Event-Related Functional Neuroimaging

of Reversal Learning in Autism Spectrum Disorders

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THESIS

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DEDICATION

To my family, on both sides of the ocean, without whom this leap of faith would not have been possible.

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I would like to acknowledge the participants and their families who volunteered their time so that this project could be completed. My warmest thanks also go to my advisor, Dr. Sweeney, for his dedicated mentorship throughout my training.

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LIST OF ABBREVIATIONS

3D	Three Dimensional
ADOS-R	Autism Diagnostic Observation Schedule - Revised
ADI-R	Autism Diagnostic Interview - Revised
ANOVA	Analysis of Variance
ASD	Autism Spectrum Disorder
BET	Brain Extraction Tool
CANTAB ID/ED	Cambridge Neuropsychological Test Automated Batter: Intradimensional/Extradimensional test
CDC	Centers for Disease control
DSM-IV TR	Diagnostic and Statistical Manual-Fourth Edition, Text Revision
FEAT	fMRI Expert Analysis Tool
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
FSL	FMRIB Software Library
FWHM	Full-Width Half Maximum
IQ	Intelligence Quotient
MCFLIRT	Motion Correction using FMRIB's Linear Image Registration Tool
MNI	Montreal Neurologic Institute
MRI	Magnetic Resonance Imaging
OCD	Obsessive-Compulsive Disorder
RBS-R	Repetitive Behavior Scales – Revised
RRB	Restricted and Repetitive Behaviors

SCQ	Social Communication Questionnaire
TE	Echo Time
TFCE	Threshold-Free Cluster Enhancement
TR	Repetition Time

SUMMARY

Many individuals with autism spectrum disorders (ASD) demonstrate Insistence on Sameness, which is characterized by restricted and repetitive patterns of thinking and behavior, and distress associated with disrupting preferred routines. Whether a primary impairment in neurocognitive processes supporting behavioral flexibility exist that could contribute to Insistence on Sameness is not well understood. Animal and human neuroimaging studies indicate that frontostriatal circuitry supports flexible behavior, but few studies have directly examined this functional neural circuitry in ASD during performance of a task requiring instances of behavioral flexibility. We used functional brain imaging during a task requiring flexible shifts in behavior to assess two possible neurobiological mechanisms of behavioral rigidity in ASD. One hypothesis was that altered activity in dorsal striatum and dorsal frontal motor and cognitive systems could impair shifting and sustaining novel response choices. A second hypothesis was that alterations in ventral striatum and associated limbic circuitry could cause problems interpreting the reinforcement cues that guide shifts in behavior. Further, uncertainty associated with response choices could exacerbate behavioral flexibility deficits in ASD, paralleling the increased distress and disability that may be seen clinically in novel or ambiguous situations. To test this third hypothesis, behavioral flexibility was examined in conditions in which the outcomes of future choice behaviors were either certain or uncertain.

Seventeen individuals with an ASD, and 23 age-, gender-, and IQ-matched control participants performed reversal learning studies during functional neuroimaging. When shifting from learned to novel responses when the outcome of responses was uncertain,

SUMMARY (Continued)

the ASD group showed reduced activation of both dorsal and ventral frontostriatal circuits. This impairment was present in the absence of task performance deficits in the ASD group relative to controls that might have confounded data interpretation. When the outcomes of novel responses were certain, there was no difference in brain activation between the groups, nor was there any difference in task performance measures.

Deficits present in both dorsal and ventral frontostriatal circuits suggest problems in integrating information from reinforcement cues with motor planning and decision making, which are essential in flexible responding. The specificity of these deficits to shifting behavior under uncertain circumstances may indicate problems responding appropriately to ambiguous reinforcement cues, and the integration of this information with multiple alternative response plans. Clinically, this may contribute to compulsive adherence to preferred behavioral patterns, and difficulty adapting to new environments and routines in individuals with an ASD. These findings provide a promising translational platform for better understanding the neurobiological substrates of Insistence on Sameness in ASD.

1. INTRODUCTION

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by pervasive disturbances in social interactions and communication, and by circumscribed interests, and restricted and repetitive behaviors (Diagnostic and Statistical Manual of Mental Disorders; 4th ed., text rev; DSM-IV-TR; American Psychiatric Association, 2000; Turner-Brown, Lam, Holtzclaw, Dichter, & Bodfish, 2011). "Insistence on Sameness" describes one cardinal feature of ASD; a compulsive adherence to routine, stereotyped and repetitive behaviors, and distress associated with transitions away from preferred to novel routines and environments (Kanner, 1943). This behavioral and cognitive rigidity places a significant burden on affected individuals and their caregivers (Bishop, Richler, Cain, & Lord, 2007; South, Ozonoff, & McMahon, 2005). The majority of psychological research into ASD has focused on social and communication impairments, whereas comparatively few studies have examined Insistence on Sameness.

It could be the case that characteristics of Insistence on Sameness, such as difficulty with breaking from preferred routines, occur as a result of primary deficits in flexible and adaptive behavioral control, and corresponding alterations in the frontostriatal circuits that subserve these functions. Few studies have tested this possibility, despite the important role of Insistence on Sameness in broader impairments in cognitive and social functioning (Geurts, Corbett, & Solomon, 2009). Because few treatment options for Insistence on Sameness are currently available, defining the nature of behavioral flexibility deficits in ASD and the neurocognitive mechanisms that support it may help to inform new treatment targets, and provide sensitive measures by which to assess treatment efficacy for novel interventions aimed at this understudied feature of

ASD. The primary aim of this study is to contribute to a better understanding of Insistence on Sameness by examining the integrity of the brain systems that support flexible behavior in individuals with ASD.

1.1. General Introduction to Autism Spectrum Disorders

Disorders on the autism spectrum share the triad of social impairments, language impairments, and restricted interests associated with autism, but individuals vary in the severity of these three symptom domains. The autism diagnostic spectrum as described in the DSM-IV includes Autism, Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS) and Asperger's Syndrome. The most recent survey data from the Centers for Disease Control (CDC) suggest that the prevalence of ASD in the population is one per 88 individuals (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2006 Principal Investigators & Centers for Disease Control and Prevention (CDC), 2009). Evidence suggests that there are prominent genetic and developmental neurobiological alterations that contribute to ASD. Recent estimates suggest a heritability of 57% (Abrahams & Geschwind, 2008; Hoekstra, Bartels, Verweij, & Boomsma, 2007). Approximately 10% of cases are associated with an identifiable genetic, neurologic or metabolic disorder (e.g., Fragile X; Cohen et al., 2005). However, no common genetic etiology or pathophysiological process has been identified for the development of ASD. The psychological impact on affected individuals and their families (Rao & Beidel, 2009) as well as the considerable financial burden associated with these disorders (estimated at an individual lifetime cost of $3.2 million; Ganz, 2007)

make investigations of etiology and development of new treatments for ASD important targets for clinical and translational research.

The heterogeneity of ASD contributes to their diagnostic complexity and the challenges associated with identifying their underlying neurobiology. However, as more sensitive diagnostic instruments and research tools are developed, increasing numbers of early diagnostic indicators are being identified in at-risk children and those with an early ASD diagnosis (Dawson et al., 2002; Klin, 1991; Mitchell et al., 2006; Ozonoff et al., 2010; Paul, Fuerst, Ramsay, Chawarska, & Klin, 2010; Pierce, Conant, Hazin, Stoner, & Desmond, 2011). There is increasing evidence to suggest that earlier diagnosis and subsequent targeted early intervention lead to better future outcomes in these patients (Dawson et al., 2010), which highlights the need for research into sensitive diagnostic indicators and specific treatment targets in ASD.

1.1.1. Signs and Symptoms of Autism Spectrum Disorders

In most children with an ASD, atypical social interactions and language delay or abnormalities are amongst the first symptoms to emerge. Early sensory abnormalities, including unusual sensory or object preoccupations (Ozonoff et al., 2008) and repetitive motor movements in high-risk infants (Loh et al., 2007) can be early manifestations of an incipient ASD. The quality and intensity of core symptoms can vary widely across individuals on the autism spectrum. Functioning can improve with early targeted behavioral therapies (Dawson & Burner, 2011; Mesibov & Shea, 2010) and sometimes concomitant medication treatment to manage common psychiatric comorbidities such as anxiety or irritability (Arnold et al., 2010; Lindsay & Aman, 2003; Steingard, Zimnitzky, DeMaso, Bauman, & Bucci, 1997). However, as social and academic demands on

individuals increase with age, symptoms may become more disabling (Tavernor, Barron, Rodgers, & McConachie, 2012).

1.1.2. Neurocognitive Profile of Autism Spectrum Disorders

In addition to the triad of ASD symptoms, a broad pattern of neuropsychological impairments has been associated with autism (Minshew, Goldstein, & Siegel, 1997). These cognitive impairments can significantly add to disease burden, functional impairments, and poor outcomes for affected individuals. Deficits in working memory (Luna et al., 2002), learning (D'Cruz et al., 2009), and response inhibition (Mosconi et al., 2009) have been reported in individuals with ASD. It is possible that some of these cognitive deficits may be "downstream" from core symptoms, which could mean that they are more directly related to clinical manifestations of ASD. For instance, restricted and repetitive behaviors have been linked to response inhibition deficits (Mosconi et al., 2009), and may indicate that rigid behavior is sustained because of a difficulty disengaging from preferred behavioral responses. Consequently, impaired frontostriatal circuitry, which controls the withholding of learned responses, might be implicated in problems with both response inhibition and clinically rigid behavior in ASD. Thus interpreted in the light of parallel imaging and animal studies, neuropsychological deficits can shed light on brain alterations related to deficits in executive control.

Higher-order cognitive processes require effective integration of information across functional domains and their respective brain systems. Disruption of these processes in ASD is believed to be an important systems-level basis for many cognitive and behavioral alterations in ASD (Barnea-Goraly et al., 2004; Geschwind & Levitt, 2007; Keller, Kana, & Just, 2007). Thus, the field has moved beyond hypotheses that

ASD result from an isolated impairment in a specific brain region, and towards a model of widespread disruption in the structure, function and development of the brain. Such diffuse and variable alterations in brain circuitry could explain the heterogeneous clinical manifestations and broad range of cognitive deficits associated with ASD. Thus an important focus of future studies is to consider neural systems dysfunction instead of focal deficits when developing models of the complex symptom and neuropsychological profile of ASD.

1.2. Insistence on Sameness in Autism Spectrum Disorders

Whilst several lines of research have addressed the social and language impairments associated with ASD, comparatively few studies have examined the neurocognitive substrates underlying rigid behavior and cognition. The frequency and intensity of these latter features may be particularly pronounced and disabling in some affected individuals, particularly in those who exhibit high levels of Insistence on Sameness, such as ritualistic behaviors and compulsive adherence to routine. Parallels have been drawn between these features of autism and compulsive behaviors seen in obsessive compulsive disorder (OCD; Jacob, Landeros-Weisenberger, & Leckman, 2009; Russel, Mataix-Cols, Anson & Murphy, 2005). In both disorders, individuals may engage in repetitive behaviors and rituals to relieve anxiety, and disruption of these routines can in turn result in significant anxiety and emotional dysregulation. Deficits in flexible choice behavior and its underlying neural circuitry may contribute to Insistence on Sameness. Therefore studies are needed that examine the functional integrity of

different brain circuits that support behavioral flexibility, and its relationship to clinical manifestations of rigid thinking and behavior.

