998; 54:313–332. [PubMed: 9481801]
- Steinglass JE, Walsh BT, Stern Y. Set shifting deficit in anorexia nervosa. *Journal of the International Neuropsychological Society*. 2006; 12:431–435. [PubMed: 16903136]
- Stevens R, Cowey A. Effects of dorsal and ventral hippocampal lesions on spontaneous alternation, learned alternation and probability-learning in rats. *Brain Research*. 1973; 52:203–224. [PubMed: 4700704]
- Stopczynski RE, Poloskey SL, Haber SN. Cell proliferation in the striatum during postnatal development, preferential distribution in subregions of the ventral striatum. *Brain Structure and Function*. 2008; 213:119–127. [PubMed: 18560887]
- Stringer KG, Martin GM, Skinner DA. The effects of hippocampal lesions on response, direction, and place learning in rats. *Behavioral Neuroscience*. 2005; 119:946–952. [PubMed: 16187822]
- Swanson LW, Cowan WM. Autoradiographic study of organization of efferent connections of hippocampal formation in the rat. *Journal of Comparative Neurology*. 1977; 172:49–84. [PubMed: 65364]
- Szeszko PR, Christian C, Macmaster F, Lencz T, Mirza Y, Taormina SP, Rosenberg DR. Gray Matter Structural Alterations in Psychotropic Drug-Naive Pediatric Obsessive-Compulsive Disorder: An Optimized Voxel-Based Morphometry Study. *Am J Psychiatry*. 2008
- Szeszko PR, MacMillan S, McMeniman M, Chen S, Baribault K, Lim KO, Rosenberg DR. Brain structural abnormalities in psychotropic drug-naive pediatric patients with obsessive-compulsive disorder. *Am J Psychiatry*. 2004; 161(6):1049–1056. [PubMed: 15169693]
- Szeszko PR, MacMillan S, McMeniman M, Lorch E, Madden R, Ivey J, Rosenberg DR. Amygdala volume reductions in pediatric patients with obsessive-compulsive disorder treated with paroxetine: preliminary findings. *Neuropsychopharmacology*. 2004; 29(4):826–832. [PubMed: 14970831]
- Takarae Y, Minshew NJ, Luna B, Sweeney JA. Atypical involvement of frontostriatal systems during sensorimotor control in autism. *Psychiatry Res*. 2007; 156:117–127. [PubMed: 17913474]
- Tchanturia K, Liao T, Uher R, Campbell IC, Treasure J. Eating Disorders Research Society. Amsterdam, Netherlands: 2004. A neuropsychological examination of the ventromedial prefrontal cortex using the Iowa Gambling Task in anorexia nervosa (AN).
- Tchanturia K, Morris RG, Anderluh MB, Collier DA, Nikolaou V, Treasure J. Set shifting in anorexia nervosa: an examination before and after weight gain, in full recovery and relationship to childhood and adult OCPD traits. *Journal of Psychiatric Research*. 2004; 38:545–552. [PubMed: 15380406]
- Tepper JM, Sharpe NA, Koós TZ, Trent F. Postnatal development of the rat neostriatum, electrophysiological, light- and electron-microscopic studies. *Developmental Neuroscience*. 1998; 20:125–145. [PubMed: 9691188]
- Teng E, Stefanacci L, Squire LR, Zola SM. Contrasting effects on discrimination learning after hippocampal lesions and conjoint hippocampal-caudate lesions in monkeys. *Journal of Neuroscience*. 2000; 20:3853–3863. [PubMed: 10804225]
- Townsend EL, Richmond JL, Vogel-Farley VK, Thomas K. Medial temporal lobe memory in childhood, developmental transitions. *Developmental Science*. 2010; 13:738–751. [PubMed: 20712740]
- Uher R, Murphy T, Brammer MJ, Dalgleish T, Phillips ML, Ng VW, Treasure J. Medial prefrontal cortex activity associated with symptom provocation in eating disorders. *Am J Psychiatry*. 2004; 161(7):1238–1246. [PubMed: 15229057]