1.2.1. Deficits in Flexible Behavior as a Model for Insistence on Sameness in Autism

Executive functions mediated by frontostriatal systems are impaired in individuals with autism (D'Cruz et al., 2009; Minshew et al., 1997; Minshew & Keller, 2010; Schmitz et al., 2006) and may be related to Insistence on Sameness. For instance, recent behavioral data from our laboratory suggest that impaired inhibitory control is related to the degree of rigid and repetitive behavior observed clinically in individuals with ASD (Mosconi et al., 2009). This suggests that a difficulty in suppressing prepotent responses, e.g., problems disengaging from preferred behavioral patterns, may contribute to Insistence on Sameness. However it is not known whether impaired response inhibition directly impacts behavioral flexibility, for instance by disrupting the ability to disengage from learned routines in order to engage in novel behaviors. In another study from our laboratory, we demonstrated that shifting from a learned to a novel response is impaired in ASD (D'Cruz et al., under review). Further, the degree of impairment is related to symptoms of restricted and repetitive behaviors, and rigid and obsessive thinking. Thus an important next step is to study the brain circuits underlying these impairments in behavioral flexibility, and ascertain whether deficits in the brain systems that subserve flexible choice behavior are related to Insistence on Sameness and related features of restricted and repetitive behaviors.

Most studies that directly examine behavioral flexibility in ASD do so using complex "extradimensional" or "strategy shifting" tasks. For extradimensional shifts, the rule defining correct responses varies across perceptual categories, which is exemplified

by the widely used Wisconsin Card Sorting Test (Robinson, Heaton, Lehman, & Stilson, 1980). For instance, the criterion for choosing a correct response might switch from color, to shape, to location. Though several studies of extradimensional set-shifting in individuals with autism have shown deficits in performance (Geurts et al., 2009; Maes, Eling, Wezenberg, Vissers, & Kan, 2010; Ozonoff et al., 2004; Yerys et al., 2009), others have shown no impairments (Barnard, Muldoon, Hasan, O'Brien, & Stewart, 2008; Goldberg et al., 2005; Ozonoff et al., 2004; Schmitz et al., 2006). Yerys et al (2009) noted that extradimensional switching errors were correlated with symptoms of repetitive behavior in ASD. It is important to note that these extradimensional tests place demands not only on behavioral flexibility but also on multiple higher-order cognitive processes that are known to be impaired in ASD, such as perceptual reasoning skills. Thus, it remains uncertain as to what degree previous findings reflect deficits in flexible behavioral control versus impaired cognition in other domains.

1.3. Reversal Learning

Reversal learning tasks provide a direct approach to examining simple flexible choice behavior. In contrast to set-shifting which is extradimensional, reversal learning tasks assess simple intradimensional shifts in behavior, e.g. shifting from choosing one spatial location to another. This is accomplished by requiring subjects to acquire a behavioral response strategy using performance feedback, and then to reverse that response to an alternative option when the previously correct choice is no longer reinforced. Therefore, reversal learning paradigms can be used to more specifically assess behavioral flexibility than most tasks used to date.

Few studies have examined reversal learning in ASD, and most have used small samples of young children who showed alterations in the ability to learn an initial response pattern in addition to reversal deficits (Coldren & Halloran, 2003; Lionello-Denolf, McIlvane, Canovas, de Souza, & Barros, 2008). If initial acquisition of a response is impaired, that can confound the interpretation of problems in switching to a new response, because such a difficulty could result from a generalized learning deficit rather than a specific impairment in response shifting. Reports from larger and primarily adolescent samples using intradimensional subtests of the CANTAB ID/ED task are inconsistent, with some reporting reversal learning deficits (Landa & Goldberg, 2005) and others not (Edgin & Pennington, 2005; Goldberg et al., 2005; Ozonoff et al., 2004; S. Ozonoff, South, & Miller, 2000). Thus whether basic shifts in choice behavior are impaired in ASD remains to be clarified, and a number of important issues remain to be resolved.

Firstly, there have been no neuroimaging studies of reversal learning in ASD to date. As such, the functional integrity of brain circuits implicated in flexible choice behavior in ASD is not known. Studies of reversal learning across species have underscored the importance of a widespread neural circuitry supporting reversal learning, including striatum, thalamus, anterior cingulate, premotor, dorsolateral, and orbital prefrontal cortex (Clarke, Robbins, & Roberts, 2008; D'Cruz, Ragozzino, Mosconi, Pavuluri, & Sweeney, 2011; Del'Guidice et al., 2009; Ghahremani, Monterosso, Jentsch, Bilder, & Poldrack, 2010; McAlonan & Brown, 2003; O'Doherty, Critchley, Deichmann, & Dolan, 2003; Roberts et al., 1990; O. J. Robinson, Standing, Devito, Cools, & Sahakian, 2010; Watanabe & Hikosaka, 2005; Xue, Ghahremani, & Poldrack, 2008).

Neuroimaging studies can detect alterations in brain function related to cognitive inflexibility, even in the absence of behavioral performance deficits on these tasks. Such approaches may thus be more sensitive to detecting subtle changes in the functional neuroanatomy of flexible choice behavior, where previous laboratory-based studies may have failed to find behavioral flexibility problems.

Secondly, studies have not systematically examined whether specific neuropsychological impairments in behavioral flexibility are related to the clinical problems of restricted and repetitive behaviors. Some studies have shown a relationship between clinical manifestations of behavioral rigidity and a variety of cognitive processes involved in the modulation of flexible behavior (Agam, Joseph, Barton, & Manoach, 2010; Langen et al., 2012; Mosconi et al., 2009). Studies have reported alterations in the structure and function of the caudate nucleus in ASD, and have linked these to restricted, repetitive, and sameness behaviors (Estes et al., 2011; Hollander et al., 2005; Langen, Durston, Staal, Palmen, & van Engeland, 2007; Langen et al., 2009; Rojas et al., 2006; Sears et al., 1999). However, no study has directly examined the functioning of these regions in the context of flexible behavioral transitions and tested for specific links between the alterations with function and Insistence on Sameness.

Thirdly, the role of development on behavioral flexibility and clinical symptoms of Insistence on Sameness is unclear. Because delayed maturation of behavioral flexibility in ASD may result in deficits that are more pronounced at younger ages, studies with older adolescents and young adults may have missed deficits evident in younger individuals. Prior studies have reported altered developmental trajectories in a number of cognitive functions in ASD (Luna, Doll, Hegedus, Minshew, & Sweeney,

2007; Ozonoff & McEvoy, 1994), but to our knowledge none to date have examined development within the domain of behavioral flexibility specifically. Also, findings from studies addressing how restricted, repetitive, and sameness behaviors change with age in ASD have been equivocal: some studies report a decrease of these symptoms with age (Bishop, Richler, & Lord, 2006; Esbensen, Seltzer, Lam, & Bodfish, 2009), whilst others note that these symptoms remain prominent across the lifespan (Lam & Aman, 2007; Piven, Harper, Palmer, & Arndt, 1996). Understanding whether there are developmental changes in the function of the frontostriatal circuits may help to clarify the trajectory of the neurocognitive substrates of behavioral rigidity with age. One aim of the current study was to develop a reversal learning paradigm that was easy to administer to even very young individuals, in order to allow examination of whether flexible choice behavior in ASD changes with age.

1.3.1. The Effect of Uncertainty of Future Outcomes on Flexible Choice Behavior

A major advantage of using reversal learning to better understand Insistence on Sameness is the ability to not only assess flexible choice behavior, but also to modulate the uncertainty of the outcomes of future choices and study its effect on behavioral flexibility. In a standard 2-choice reversal learning task, participants are presented with two response options (Palencia & Ragozzino, 2006). Once one response is no longer correct, the alternative response is certain to be the correct choice. By increasing the number of response options participants can no longer be certain about what the new correct choice might be. Uncertainty about future outcomes could serve to exacerbate an existing impairment in flexible choice behavior. This is particularly important for the

study of Insistence on Sameness in ASD, as environmental novelty is often associated clinically with anxiety and behavioral dysregulation.

Reversal learning studies can be used to test the functional integrity of frontostriatal circuits mediating flexible choice behavior. Functional brain imaging studies of reversal learning have documented a well-characterized network of brain regions that subserve reversal learning, including dorsolateral and ventrolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, and dorsal and ventral striatum (D'Cruz et al., 2011; Ghahremani et al., 2010; O'Doherty et al., 2003). As such, reversal learning studies allow for a direct assessment of two neurocognitive models of Insistence on Sameness described below.

1.4. Preliminary Studies of Reversal Learning

1.4.1. Probabilistic Reversal Learning Laboratory Study

In my graduate work, I carried out studies to better understand the neurocognitive bases of flexible choice behavior in ASD. In one study, I used a two-choice probabilistic reversal learning study in ASD individuals that paralleled studies used in rodent models of Insistence on Sameness in Dr. Ragozzino's lab. In this type of paradigm, accurate reinforcement for response choices is provided on only a proportion of trials, which allows for an examination of the effect of inconsistent reinforcement on behavioral flexibility. The intermittent non-reinforcement used in probabilistic tasks increases the difficulty associated with establishing, maintaining, and reversing a behavioral set which makes these tasks more sensitive to behavioral flexibility deficits. During probabilistic reversal learning, misleading feedback can slow learning of new responses after reversal,

or increase the likelihood of reverting back to a previously preferred response. A psychometric advantage is that probabilistic paradigms may be less susceptible to ceiling effects in test performance that could have contributed to the failure to identify deficits in prior studies in ASD, in which all correct responses were accurately reinforced. The unpredictable and inconsistent nature of reinforcement for choice behaviors used in probabilistic tasks also corresponds more closely to the behavioral flexibility demands of typical day-to-day life.

In the probabilistic reversal learning study, I documented performance deficits in maintaining new responses after behavioral reversals in an independent sample of ASD participants and matched controls (D'Cruz et al., under review, 2012). The degree of reversal learning impairment was related to symptoms of Insistence on Sameness but not social and communication deficits. In addition, there was increased instability of these new responses after misleading non-reinforcement in the ASD group (i.e. lose:shift errors). The degree of reversal learning impairment was related to symptoms of Insistence on Sameness. These results suggest that a neuropsychological impairment in flexible choice behavior may contribute clinically to rigid patterns of behavior and cognition. The results also suggest that a heightened response to non-reinforcement, reflected in increased rates of lose:shift errors, could contribute to a persistent preference for previously learned, but no longer reinforced, response patterns.

This study was important for the development of reversal learning paradigms for use in human clinical populations, and paved the way for a subsequent wave of studies to define the neurocognitive substrates of these and other behavioral flexibility impairments in ASD.

1.4.2. Imaging Studies of Reversal Learning

For my preliminary examination, I carried out an fMRI study of reversal learning in typically developing control participants (D'Cruz et al., 2011). The primary aim was to define the functional neuroanatomy of behavioral flexibility in typical development. A further goal was to understand how modulating the uncertainty of the outcomes of future behavior affected behavioral flexibility, particularly because of the clinical problem of increased distress and dysregulation associated with unfamiliar and uncertain situations in ASD individuals. Another study aim was to develop and validate a translational paradigm that closely paralleled the rodent studies of reversal learning using T-mazes and radial arm mazes used by Dr. Ragozzino. Therefore, tasks that assessed behavioral flexibility in the context of certain versus uncertain outcomes were developed, iteratively refined, and validated in a sample of typically developing healthy participants in an fMRI study. Certainty of future outcomes was modulated by altering the number of possible correct response choices following a change in the response-outcome contingency.

In 2-choice reversal learning tasks, participants switch between only two responses. Multiple choice reversal learning is qualitatively different, in that at reversal, it requires participants to respond to non-reinforcement of a learned response by selecting a new response from among several alternatives that have uncertain consequences. In an fMRI study, 15 participants performed 2- and 4-choice reversal learning tasks (D'Cruz et al., 2011). Upon reversal in both tasks, activation was observed in brain regions associated with processing changing reinforcement contingencies (midbrain, ventral striatum, insula), as well as in neocortical regions that support cognitive control and behavioral planning (prefrontal, premotor, posterior parietal, and anterior cingulate

cortices). Activation in both systems was greater in the 4- than in the 2-choice task. Therefore, reinforcement uncertainty for future responses enhanced activity in brain systems that process performance feedback, as well as in areas supporting anticipated future response choice and behavioral planning. Thus, these tasks were shown to elicit activation in dorsal cognitive and ventral motivational brain systems, and therefore provided paradigms for evaluating the two neurocognitive systems supporting flexible choice behavior in ASD to be assessed in the current clinical study.