- Uryu K, Butler AK, Chesselet M. Synaptogenesis and ultrastructural localization of the polysialylated neural cell adhesion molecule in the developing striatum. *The Journal of Comparative Neurology*. 1999; 405:216–232. [PubMed: 10023811]
- Vafaei AA, Rashidy-Pour A. Reversible lesion of the rat's orbitofrontal cortex interferes with hippocampus-dependent spatial memory. *Behavioural Brain Research*. 2004; 149:61–68. [PubMed: 14739010]
- Van Hoeken, D.; Seidell, J.; Hoek, HW. Epidemiology. In: Treasure, J.; Schmidt, U.; Van Furth, E., editors. *Handbook of Eating Disorders*. Vol. 2. Chichester, England: John Wiley and Sons Inc; 2004. p. 11-34.
- Via E, Radua J, Cardoner N, Happé F, Mataix-Cols D. Meta-analysis of gray matter abnormalities in autism spectrum disorder should asperger disorder be subsumed under a broader umbrella of autism spectrum disorder. *Archives of General Psychiatry*. 2011; 68:409–418. [PubMed: 21464365]
- Vloet TD, Marx I, Kahraman-Lanzerath B, Zepf FD, Herpertz-Dahlmann B, Konrad K. Neurocognitive performance in children with ADHD and OCD. *J Abnorm Child Psychol*. 2010; 38:961–969. [PubMed: 20467805]
- Wagner A, Aizenstein H, Mazurkewicz L, Fudge J, Frank GK, Putnam K, Kaye WH. Altered insula response to taste stimuli in individuals recovered from restricting-type anorexia nervosa. *Neuropsychopharmacology*. 2008; 33(3):513–523. [PubMed: 17487228]
- Wagner A, Aizenstein H, Venkatraman VK, Fudge J, May JC, Mazurkewicz L, Kaye WH. Altered reward processing in women recovered from anorexia nervosa. *Am J Psychiatry*. 2007; 164(12):1842–1849. [PubMed: 18056239]
- Walenski, M.; Tager-Flusberg, H.; Ullman, M. Language in autism. In: Moldin, S.; Rubenstein, J., editors. *Understanding autism, From basic neuroscience to treatment*. Boca Raton, FL: Taylor and Francis; 2006. p. 175-203.
- Walitza S, Wendland JR, Gruenblatt E, Warnke A, Sontag TA, Tucha O, Lange KW. Genetics of early-onset obsessive-compulsive disorder. [Review]. *European child & adolescent psychiatry*. 2010; 19(3):227–235.10.1007/s00787-010-0087-7 [PubMed: 20213231]
- Wallace GL, Happé F, Giedd JN. A case study of a multiply talented savant with an autism spectrum disorder, neuropsychological functioning and brain morphometry. *Philosophical Transactions of the Royal Society B, Biological Sciences*. 2009; 364:1425–1432.
- Walsh KH, McDougle CJ. Psychotherapy and medication management strategies for obsessive-compulsive disorder. *Neuropsychiatric disease and treatment*. 2011; 7:485–494.10.2147/NDT.S13205 [PubMed: 21931490]
- Wang J, Aigner T, Mishkin M. Effects of neostriatal lesions on visual habit formation in rhesus monkeys. *Society for Neuroscience Abstracts*. 1990; 16:617.
- Wechsler, D. *Wechsler Intelligence Scale for Children*. 3. San Antonio, TX: The Psychological Corporation; 1991. (WISC-III)
- Weng SJ, Carrasco M, Swartz JR, Wiggins JL, Kurapati N, Liberzon I, Risi S, Lord C, Monk CS. Neural activation to emotional faces in adolescents with autism spectrum disorders. *J Child Psychol Psychiatry*. 2011; 52:296–305. [PubMed: 21039484]
- White NM. Addictive drugs as reinforcers, multiple partial actions on memory systems. *Addiction*. 1996; 91:921–949. [PubMed: 8688822]
- White NM, McDonald RJ. Multiple parallel memory systems in the brain of the rat. *Neurobiology of Learning and Memory*. 2002; 77:125–184. [PubMed: 11848717]
- White NM, Salinas JA. Mnemonic functions of dorsal striatum and hippocampus in aversive conditioning. *Behav Brain Res*. 2003; 142:99–107. [PubMed: 12798270]
- Wills TJ, Cacucci F, Burgess N, O'Keefe J. Development of the hippocampal cognitive map in preweanling rats. *Science*. 2010; 328:1573–1578. [PubMed: 20558720]
- Wolpe J. Experimental neuroses as learned behaviour. *British Journal of Psychology*. 1952; 43:243–268.
- Yu KK, Cheung C, Chua SE, McAlonan GM. Can Asperger syndrome be distinguished from autism? an anatomic likelihood meta-analysis of MRI studies. *Journal of Psychiatry and Neuroscience*. 2011; 36:412–421. [PubMed: 21406158]

- Zarei M, Mataix-Cols D, Heyman I, Hough M, Doherty J, Burge L, James A. Changes in gray matter volume and white matter microstructure in adolescents with obsessive-compulsive disorder. *Biological psychiatry*. 2011; 70(11):1083–1090.10.1016/j.biopsych.2011.06.032 [PubMed: 21903200]
- Zimmerman RR, Torrey CC. The ontogeny of learning. *Behavior of Nonhuman Primates, Modern Research Trends*. 1965; 2:405–447.
- Zola SM, Squire LR. Relationship between magnitude of damage to the hippocampus and impaired recognition memory in monkeys. *Hippocampus*. 2001; 11:92–98. [PubMed: 11345130]
- Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal-formation produce severe memory impairment. *Journal of Neuroscience*. 1989; 9:4355–4370. [PubMed: 2593004]

Key Points

- The “multiple systems” hypothesis of memory organization proposes that in the mammalian brain there exist dissociable types of memory that are mediated by anatomically distinct brain regions.
- Extensive evidence indicates that among these “memory systems” are a cognitive/declarative memory system mediated by the hippocampus and a stimulus-response/habit memory system mediated by the dorsal striatum.
- Behavioral research indicates that memory systems may mature at different rates, with the dorsal striatum-dependent habit memory system typically maturing at an earlier age than the hippocampus-dependent cognitive memory system.
- Differing rates of development or abnormal functioning of cognitive and habit memory systems may contribute to the habit-like behavioral features of some childhood/adolescent psychiatric disorders such as Tourette syndrome, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, eating disorders, and autism spectrum disorders.
- Future research should directly compare the memory deficits and developmental trajectories between cognitive and habit memory systems specifically in children and adolescents with these disorders, which may lead to more efficient strategies for treating habit-like behavioral symptoms.