1.5. Neurocognitive Models of Insistence on Sameness

Converging findings from a number of preclinical and neuropsychological studies document that frontostriatal brain circuitry is crucial for supporting flexible behavior. Lesions and neurochemical alterations in this circuitry have been associated with increased rates of repetitive behavior in animal models (Lewis, Tanimura, Lee, & Bodfish, 2007) and diverse clinical populations (Hollander et al., 2005), and also with difficulty in adapting behavior under changing environmental contingencies (Clarke et al., 2005). Thus, impaired frontostriatal function may contribute to disruption in the ability to transition smoothly between behaviors, and may cause cognitive and behavioral inflexibility. The current study examined two potential neurocognitive mechanisms of Insistence on Sameness involving separate but partially overlapping components of this frontostriatal circuitry.

1.5.1. Cognitive Flexibility Model

One possible mechanism for behavioral inflexibility in individuals with ASD is that cognitive impairments preclude their ability to change behavioral set. Clinically, this

may present as a difficulty changing from a preferred routine to a new behavior that might be more adaptive in the current context. Flexible behavior requires the engagement of a number of cognitive processes, including the ability to suppress a prepotent response tendency and to select a new response. Also crucial is the ability to maintain a new response without reverting back to the prepotent tendency. As such, Insistence on Sameness may be the result of "getting stuck" within one response pattern, because the neural circuitry responsible for flexibly altering behavior is impaired.

A number of brain regions are concerned with the cognitive shifting, motor planning, and attention processes which are required for flexible behavioral control (See Figure 1). These include cognitive and motor subdivisions of anterior cingulate cortex, dorsal striatum, and premotor, dorsolateral prefrontal, and parietal cortex. Frontal systems, including dorsolateral prefrontal and cognitive regions of anterior cingulate cortex, mediate changes in behavioral set (Damasio & Maurer, 1978; Dias, Robbins, & Roberts, 1996; Hollander et al., 2005; Shafritz, Dichter, Baranek, & Belger, 2008). Dorsolateral prefrontal and orbitofrontal cortex have been implicated in inhibiting learned behaviors (Budhani, Marsh, Pine, & Blair, 2007; Hampton & O'Doherty, 2007; Kenner et al., 2010; Velanova, Wheeler, & Luna, 2008). In addition to behavioral flexibility deficits following prefrontal lesions, difficulty disengaging from learned response patterns and establishing new ones has been documented with inactivation of dorsal striatum (Ragozzino, 2007).

When a previous response-outcome association and its associated behavioral plan have been inhibited, a new response plan can be more readily generated. The selection and implementation of alternative behaviors is dependent upon dorsomedial striatum

(Balleine, Delgado, & Hikosaka, 2007), motor cingulate (Picard & Strick, 1996), and the pre-supplementary motor area (Matsuzaka & Tanji, 1996). Taken together, these findings suggest that alterations of dorsal areas of the striatum, prefrontal, and premotor cortex may contribute to difficulty transitioning smoothly between behaviors by disrupting the ability to disengage from preferred responses and to plan, select, and sustain newly adaptive behaviors.

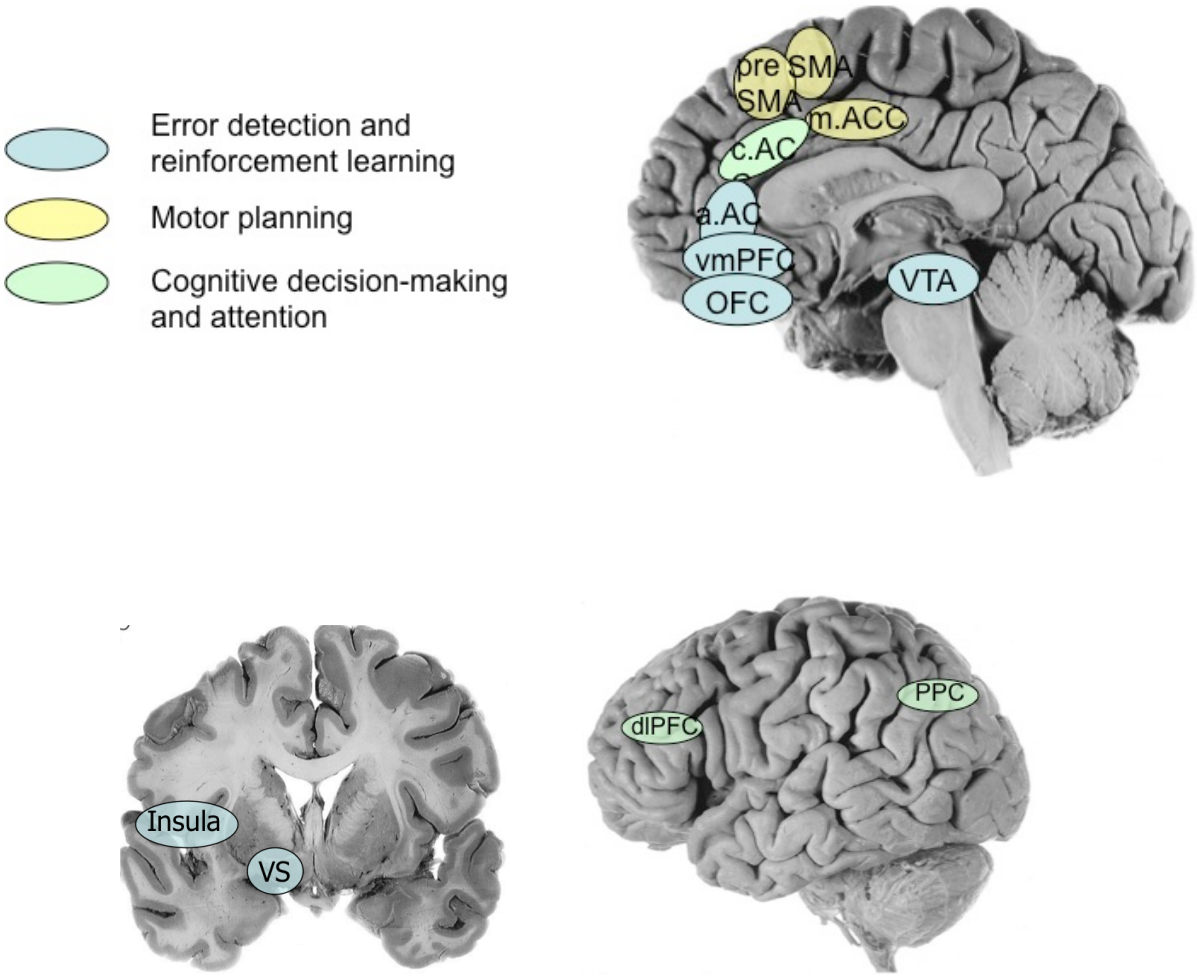

Figure 1. Schematic showing locations of brain areas involved in processes required for reversal learning, including cognitive decision-making, attention, motor planning, and reinforcement learning areas.

Pre-SMA: pre-supplementary motor area; SMA: supplementary motor area; mACC: motor subdivision of anterior cingulate cortex; cACC: cognitive subdivision of anterior cingulate cortex; aACC: affective subdivision of anterior cingulate cortex; vmPFC: ventromedial prefrontal cortex; OFC: orbitofrontal cortex: VTA; ventral tegmental area; VS: ventral striatum; dlPFC: dorsolateral prefrontal cortex; PPC: posterior parietal cortex.

1.5.2. Reinforcement Learning Model

Flexible behavior requires not only the ability to make decisions to change response patterns, but crucially, to recognize and respond appropriately to external contingencies that cue an individual to alter a repetitive behavioral pattern. While the cognitive deficit model of impaired behavioral flexibility implicates dorsal frontostriatal circuitry, altered reinforcement learning implicates ventral striatum, midbrain, and affective regions of anterior cingulate cortex (See Figure 1; Elliott, Friston, & Dolan, 2000).

Animal and human studies indicate that the ventral striatum is sensitive to changes in reinforcement contingencies (Gregorios-Pippas, Tobler, & Schultz, 2009). When response-outcome contingencies change during reversal learning, subjects expecting ongoing positive reinforcement for learned responses instead receive unexpected non-reinforcement. This feedback elicits a response known as the *negative reward prediction error signal* in the nucleus accumbens (human ventral striatum), which is manifested by a decrease in phasic dopamine signaling relative to activity during previously rewarded trials (Schultz, Dayan, & Montague, 1997). Human neuroimaging studies have shown increased activation in the ventral striatum in response to unexpected negative feedback (Glascher, Hampton, & O'Doherty, 2009; Rolls, McCabe, & Redoute, 2008). This characteristic response to unexpected non-reinforcement is believed to serve an important role in facilitating adaptive behavior based on performance feedback. In anterior cingulate, a parallel signal reflecting a violation of expectancies is detected in electrophysiological studies, known as the *error related negativity* in human anterior

cingulate cortex (Baker & Holroyd, 2009), a candidate region for integrating this feedback-related information with action planning (Hayden & Platt, 2010).

In humans, the BOLD signal in response to unexpected non-reinforcement has been shown to both increase (D'Cruz et al., 2011; Pagnoni, Zink, Montague, & Berns, 2002; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006) and decrease (D'Ardenne, McClure, Nystrom, & Cohen, 2008). These differences may result from a number of factors including variability in the types of reinforcing cues used, the magnitude of the expectancy violation, the behavioral relevance of the non-reinforcement, or possible punishment in addition to non-reinforcement. The relevance of this mesencephalic-ventrostriatal-frontal circuitry for reversal learning is demonstrated by observations that across species, lesions of the ventral striatum and anterior cingulate result in perseverative responding, i.e., repeated selection of previously reinforced responses, despite these responses no longer being reinforced (Clarke et al., 2008; Ferry, Lu, & Price, 2000; Hasler, Mondillo, Drevets, & Blair, 2009; Newman & McGaughy, 2011).

In ASD, diminished response to reward, including social (Masten et al., 2011; Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack, & Bookheimer, 2010) and monetary reinforcers (Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2012; Kohls et al., 2012), has been reported in ventral striatum and anterior cingulate cortex. Incentives shown to be especially salient for ASD individuals have also cued atypical responses in these reward circuits (Dichter et al., 2012; Sasson, Elison, Turner-Brown, Dichter, & Bodfish, 2011). Whether there are alterations in reinforcement learning circuitry in the context of flexible choice behavior in ASD, and in response to non-rewarding cues, remains to be clarified. Clinically, investigation of reward circuitry is particularly

pertinent to Insistence on Sameness given the reduced impact of cues that typically reinforce and support adaptive flexible behavior.

1.5.3. Integration of Cognitive Shifting and Reinforcement Learning Systems

Reversal learning offers a promising platform for advancing understanding of the interaction of cognitive and affective/motivational brain systems, and their relevance for supporting flexible behavior. There is currently widespread interest in alterations of the interaction of cognitive and affective systems, and its contribution to impaired functioning in clinical populations (Frank & Fossella, 2011; Pavuluri & Sweeney, 2008). This is particularly important in a heterogeneous disorder such as ASD, which is characterized by pervasive and diverse patterns of dysfunction in behavior, mood, and cognition. Thus understanding whether integration of information between the two neurocognitive systems outlined above is impaired in ASD, and how this might affect flexible behavior in ASD, is an important goal for future research.

1.5.4. Concluding Remarks

Whether either cognitive and/or reinforcement learning processes are dysfunctional in ASD in a way that contributes to rigid behavior and cognition has not yet been examined. We developed novel reversal learning paradigms that assessed flexible behavior during functional neuroimaging studies to investigate the relative contributions of these neurocognitive mechanisms to the problem of Insistence on Sameness in ASD.

1.6. Current Study

In the current study, 17 individuals with an ASD and 23 age-, gender-, and IQ-matched healthy control participants performed reversal learning tasks during fMRI. We performed analyses designed to test the two proposed neurobehavioral mechanisms of behavioral rigidity in ASD: (1) impairment in dorsal premotor, prefrontal and parietal cortex, and dorsal striatum, associated with implementing cognitive changes in behavioral set (Cognitive Flexibility model) and (2) impairment in recognizing and responding to changes in rewards that motivate individuals to switch set, associated with ventral striatum and the affective division of anterior cingulate (Reinforcement Learning model). Using a 4-choice reversal learning task and a 2-choice reversal learning control task as in our previous study (D'Cruz et al., 2011), the effect of uncertainty of future outcomes was varied in order to assess whether impairments in flexible choice behavior were more pronounced in ASD when outcomes are uncertain versus certain, and whether this manipulation is accompanied by change in the extent of alteration in brain systems supporting cognitive flexibility and/or reinforcement learning.

Two secondary exploratory analyses were conducted. First, given the multiple previous reports of altered cognitive development in ASD (Luna et al., 2007; Solomon, Smith, Frank, Ly, & Carter, 2011), we tested performance and brain activation in relation to subject age across a broad age range to determine whether there were indications of an altered trajectory in the development of behavioral flexibility and its related functional brain systems in ASD. Second, we investigated the relationship of reversal learning task performance, as well as brain activation during flexible choice behavior, with independently ascertained clinical ratings of Insistence on Sameness in the ASD group.

2. METHODS

2.1. Study Participants

Seventeen individuals with an ASD (5 females) and 23 typically developing controls (5 females) participated in the study (Table I). Individuals with an ASD were recruited from outpatient clinics at the University of Illinois Medical Center and via flyers posted in the community. Participants in the ASD group met cut-off points for an ASD on the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000). The 15 of 17 individuals meeting this criterion that had a parent available to provide historical information also met cut-off points for an ASD on the Autism Diagnostic Inventory-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994). In addition, all participants in the ASD group received a consensus clinical diagnosis of DSM-IV-TR Autistic Disorder (n=7), Asperger's Disorder (n=9), or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS; n=1). There were no performance differences amongst the three diagnostic groups, and therefore ASD participants were pooled for statistical analyses as planned. Control participants were recruited from the community and were required to have a Social Communication Questionnaire score of eight or lower (SCQ; Berument, Rutter, Lord, Pickles, & Bailey, 1999), no personal history of psychiatric or neurologic disorders, and no first- or second-degree relative with a suspected ASD or other familial neuropsychiatric illness. The ASD and control groups did not differ significantly on age, gender, and Full-Scale IQ. All participants were free of medications known to affect cognitive abilities, including antipsychotics, psychostimulants, antidepressants, and anticonvulsants. Participants were at least seven years of age (up to 44 years of age), and had Full-Scale, Verbal and Performance IQs $\geq$ 70.

TABLE I
DEMOGRAPIC AND COGNITIVE CHARATERISTICS OF STUDY PARTICIPANTS

	ASD group (n=17, 5 females)	Controls (n=23, 5 females)	Significance
Age (years)	17.4 (8.6), 9-44	18.6 (8.4), 7-38	*n.s.*
Full-scale IQ	103.9 (15.5), 87-140	110.9 (9.9), 95-133	*n.s.*
Verbal IQ	100.4 (15.9), 71-120	113.0 (10.6), 93-133	*p=.004*
Performance IQ	106.7 (16.6), 84-145	107.5 (9.3), 91-128	*n.s.*

For individuals with an ASD diagnosis, a family member completed the Repetitive Behavior Subscales-Revised (RBS-R; Bodfish, Symons, Parker, & Lewis, 2000), a questionnaire used to assess repetitive, ritualistic, and obsessive-compulsive behaviors in the ASD participants (See Table II for a summary of clinical characteristics of participants in the ASD group). All participants completed informed consent or assent, and study procedures were approved by the Institutional Review Board at the University of Illinois at Chicago.

TABLE II
CLINICAL CHARACTERISTICS OF INDIVIDUALS IN THE ASD GROUP

Clinical Measure	ASD Group Scores
Autism Diagnostic Interview – Revised	
A – Social interaction	20.0 (5.8), 7-29
B – Communication and language	14.7 (4.2), 10-25
C – Restricted and repetitive behaviors	6.3 (2.4), 3-11
D – Severity	2.5 (1.4), 0-5
Repetitive Behavior Scale - Revised	
Stereotypies	3.2 (2.9), 0-8
Self-injury	2.4 (2.6), 0-8
Compulsions	3.1 (3.6), 0-11
Rituals	4.8 (4.7), 0-18
Sameness	9.9 (8.0), 1-28
Restricted interests	4.2 (2.7), 0-10
Total score	27.7 (20.1), 5-69

2.2. fMRI Behavioral Paradigms

2.2.1. 2-Choice Reversal Learning Task

Participants were presented with two identical stimuli (one stimulus each on the left and right side of the display screen) and instructed to select the stimulus that was in the correct location by pressing a button corresponding to its location on the screen (Figure 2). Participants held a button box with four buttons placed on their torso with both hands, and used the two outer buttons to indicate their response choice (left hand for stimulus on the left, and right hand for right stimulus choice). Immediate feedback was provided in the form of check marks (correct) or crosses (incorrect), which appeared directly above the stimulus selected until the end of the trial.

Requirements to change response set were imposed by making the other stimulus location the correct response choice. In order to reduce the predictability of the reversal

in reinforcement contingencies, and therefore the predictability of receiving negative feedback on a given trial, the correct location changed after a variable number (four to six) of consecutive correct responses. Each trial (including presentation of stimulus, participant response, and feedback presentation) lasted for 2.5 seconds, followed by a 500 millisecond inter-trial interval during which a blank screen was presented. 180 trials were presented over a fixed task duration of 9 minutes.

2.2.2. 4-Choice Reversal Learning Task

In the 4-choice task, participants were presented with four identical stimuli placed along the horizontal axis of the display screen (Figure 2). They were told to choose the stimulus that was in the correct location, this time using all four response buttons. Two buttons were assigned to each hand. Each of the four stimulus locations had an equal probability of being the correct stimulus choice. The 4- and the 2-choice tasks were similar, with the following two exceptions. First, in order to reduce demands on working memory imposed by having to keep track of which locations were previously determined to be incorrect response choices, feedback indicating that a response choice was incorrect remained on screen until participants selected the new correct location in a subsequent trial. Second, this paradigm incorporated a predetermined rate of incorrect trials at the point of reversal. When the correct stimulus location changed, the new correct response choice could be at one of the three alternative locations. To ensure similar rates of non-reinforcement amongst participants at the reversal, the first choice was correct on 15% of trials, the second choice was correct on 33% of trials, and the third and final choice was always correct. The 2- and 4-choice tasks were presented in counterbalanced order across participants. There was no effect of the order of task presentation on brain activity or

behavioral measures of task performance, and thus task order was not considered a factor in data analysis.

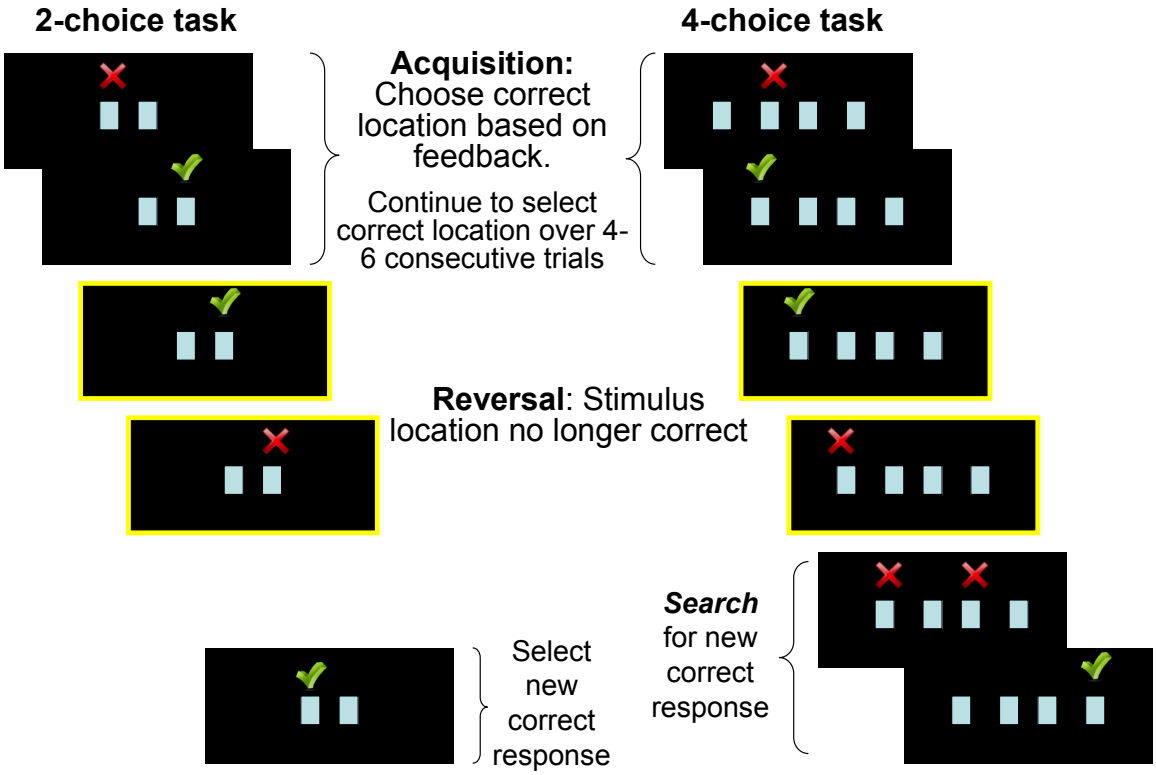

Figure 2. Schematic presentation of 2- and 4-choice reversal learning tasks. Events highlighted show trials selected to examine activation at reversal, i.e. participants' response to unexpected non-reinforcement versus ongoing positive reinforcement of a learned response.

2.3. MRI Image Acquisition

MRI studies were performed using a 3.0 Tesla whole body scanner with a standard quadrature coil (Signa, General Electric Medical System, Milwaukee, WI). Functional images were acquired using a single shot gradient-echo echo-planar imaging sequence (15 axial slices; TR = 1000ms; TE = 25ms; flip angle = 90°; slice thickness =

5mm; gap = 1mm; acquisition matrix = 64x64; voxel size = 3.12mm x 3.12mm x 5mm; field of view (FOV) = 20x20 cm^2; 540 images). This protocol provided a field of view typically extending from the dorsal neocortex to dorsal pons, and therefore covered the neocortical and striatal regions of primary interest. Anatomical images collected to align and register the functional images were acquired with a 3D volume inversion recovery fast spoiled gradient-recalled at steady state pulse sequence (120 axial slices; flip angle = 25°; slice thickness = 1.5mm; gap = 0mm; FOV = 24x24 cm^2).

2.4. Image Preprocessing and Analysis

Event-related fMRI analyses were carried out using FSL 4.1.0 (FMRIB Software Library; S. M. Smith et al., 2004) within the FEAT (fMRI Expert Analysis Tool) and Randomise (http://www.fmrib.ox.ac.uk/fsl/randomize) tools. Brain Extraction Tool (BET) software was used to remove non-brain tissue from each participant's structural images (Smith, 2002). MCFLIRT motion correction was applied to functional datasets (Jenkinson, Bannister, Brady, & Smith, 2002). A high-pass temporal filter with a cut-off of 100 milliseconds was applied to the data. Spatial smoothing was conducted using a Gaussian kernel of full-width half-maximum 6mm. Functional data were registered to the high-resolution structural scan, and then transformed into standard MNI (Montreal Neurological Institute) space using the MNI152 template.