Figure 1.

Basal ganglia and medial temporal lobe structures in a human brain. Magnetic resonance imaging of a single human brain in vivo shows renderings of the cortical surface (in translucent gray), basal ganglia nuclei [C=caudate (magenta), P=putamen (cyan), G=globus pallidus (yellow)], and medial temporal lobe structures [A=amygdala (purple), H=hippocampus (green)] in various rotational views. The present review examines how maturation of these learning and memory structures may be relevant for some psychopathologies occurring in childhood and adolescence.

Table 1

Summary of multiple memory systems in childhood and adolescent psychiatric disorders. Although data are limited and in some cases inconsistent, this table summarizes research on striatal- and hippocampal-dependent memory systems in ASD, TS, OCD, ADHD, AN, and BN. We speculate that the early-maturing striatal-dependent memory system underlies the emergence of habit-like symptoms in all of these disorders. In ASD, both learning systems are impaired, suggesting a generalized deficit in learning, consistent with theory and genetics (see review Goh & Peterson, 2012) and leading to greater frequency of repetitive and stereotyped behaviors. In TS and ADHD, habit learning is impaired and the later-maturing hippocampal-dependent system may attenuate tic symptoms through adolescence. In OCD, enhanced habit memory and impaired cognitive memory may contribute to compulsive behavior. In BN, increased striatal activation during habit learning suggests abnormal processing that may lead to fragmented behaviors similar to TS, but in the feeding domain and without hippocampal compensation. In AN, increased activation of striatal regions and impaired hippocampal-dependent memory may contribute to habit-like refusal to eat.

Disorder	Early Maturing – Dorsal Striatum			Later Maturing--Hippocampus		
	Imaging Anatomy	Imaging Function	Habit Learning Behavior	Imaging Anatomy	Imaging Function	Declarative Learning Behavior
ASD	Enlarged ¹	Increased ²	Impaired ³	Reduced ⁴	Unknown	Impaired ⁵
TS	Reduced ⁶	Increased ⁷	Impaired ⁸	Compensatory Enlargement ⁹	Unknown	Normal ¹⁰
OCD	Reduced ¹¹	Reduced ¹²	Excessive ¹³	Reduced ¹⁴	Compensatory Increase ¹²	Impaired ¹⁵
ADHD	Reduced ¹⁶	Reduced ¹⁷	Impaired ¹⁸	Compensatory Enlargement ¹⁹	Unknown	Normal ²⁰ or Impaired ²¹
AN	Unknown	Increased ²²	Unknown	Reduced ²³	Unknown	Impaired ²⁴
BN	Unknown	Increased on SR tasks ²⁵	Normal ²⁵	Unknown	Unknown	Impaired ²⁶

AN: anorexia nervosa; ADHD: attention-deficit hyperactivity disorder; ASD: autism spectrum disorders; BN: bulimia nervosa; OCD: obsessive-compulsive disorder; TS: Tourette's syndrome.

References:

- ¹ Sears et al., 1999; Hollander et al., 2005; Rojas et al., 2006; Langen et al., 2007; Langen et al., 2009.
- ² Takarae et al., 2007; Weng et al., 2011.
- ³ Mostofsky et al., 2000; Gordon and Stark, 2007.
- ⁴ Via et al., 2011; Yu et al., 2011.
- ⁵ Boucher, Mayes, and Bigham, 2012.
- ⁶ Peterson, Thomas, Kane et al. 2003.
- ⁷ Marsh, Zhu, Wang, et al., 2007.

- ⁸ Marsh, Alexander, Packard, et al., 2004.
- ⁹ Peterson, Choi, Hao, et al., 2007.
- ¹⁰ Crawford, Channon, & Robertson, 2005.
- ¹¹ Rosenberg et al., 1997; 1998.
- ¹² Rauch et al., 1997; 2001.
- ¹³ Gillan et al., 2011; 2013.
- ¹⁴ Carmona, Bassas, Rovira, et al., 2007.
- ¹⁵ Chang, McCracken, & Piacentini, 2007.
- ¹⁶ Sobel, Bansal, Maia et al., 2010.
- ¹⁷ Cubillo et al, 2012.
- ¹⁸ Karatkin, White, & Bingham et al., 2009.
- ¹⁹ Plessen, Bansal, Zhu et al., 2006.
- ²⁰ Barnes, Howard, Howard, Kenealy & Vaidya, 2010
- ²¹ Rhodes, Coghill, and Matthews, 2004.
- ²² Wagner et al., 2007.
- ²³ Connan et al., 2006.
- ²⁴ Nikendei et al., 2011.
- ²⁵ Celone et al., 2011.
- ²⁶ Murphy et al., 2004.