2.5. Modeling of Activation Responses

The time of onset of performance feedback, which immediately followed response choices, was used to identify the trial-wise events of interest for event-related

analysis of the functional time-series data. As indicated in Figure 2, the following epochs of the time-series data were modeled in both the 2- and 4-choice reversal learning tasks: (1) the first instance of non-reinforcement for a learned response at reversal (indicating that participants' previous response set was no longer correct), and (2) expected reinforcement of correct responses (i.e. reinforcement of the second consecutive correct response and all later correct responses in a set). A double-gamma hemodynamic response function was applied to each model.

In order to examine brain activation related to processing unexpected non-reinforcement and planning a behavioral reversal, differences in response to unexpected non-reinforcement and expected reinforcement were contrasted separately for the 2- and 4-choice tasks. For group analyses, FSL's Randomise v2.1 tool was used to generate a test statistic map through permutation-based non-parametric testing. This approach bypasses the problem of multiple comparisons inherent in traditional voxelwise hypothesis testing. Threshold-Free Cluster Enhancement (TFCE; Smith & Nichols, 2009) was used to identify significant clusters of activation without the need to set an arbitrary cluster-size threshold. Specifically, for each group, a nonparametric one-sample t-test with variance smoothing of 6mm FWHM, and TFCE with an experiment-wise Type 1 error rate of $p < .01$, were used to identify clusters of statistically significant activity at reversal. To identify differences in activity at reversal between the ASD and control groups, a non-parametric two-sample t-test with 500 permutations, and the same TFCE procedure and parameters were applied.

2.6. Performance Measures on the Reversal Learning Tasks

In both the 2- and 4-choice tasks, the total number of reversals completed overall, as well as the number of incorrect and correct responses made in each set, were recorded for each participant. Errors following a reversal were classified as either *perseverative errors* or *failures to maintain set*. *Perseverative errors* occurred after reversal in the response-outcome contingency, when participants chose the previously reinforced response before choosing the new correct response. *Failures to maintain set* occurred when participants chose the previously reinforced response after having selected the new correct choice at least once. On the 2-choice task, these responses were effectively regressive errors made back to the previously correct response choice. On the 4-choice task, failures to maintain set could be responses made away from the correct choice to any of the other three possible choices. Thus, the number of perseverative errors provided an index of how quickly a participant shifted their response after reversal, whilst the number of failures to maintain set provided a measure of how well the new correct choice pattern was maintained.

2.7. Correlation of fMRI Data with Clinical Measures and Age

For participants in the ASD group, the relationship of reversal learning performance to clinical manifestations of Insistence on Sameness was examined using clinical ratings of rigid and repetitive behaviors, insistence on routine and obsessive-compulsive symptoms reflected in the total scores from the RBS-R and the ADI-R (using the C algorithm). For the 4-choice task, each participant's peak activation t-statistic value at reversal was extracted from *a priori* regions of interest using existing predefined

masks. Cortical regions including dorsolateral prefrontal cortex, premotor areas, and posterior parietal cortex were described using a mask from our laboratory which has been verified across a number of imaging studies. Because of hypotheses about the relative contribution of cognitive and affective processes to behavioral flexibility impairments, anterior cingulate was subdivided into regions known to have distinct and relevant functional subdivisions, specifically motor cingulate (Picard & Strick, 1996), and cognitive and affective subdivisions of the anterior cingulate (Bush, Luu, & Posner, 2000). Subcortical regions of interest, including ventral striatum, head of the caudate nucleus, insula, and thalamus were defined from pre-existing Harvard-Oxford masks within the FSL analysis package. The peak t-score for each ASD participant in each region of interest was then correlated with the clinical ratings described above. To determine the specificity of any association between behavioral flexibility impairments on the reversal learning tests and clinical ratings of Insistence on Sameness relative to other features of ASD, correlational analyses were conducted to assess the relationship of brain activation at reversal with social and communication deficits using the A and B algorithms of the ADI-R respectively. The relationship of regional brain activation to age and general cognitive function (IQ) was also examined.

3. RESULTS

3.1. Imaging Results

3.1.1. Activation During the 2-Choice Reversal Learning Control Task

For controls in the 2-choice reversal learning task, non-reinforcement of learned responses relative to expected reinforcement of correct responses at reversal trials led to significant activation in bilateral primary visual cortex only (Table III). The ASD group showed significant activation in the 2-choice task at reversal in left motor cingulate cortex, left premotor cortex, and in bilateral posterior parietal cortex (Table III). Comparison of the activation in controls versus the ASD group at reversal, both at the whole-brain level as well as in ROI analyses, yielded no significant group differences in the 2-choice reversal learning task.

TABLE III
REGIONS IN THE TWO-CHOICE REVERSAL LEARNING TASK SHOWING SIGNIFICANT ACTIVATION AT REVERSAL FOR ASD AND CONTROL PARTICIPANTS

Region	Hemisphere	Controls				ASD			
		Max. t-value	Co-ordinates (MNI)			Max. t-value	Co-ordinates (MNI)		
			x	y	z		x	y	z
Motor cingulate	L	--	--	--	--	4.60	-6	6	44
Premotor cortex	L	--	--	--	--	5.47	-58	6	28
Posterior parietal cortex	R	--	--	--	--	4.49	44	-30	44
	L	--	--	--	--	-40	-32	44	5.21
Primary visual cortex	R	5.63	12	-76	-6	--	--	--	--
	L	4.91	-14	-70	-6	--	--	--	--

3.1.2. Activation During the 4-Choice Reversal Learning Task

In controls, significant activation at reversal during the 4-choice task was present bilaterally in ventral striatum, thalamus, insula, motor, cognitive, and affective subdivisions of anterior cingulate, dorsolateral prefrontal cortex, premotor cortex, pre-supplementary motor area, posterior parietal cortex, primary visual cortex, lateral extrastriate cortex and precuneus, and in left caudate and left orbitofrontal cortex (Figure 3, Table IV). In the ASD group, significant activation at reversal was observed in bilateral premotor cortex (Figure 3, Table IV).

TABLE IV
SUMMARY OF REGIONS IN THE FOUR-CHOICE REVERSAL LEARNING TASK SHOWING SIGNIFICANT ACTIVATION AT REVERSAL FOR ASD AND CONTROL PARTICIPANTS

Region	Hemisphere	Controls				ASD			
		Max. t-value	Co-ordinates			Max. t-value	Co-ordinates		
			x	y	z		x	y	z
Ventral striatum	R	5.14	16	14	-6	--	--	--	--
	L	3.84	-14	14	-6	--	--	--	--
Thalamus	R	5.60	10	-18	4	--	--	--	--
	L	5.18	-10	-20	4	--	--	--	--
Dorsal caudate	L	3.76	-10	8	6	--	--	--	--
Orbitofrontal cortex	L	3.88	-28	58	-12	--	--	--	--
Insula	R	6.70	34	26	-6	--	--	--	--
	L	7.86	-30	22	-6	--	--	--	--
Motor cingulate	R	8.81	2	16	40	--	--	--	--
	L	8.87	-2	16	42	--	--	--	--
Anterior cingulate cortex, cognitive division	R	--	--	--	--	--	--	--	--
	L	3.76	-8	22	24	--	--	--	--
Anterior cingulate cortex, affective division	R	4.92	10	38	20	--	--	--	--
	L	3.66	-8	32	20	--	--	--	--
Dorsolateral prefrontal cortex	R	4.04	40	26	26	--	--	--	--
	L	5.47	-46	30	30	--	--	--	--
Premotor cortex	R	7.41	52	8	26	--	--	--	--
	L	7.38	-56	2	30	--	--	--	--
Pre-supplementary motor area	R	4.19	8	0	56	6.37	26	0	50
	L	5.56	-10	2	54	5.45	-24	-6	50
Posterior parietal cortex	R	7.07	46	-30	42	--	--	--	--
	L	8.93	-46	-36	46	--	--	--	--
Primary visual cortex	R	5.15	18	-74	8	--	--	--	--
	L	5.22	-10	-90	0	--	--	--	--
Lateral extrastriate cortex	R	6.38	28	-66	44	--	--	--	--
	L	6.61	-16	68	54	--	--	--	--

Precuneus	R	6.61	10	-70	46	--	--	--	--
	L	5.72	-10	-68	52	--	--	--	--

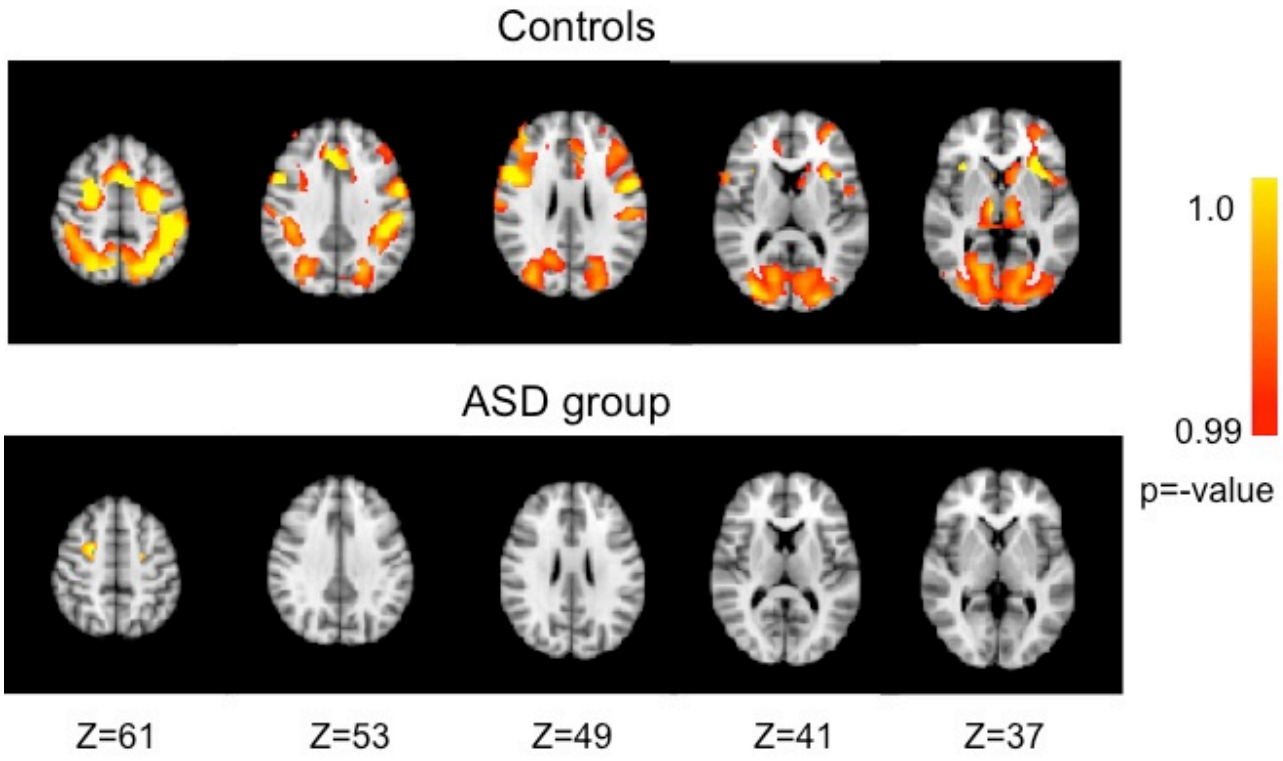

Figure 3. Activation in controls and ASD participants for the contrast of unexpected non-reinforcement versus expected positive reinforcement of a learned response in the 4-choice task.

The activation of each group at reversal was compared to identify brain regions with differential activation in patients versus controls when reversing a learned response to an alternative response with an uncertain outcome on the 4-choice task. Patients showed reduced activation relative to controls at reversal in the following regions: ventral striatum, thalamus, motor, cognitive, and affective subdivisions of anterior cingulate, , premotor cortex, pre-supplementary motor area, posterior parietal cortex, lateral extrastriate cortex and precuneus, and in left dorsolateral prefrontal cortex (Figure 4; Table V).

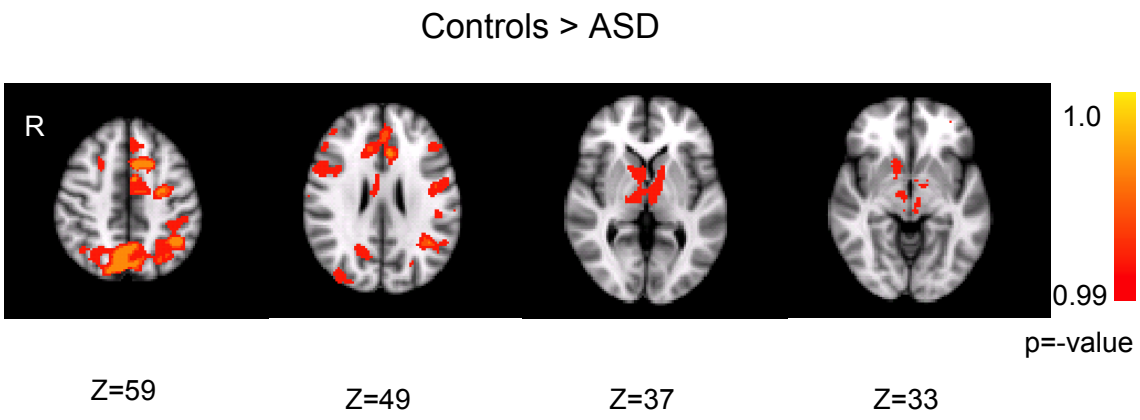

Figure 4. Regions for which significantly reduced activation was observed in the ASD group compared to the control group, for the contrast of unexpected non-reinforcement versus expected positive reinforcement of a learned response in the 4-choice task.

TABLE V
REGIONS FOR WHICH ACTIVATION IN THE 4-CHOICE TASK AT REVERSAL WAS GREATER IN THE CONTROL GROUP THAN IN THE ASD GROUP

Region	Hemisphere	Max. t-value	Co-ordinates (MNI space)		
			x	y	z
Ventral striatum	R	2.98	10	8	-2
	L	--	--	--	--
Thalamus	R	3.05	12	-18	6
	L	3.15	-6	-8	4
Motor cingulate	R	3.40	2	16	40
	L	4.05	-10	12	40
Anterior cingulate cortex, cognitive division	R	3.43	2	34	30
	L	3.59	-2	36	30
Anterior cingulate cortex, affective division	R	3.56	2	36	20
	L	3.86	-2	40	20
Dorsolateral prefrontal cortex	R	--	--	--	--
	L	5.06	-46	30	30
Premotor cortex	R	3.31	40	-8	34
	L	4.29	-28	10	42
Pre-supplementary motor area	R	3.59	2	20	56
	L	3.45	-2	20	56
Posterior parietal cortex	R	2.96	42	-38	46
	L	4.10	-42	-54	46
Lateral extrastriate cortex	R	4.52	32	86	14
	L	--	--	--	--
Precuneus	R	4.40	4	-74	46
	L	3.46	-4	-74	46

3.2. Behavioral Performance Results

In the 4-choice task, the ASD and control groups did not differ in the mean number of reversals completed ($F(1, 38)=1.36$, $p=0.25$) (see Table VI for a summary of performance measures). There was also no difference between the groups in the number of responses labeled "1st Incorrect" ($F(1, 38)=0.96$, $p=0.33$) or "2nd + Correct" ($F(1, 38)=0.13$, $p=0.73$) in the 4-choice task (i.e. the two trial events of interest), such that the

number of responses contributing to fMRI analyses did not differ significantly between the groups.

The ASD and control groups did not differ in their rates of perseverative errors ($F(1, 38)=1.58$, p=0.22) or failures to maintain set ($F(1, 38)=0.99$, p=0.33). In the 4-choice task, a repeated-measures ANOVA of latency by response type (1st incorrect response, 2nd+ correct response) and group (ASD, controls) was conducted. There was no difference in response times between the groups ($F(1, 38)=0.23$, p=0.64), or in the time taken to make the two types of response ($F(1, 38)=2.25$, p=0.14). The interaction of group with response type was not significant ($F(1, 38)=0.03$, p=0.86).

In the 2-choice control task, the ASD and control groups did not differ in the number of reversals made ($F(1, 38)=2.45$, p=0.12), nor in the number of "1st Incorrect" ($F(1, 38)=2.20$, p=0.15) or "2nd+ Correct" responses ($F(1, 38)=0.28$, p=0.60) that contributed to the fMRI analyses. There were no group differences in perseverative errors ($F(1, 38)=3.27$, p=0.08), nor in the number of failures to maintain set ($F(1, 38)=1.98$, p=0.17) on the 2-choice task. A repeated-measures ANOVA of latency of response type in the 2-choice task (1st incorrect response, 2nd+ correct responses) by group (ASD, controls) was conducted. There was no difference in response times between the groups ($F(1, 38)=0.37$, p=0.55), or in the time taken to make the two types of response ($F(1, 38)=0.06$, p=0.81). The interaction of group with response type was not significant ($F(1, 38)=0.56$, p=0.55).

TABLE VI
SUMMARY OF PERFORMANCE MEASURES FOR ASD PARTICPANTS AND CONTROLS ON THE 4- AND 2-CHOICE REVERSAL LEARNING TASKS

	ASD Group	Controls	Significance
4-choice task			
Number of reversals	23.7 (1.7), 20-26	24.3 (1.8), 19-26	*n.s.*
Perseverative errors	1.1 (1.7), 0-6	0.5 (1.3), 0-5	*n.s.*
Failures to maintain set	4.7 (5.3), 0-17	3.0 (5.1), 0-22	*n.s.*
2-choice task			
Number of reversals	27.8 (4.6), 13-33	30.0 (3.7), 21-33	*n.s.*
Perseverative errors	7.1 (9.0), 0-38	3.2 (4.6), 0-17	*n.s.*
Failures to maintain set	7.8 (9.0), 0-40	4.4 (6.1), 0-24	*n.s.*

3.3. Correlation of Clinical Measures with Reversal Learning Performance

For each participant in the ASD group, the peak activation during reversal in the 4-choice task was extracted from key regions of interest (described above, see Section 2.7) and correlated with each individual's score on clinical measures assessing Insistence on Sameness behaviors (ADI-C subscale, and RBS-R subscale and total scores). Non-parametric correlation analysis (Spearman's rho) was used to account for the non-normal distribution of patients' clinical scores. Correlations of brain activation at reversal with all clinical ratings on Insistence on Sameness were not significant in any cortical or subcortical regions of interest. Additionally, there was no significant relationship between measures of social and communication deficits as measured by the ADI-R A- and B-subscales respectively with brain activation during 4-choice reversal learning task in the ASD group. Behavioral performance measures, such as the number of errors and reaction times, were also unrelated to any clinical rating measures.

3.4. Developmental Analyses

In order to examine whether age was related to the magnitude of brain activation during reversal of learned responses in ASD and typical development, non-parametric

correlational analyses of age with peak activation in the ROIs described above was carried out separately for the ASD and control groups. There was no significant relationship between age and activation in any ROI at reversal in the 4-choice and 2-choice control tasks for either group. In both tasks, no relationship was found between age and performance measures, including trials to achieve acquisition and reversal criteria, perseverative errors, and failures to maintain set. Performance and brain activation measures were not related to participants' full-scale IQ for on either task for either group.

4. DISCUSSION

The current fMRI study used a reversal learning paradigm to examine the functional integrity of brain circuitry supporting flexible choice behavior in ASD. When changing from a learned response preference to a new response choice, the ASD group demonstrated reduced activation relative to controls in a number of brain regions including; 1) ventral striatum, which supports reinforcement learning processes; 2) cognitive and affective subdivisions of anterior cingulate cortex that support decision making and performance monitoring; 3) frontoparietal areas supporting spatial attention; and 4) frontal lobe motor planning systems. An attenuated response in ventral striatum to non-reinforcement cues that signal a need to change behavior may contribute to reduced bottom-up drive to rostral frontal and dorsal parietal attention and alerting systems, and a subsequent failure to attend to possible new response options. A reduced response to non-reinforcement could also impair cognitive and motor planning processes, and result in a failure to disengage from a preferred response in order to sustain new adaptive behaviors. This study is the first to provide clarification about impaired functioning in the brain systems underlying flexible choice behavior in ASD, and represents a powerful first step in understanding the neurocognitive substrates of Insistence on Sameness.

Importantly, the functional deficits we observed in frontostriatal and parietal systems were specific to task conditions in which the outcomes of future choice behaviors were uncertain; deficits were not seen when the outcomes of new response patterns were fully predictable. Thus from a clinical perspective, behavioral flexibility problems may be particularly pronounced when several alternative responses must be generated and selected from. This may contribute to a worsening of rigid behavior and

Insistence on Sameness symptoms in novel situations, in which the outcomes of future behaviors are ambiguous.

4.1. Neurocognitive Models of Flexible Choice Behavior

The findings from the present study suggest that behavioral flexibility deficits in ASD could arise from a number of different and interacting alterations in the brain systems that support cognitive decision-making, motor planning, and reinforcement learning. We did not detect altered activation in any one distinct brain circuit in ASD in relation to implementing new choice behaviors after reversal, which suggests that there is not a selective impairment of any one of these brain systems. Instead, the current findings indicate a deficit in integrating information between affective and cognitive systems, which is necessary in order to successfully and flexibly adapt behavior to changing environmental contingencies.

Behavioral shifting, motor planning, and response inhibition processes are subserved by dorsal striatum, the cognitive division of anterior cingulate cortex, rostral frontal midline regions including the pre-supplementary motor area and motor cingulate, and dorsolateral prefrontal cortex. In contrast, reinforcement learning is more reliant upon limbic cortex, especially ventral striatum and its projections to the affective subdivision of anterior cingulate and ventromedial prefrontal cortex. Parsing out the role of the components of these circuits in flexible choice behavior may shed more light on the potentially differentiable causes and treatments of behavioral rigidity in ASD.

4.1.1. Cognitive Components of Response Shifting

Successful reversal learning requires several interacting cognitive processes including the ability to inhibit prepotent response tendencies, and to select and engage in new adaptive response patterns. When participants reversed learned responses, we observed activation in typically developing controls in regions known to be involved in motor planning and attention, including dorsolateral prefrontal, premotor, and posterior parietal cortices. Significantly reduced activation of these regions in the ASD group indicates a deficit in recruiting the neurocognitive systems necessary for withholding learned response patterns, and/or planning and enacting new adaptive responses.

Reduced activation of dorsolateral prefrontal cortex in the ASD group may indicate impairments in a number of cognitive processes supported by this region that are necessary for flexibly updating behavior. The role of dorsolateral prefrontal cortex in withholding prepotent response tendencies (Kenner et al., 2010; Velanova et al., 2008; Xue et al., 2008) suggests that a deficit in response inhibition may contribute to difficulty disengaging from preferred responses in ASD. This is consistent with previous reports of response inhibition deficits in ASD (Goldberg et al., 2002; Langen et al., 2012; Minshew, Luna, & Sweeney, 1999; Mosconi et al., 2009). Inhibition deficits on an anti-saccade task, which is known to place a high demand on dorsolateral prefrontal cortex, have been related to restricted and repetitive behaviors in ASD (Mosconi et al., 2009). The findings in the present study are the first to indicate a neural mechanism by which such deficits adversely impact the ability to engage in new choice behaviors.

A similarly reduced activation in ASD at reversal was seen in the posterior parietal cortex and precuneus, which play a prominent role in supporting visual attention

processes (Cavanna & Trimble, March 2006; Merriam & Colby, 2005). In ASD, a lack of adequate attention to alternative response options may reduce the likelihood that individuals attend to and select alternative response patterns over known and preferred alternatives. This could sustain learned response preferences over available alternative responses, and contribute to rigid patterns of behavior in ASD.

The ASD group also showed reduced activation at reversal in the 4-choice task in a number or regions involved in motor planning. For instance, alterations were seen in activation of the pre-supplementary motor area, which is immediately rostral to the supplementary motor area; by integrating inputs from prefrontal cortex with information from premotor cortex concerning action planning, pre-supplementary motor area is associated primarily in planning voluntary behavior. Consistent with 4-choice reversal learning, in which several alternative plans must be evaluated at reversal, the pre-supplementary motor area is implicated in generating and updating internally generated motor plans (Halsband, Matsuzaka, & Tanji, 1994; Shima, Mushiake, Saito, & Tanji, 1996). This region is also observed in tasks where there is a concomitant shift in both response strategy and behavior, and is believed to integrate cognitive decision-making processes with corresponding shifts in response plans (Hartstra, Oldenburg, Van Leijenhorst, Rombouts, & Crone, 2010; Konishi et al., 2011). Our findings suggest that alterations in the function of the pre-supplementary motor area may result in difficulty in deciding to shift behavior and subsequently in planning new responses, which may contribute to reduced behavioral flexibility in ASD.

In addition, several other areas that are associated with the higher-order control of motor output were less active in the ASD group at reversal. For instance, the ASD group

also showed reduced activation in motor cingulate cortex (Picard & Strick, 1996). Like the pre-supplementary motor area, the cingulate supports the integration of cognitive decision-making processes with motor planning, and has been shown to be engaged during reversal of conditioned associations (Paus, Petrides, Evans, & Meyer, 1993). Activation of the cognitive subdivision of the anterior cingulate is consistently reported in tasks requiring action selection and decision-making in the context of competing attentional demands (for a review, see Bush et al., 2000). Reduced activation in motor cingulate at reversal may suggest a deficit in managing competing information regarding possible alternative response choices, and disrupt the ability to effectively engage in new behavioral plans.

There was no significantly reduced activation of the caudate nucleus at reversal in the ASD group relative to controls. In light of animal models of reversal learning, the failure to detect an abnormality in this region may highlight the specificity of deficits in neural systems supporting behavioral flexibility in ASD. In rodents, inactivating dorsomedial striatum selectively impairs reversal learning by causing an increase in the rate of failures to maintain new response sets without increasing perseverative errors immediately after reversal (Ragozzino & Choi, 2004; Ragozzino, Jih, & Tzavos, 2002). Thus the caudate nucleus appears to be important for sustaining new response patterns over time. In a previous study using the same task in typically developing controls, the caudate was activated at reversal of learned responses (D'Cruz et al., 2011). In the current study, caudate activation in controls was lower in intensity than activation in other regions of interest, meaning that significant differences between the groups may have been harder to detect.

The distribution of reduced activation in our task comprises ventral striatum and dorsolateral prefrontal cortex but not dorsal caudate, and is suggestive of failure in brain systems needed to inhibit learned responses and initiate new response choices, rather than deficits in sustaining new adaptive behaviors, as contributing to behavioral flexibility impairments in ASD. Whereas ventral striatum is involved in detecting a need to update behavior due to changes in reinforcement contingencies, dorsal striatum is more robustly engaged when individuals perform well-learned motor sequences or habitual response patterns (Everitt & Robbins, 2005; Vanderschuren, Di Ciano, & Everitt, 2005; Yin, Knowlton, & Balleine, 2004). In the present study, response sets involved short sets of simple button presses which may have attenuated the signal in dorsal striatum in both patients and control participants, and resulted in a failure to detect significant differences in activation between the groups.

Together, our results indicate that when flexibly shifting behavior, there is a disruption in the cognitive, motor and attentional systems needed for planning and organizing new responses in ASD. With regards to clinical manifestations of Insistence on Sameness, deficits of this nature could impair the ability to disengage from well-learned behaviors in order to generate and sustain new behavioral responses when preferred responses are no longer contextually adaptive.

4.1.2. Reinforcement Learning Processes in Response Shifting

The ability to appropriately respond to unexpected non-reinforcement, which cues participants to change a learned behavior to a new adaptive response, is crucial for reversal learning. In the present study, during reversal trials on the 4-choice task, i.e. when expected reinforcement was not received, reduced activation in the ASD group

relative to controls was observed in the ventral striatum and the affective subdivision of the anterior cingulate. Our results suggest that there may be a reduced alerting response to cues that signal changes in behavior, which demand attention and subsequent planning for voluntary action. Functional alterations in the cognitive division of anterior cingulate cortex in ASD are commonly reported in tasks involving error and performance monitoring (Agam et al., 2010; Henderson et al., 2006; Santesso et al., 2010; Sokhadze et al., 2010; Thakkar et al., 2008; Vlamings, Jonkman, Hoeksma, van Engeland, & Kemner, 2008). Clinically, a diminished response to signals indicating a change in the environmental contingencies for a given behavior could sustain well-established patterns of behavior that are no longer reinforced over new responses that would be rewarded.

Another possibility is that there is a generalized insensitivity to a broad range of reward cues in ASD, independent of their valence. This is consistent with recent studies that suggest a reduced response in ventral striatum and anterior cingulate to secondary reinforcers such as positive social cues, money, and personally rewarding stimuli (Dichter et al., 2012; Groen et al., 2008; Kohls et al., 2011; Scott-Van Zeeland et al., 2010). The current results extend these previous findings to suggest that non-reinforcement also triggers a less robust response in ventral striatal and affective cingulate reward circuits in ASD. Together these results suggest widespread deficits in responding to, and learning from, a broad range of reinforcers in ASD. In light of the present findings, reward processing deficits may play a specific role in rigid behavior in ASD by sustaining learned responses even in the face of feedback that conveys that an alternative response strategy would be more likely to be positively reinforced.

It is important to note that prior studies of reward circuitry function in ASD have examined the response to positive reinforcers such as reward: this is the first study to examine the limbic response to unexpected non-reinforcement. Our finding of reduced activation in reinforcement learning systems demonstrates that a blunted response to non-reinforcement may also be present in ASD. This could contribute to deficits in self-monitoring and flexibly adapting behavior in response to environmental cues.

4.1.3. Integration of Cognitive and Affective Processes in Behavioral Flexibility

The pattern of functional alterations in cognitive decision-making and motor response planning regions, together with deficits in the limbic circuitry supporting reinforcement learning, suggests that an impaired interaction of these systems may contribute to behavioral flexibility deficits in ASD. The ventral striatal and affective cingulate deficits in the ASD group may indicate reduced bottom-up drive from limbic circuitry in response to unexpected non-reinforcement that cues a change in behavior by dorsal cognitive systems. When reinforcement is expected but is not received, there may be a reduction in the dopaminergic signals that propagate from the ventral tegmental area to the ventral striatum and anterior cingulate cortex. This could result in a corresponding reduction in activity upstream in alerting, attention, and motor planning systems. For instance, there may be a subsequent failure to adequately engage decision-making and motor planning processes, via projections from anterior cingulate to dorsolateral prefrontal cortex, and midline cognitive and motor integration centers, such as the pre-supplementary motor area and motor cingulate cortex. Ventral striatum also has direct inputs to motor and cognitive subdivisions of the anterior cingulate cortex, so an attenuated limbic response could reduce the drive and capacity to generate new motor

plans. Thus rigid patterns of behavior could arise when environmental cues signal the need to change responses, at least in part, from reduced drive from limbic structures to frontal and parietal cortex.

Several brain regions in which the ASD group showed deficits at reversal have been implicated in supporting the interface of cognitive and motivational processing. For instance, in addition to its role in distinct cognitive, motor, and affective functions, the anterior cingulate cortex is also a candidate region for integrating feedback-related information with action planning, and updating expectations about response-outcome contingencies (Bush et al., 2000; Hayden & Platt, 2010; Hillman & Bilkey, 2010). ASD individuals may engage in repetitive patterns of behavior if information regarding response-outcome contingencies is not integrated with plans for potential new adaptive actions.

A direct link between reward processing and the motor planning and attentional components of behavioral control has been reported in both humans and non-human primates. Specifically, reward magnitude modulates the accuracy and latency of saccadic eye movements (Ross, Lanyon, Viswanathan, Manoach, & Barton, 2011; Uchida, Lu, Ohmae, Takahashi, & Kitazawa, 2007). In addition, several studies have shown that as the relevance of external cues for future behavior increases, there is an associated increase in activation seen in dorsal premotor and parietal attention systems (D'Cruz et al., 2011; Egner et al., 2008; Zenon, Filali, Duhamel, & Olivier, 2010). Thus a problem with effectively representing environmental reinforcement contingencies in frontal motor planning areas in ASD may also contribute to the pattern of activation we observed.

Taken together, the well-documented relationship between the relevance of motivational cues with activity in cognitive decision-making, motor planning, and attentional systems suggests that reduced bottom-up drive from reinforcement learning systems may account for distributed pattern of frontostriatal dysfunction we observed. An attenuated response to non-reinforcement that signals the need to change behavior may lead to under-recruitment of the frontal and parietal systems required to plan and enact new response plans.

4.2. The Role of Uncertainty on Behavioral Flexibility in Autism Spectrum Disorders

A critical advantage of our study was the ability to examine flexible choice behavior in ASD under circumstances in which the outcomes of response choices were certain and uncertain. In a previous study using the same tasks in typically developing control participants, we demonstrated that greater uncertainty of future outcomes resulted in increased activation in the dorsal and ventral frontostriatal circuitry required to respond to changes in environmental contingencies and correspondingly shift response plans. In the present study, only behavioral reversals in the 4-choice task, i.e. reversals during uncertain circumstances, failed to elicit this typically increased response in frontal, striatal, and parietal systems in ASD: there was no difference in activation between the groups in the 2-choice task. An impairment in generating the heightened response expected when future behavioral outcomes are uncertain could contribute to a worsening of rigid behavior in novel or unexpected situations in ASD. Thus behavioral flexibility deficits may be particularly pronounced in ASD when reinforcing cues signal the need

for increased attention to the environment and subsequent action planning, as could be the case when adapting behavior to uncertain circumstances.

Difficulty adapting behavior when using several possible response plans implicate a number of altered cognitive processes in ASD. For instance, reduced activation in dorsolateral prefrontal cortex in ASD in the 4-choice task might indicate a broader pattern of frontal systems dysfunction, in which executive deficits associated with planning and organizing multiple possible response plans impairs the ability to manage and select alternative behavioral strategies. When multiple alternative response options are available, attentional demands increase because of the need to attend to several different environmental cues to select a new response. In addition, alternative action plans must be developed and effectively integrated with decision-making processes in association areas such as the pre-supplementary motor area.

The absence of group differences in activation in the 2-choice reversal learning task could indicate that the processes supporting behavioral flexibility are unimpaired in ASD when new response strategies are well-defined and certain to be correct. This interpretation is consistent with our laboratory reversal learning study, in which on a 2-choice non-probabilistic training task, ASD individuals were able to adequately reverse a learned response when all responses were accurately reinforced. It is also possible that, as in our study of typical development using these same tasks, 2-choice reversal learning elicits much less activity in cognitive and reward circuits than 4-choice tasks (D'Cruz et al., 2011), which may make it difficult to detect group differences in the 2-choice task in the present clinical study. Unthresholded activation maps were explored in order to investigate the possibility that sub-threshold effects of interest might be observed in the

data. The data were not consistent with the idea that a lack of power resulted in a failure to detect group differences in the 2-choice task. Thus the specificity of impairments in the current study to the 4-choice task suggests that uncertainty of future outcomes selectively and uniquely affects flexible choice behavior in ASD.

4.3. Reversal Learning Behavioral Performance

No deficits in reversal learning task performance were detected in the ASD group relative to controls. This could mean that intradimensional reversals in behavior on tasks in which there is accurate reinforcement for all responses are unimpaired in ASD, consistent with some current literature (Corbett, Constantine, Hendren, Rocke, & Ozonoff, 2009; Goldstein, Faeder, & Hlavacek, 2004; Goldstein, Johnson, & Minshew, 2001; Hughes, Russell, & Robbins, 1994). However the tasks used in the current study were designed to minimize performance differences between the patients and controls in order to maximize the ability to interpret activation differences between the groups. Other studies do document impaired intradimensional shifts using probabilistic (D'Cruz et al, under review) or other spatial reversal learning tasks (Coldren & Halloran, 2003; Lionello-Denolf et al., 2008). Thus the use of a more demanding reversal learning paradigm, and/or a more clinically impaired group of ASD participants, might elicit performance deficits but would complicate the interpretation of altered brain activity.

4.4. Relationship of Reversal Learning to Clinical Symptoms

In our study, we did not detect a relationship between clinical measures of Insistence on Sameness with either reversal learning performance or brain activation.

This highlights a particular challenge of clinical functional imaging studies mentioned above, in which a lack of performance impairments is preferable for interpreting brain activation differences but limits the variability required to look at clinical correlations. The variable levels of deficit that might be seen on a more challenging reversal learning task might make it easier to detect meaningful activation by performance correlations. However this would significantly weaken the primary aim of this study, which was designed to establish whether there were differences in brain functions supporting reversal learning between ASD individuals and controls. However, now that the impairments in neural systems are established, future studies could parametrically vary task difficulty to better assess links between neurocognitive and clinical profiles in ASD.

Another factor that limits the ability to detect significant relationships with clinical symptoms is the relatively small variance in the clinical ratings of behavioral and cognitive rigidity for our ASD group. This limited range of symptom severity is unsurprising, since only older and relatively higher functioning individuals were able to successfully meet the demands of an fMRI scanning session. Individuals with high anxiety or difficulty not moving during scans were unable to complete an MRI study, and these may also be the individuals for whom rigid behavior is a prominent clinical feature.

Methodological issues inherent in functional imaging studies may also account for a difficulty detecting correlations in brain activation with clinical symptoms. Individual variability in BOLD responses related to neurovascular coupling rather than neuronal activity account for a significant proportion of between-subject variance (Garrett, Kovacevic, McIntosh, & Grady, 2010; Kannurpatti, Motes, Rypma, & Biswal, 2011). An additional source of variability in brain data comes from the decision to include

participants across a broad range of ages. Participant age was not significantly correlated with brain activation for either group in either task. However, differences in brain anatomy and physiology, including head size and vascular development, can increase noise in the BOLD signal. Together, these factors (discussed further in the next section) can lead to an underestimation of correlations with clinical measures that themselves often have imperfect validity and reliability. How best to account for these factors when conducting research studies in more severely impaired patient populations is the focus of current discussion and research in the field of clinical neuroimaging (Matthews, Honey, & Bullmore, 2006). With appropriate regard to those considerations, no significant relationships between task performance or activation effects with clinical features of autism were identified in the present study.

4.5. Effects of Development on Behavioral Flexibility

Whereas most functional brain imaging studies have modest sample sizes focused on a specific age range, the current study was unusual in its scope in that it was designed to examine behavioral flexibility across a wide span of ages in exploratory analyses. Results from the current study were not indicative of significant age-related changes in reversal learning performance and corresponding brain activation across development. Interpreting "non-effects" is dangerous, as methodological issues may limit the ability to positively detect such effects. However, one might well believe that prominent age-related effects could be examined if they were robust in either subject group, which was not the case in the current study. The sampling bias inherent in fMRI studies of ASD may have made it difficult to detect delayed maturation of cognitive and brain

functioning, because such deficits might be most prominent in early to mid-childhood. Very young individuals are typically unable to meet the demands of a functional imaging scan session, so a study such as the present investigation using fMRI would not be well positioned to detect early neurodevelopmental alterations. Further, it is important to note that non-significant age-related deficits are specific to the task and cognitive domain evaluated in the present study. In the previously mentioned laboratory study with probabilistic reversal learning (D'Cruz et al., under review), individuals with an ASD who were under 14 years of age performed more poorly on a probabilistic reversal learning study than did age-matched controls. This suggests that at least some processes associated with flexible choice behavior may have an altered developmental trajectory in ASD. Approaches like those of the current study that use relatively simple and easily translatable cognitive paradigms, provide a promising platform for the further work in younger individuals, which is needed to clarify any early developmental alteration in the neurocognitive substrates of Insistence on Sameness.

4.6. Previous Studies of Reversal Learning in Autism Spectrum Disorders

In my independent behavioral study of probabilistic reversal learning in ASD described in the Introduction, ASD individuals demonstrated impaired task performance, including difficulty maintaining new response strategies after reversal. In addition, ASD individuals frequently changed from a correct to an incorrect response after receiving unexpected and inaccurate non-reinforcement in the reversal phase of the task. Together, those findings suggest that there is difficulty maintaining new adaptive behaviors in ASD, which may be exacerbated by a heightened sensitivity to non-reinforcement. On

the surface, this stands in contrast with the present imaging findings that suggest a reduced response in reinforcement learning circuits to non-reinforcing cues that signal a change in behavior.

Fourteen of the 17 ASD participants, and 21 of the 23 controls in the present study also completed the probabilistic reversal learning task described above in the laboratory. In an exploratory analysis, we examined the task performance of this smaller subset of participants, and failed to find any probabilistic reversal learning impairments. In addition to the current sample comprising an overall higher functioning and older group of individuals than those in the previous laboratory study, a number of differences between the behavioral and fMRI tasks could account for the discrepancies in behavioral findings between the two studies.

In the probabilistic reversal learning task, individuals completed a greater number of correct responses (eight out of ten consecutive correct choices) before reversal than in the 2- and 4-choice tasks used in the present brain imaging study (four to six correct choices). This could mean that unexpected non-reinforcement at reversal in the probabilistic task generated a heightened alerting response that was less prominent when shifting away from a less-established response pattern in the fMRI task. Second, in the probabilistic task, intermittent non-reinforcement for correct responses was presented throughout. The more frequent violations of reward expectancies on the task performed during laboratory studies could have also heightened the response to unexpected non-reinforcement. Correct response choices on the probabilistic task were reinforced with coins, whereas potentially less rewarding stimuli were used as reinforcers in the imaging task (check marks and crosses). It is possible that a less-diminished response to non-

reinforcement in ASD may have been observed in the imaging task if more salient reinforcers were used.

It is important to note that non-reinforcement cues carry different information in the fMRI and laboratory tasks. In the deterministic fMRI paradigm, non-reinforcement always signals that a change in response is appropriate. In contrast, non-reinforcement in the probabilistic task is misleading on 20% of trials, and does not indicate that a shift in behavior is needed. Thus there may be a deficit in ASD in accurately identifying and ignoring inaccurate non-reinforcement cues. This could result in an attenuated response to behaviorally relevant non-reinforcement seen in the fMRI study, and the heightened response to misleading non-reinforcement on the probabilistic task. Future studies are needed to clarify the role of altered processing of different types of reinforcement and non-reinforcement cues and its impact on flexible choice behavior in ASD.

4.7. Behavioral Performance and Functional Brain Alterations

In the present study there was an absence of behavioral task performance deficits in the presence of prominent functional alterations in brain circuitry. Whilst a lack of performance deficits is advantageous in that brain deficits are more readily interpretable as discussed above, such results also limit the ability to determine the relevance of the observed functional alterations for real-world behavior and clinical symptoms of interest. Neuroimaging may be a particularly sensitive tool for characterizing neurocognitive dysfunction over neuropsychological task performance. Further, there are no assessment tools or questionnaires directly targeted at measuring Insistence on Sameness. The brain activation alterations in the current study could indicate a fundamental neurocognitive

deficit in flexible choice behavior that may underlie this clinical feature. The pattern of alterations suggests domains of function that should be addressed in the development of future clinical assessment tools.

4.8. Future Directions

The present study provides strong evidence for dysfunction in ASD in the distributed frontostriatal systems that subserve flexible behavior by supporting cognitive processing and reinforcement learning. The findings thus provide a promising platform for future studies into the cognitive and biological bases of Insistence on Sameness. Future studies might examine the functional ways in which a reduction in motivational signaling in the limbic system may influence neocortical cognitive and motor systems, through both neurochemical and neuroanatomical pathways. Neuropsychological and imaging studies, as well as animal models, are needed to parse apart the roles of the two neurocognitive systems targeted in the present study and their contribution to the clinical problems associated with rigid behavior in ASD.

4.8.1. Future Clinical Studies of Neurocognitive Models of Insistence on Sameness

One way to assess the ways in which cognitive response shifting processes are impaired in ASD could be to use tasks that place a greater demand on these systems than did those used in the current study. This might be achieved by parametrically increasing the number of correct responses required prior to reversal of the response-outcome contingency, or by probabilistically reinforcing responses. Activity in cognitive and motor systems, including dorsal caudate, cognitive and motor cingulate, and the pre-supplementary motor area could be examined during early and later responses in a set

given a sufficient number of trials before reversal. In this way it would be possible to assess whether there was difficulty in initial shifting to new responses or consistently maintaining a new response set over time, as was the case in probabilistic reversal learning task mentioned previously (D'Cruz et al., under review). Given the role of the caudate nucleus in supporting habitual behavior (Bischoff-Grethe, Goedert, Willingham, & Grafton, 2004), recruitment of dorsal striatum during reversal learning might be achieved by requiring shifts in behavior away from well-learned motor sequences to novel response patterns.

A parallel reinforcement learning task without reversals would be useful in assessing the integrity of ventral striatal and frontal reward systems. Most important from the perspective of behavioral flexibility would be a probabilistic reversal learning paradigm during fMRI. This approach would allow for an assessment of the ventral striatal and affective cingulate response to unexpected non-reinforcement when it cued a need to shift responses, as well as when it was irrelevant for future choice behavior. However, using probabilistic tasks during fMRI in a clinical sample may be challenging given the increased difficulty associated with establishing and shifting a response in these tasks, and because of expected performance differences that would complicate interpretation of the brain imaging data.

4.8.2. Future Translational Studies of Behavioral Flexibility

Importantly, studies of reversal learning are readily conducted in rodent models, and thus are a useful methodology for translational approaches assessing potential mechanistic neurobiological models of behavioral inflexibility and evaluating drug effects on behavioral deficits (Brown, Amodeo, Sweeney, & Ragozzino, 2012;

Ghahremani et al., 2010; Glascher et al., 2009; M. E. Ragozzino, Mohler, Prior, Palencia, & Rozman, 2009). The 2-choice and multi-choice reversal learning studies presented here were designed to have strong parallels with T-maze and radial maze studies of reversal learning in rodents. For instance, animal models could be a useful approach for developing biochemical models of how reduced drive from limbic circuits could maintain preferred behaviors. Such models could also provide a better understanding of the neurochemistry of regions of interest that are crucial in flexibly adapting behavior and their sensitivity to targeted pharmacologic treatments. For instance, reversal learning studies could be used to assess whether dopaminergic agents modulate activity in ventral striatum in order to facilitate flexible choice behavior.

Both laboratory-based and imaging studies of reversal learning paradigms may be a useful tool in characterizing patients' neurocognitive profile of Insistence on Sameness behaviors, in conjunction with clinical interview and traditional neuropsychological testing. In clinical pharmacologic studies with patients, reversal learning fMRI studies may detect post-treatment changes in the brain that are the direct target of drug intervention.

4.8.3. Considerations from the Current Study

A number of issues were raised in the current study that future studies of behavioral flexibility in ASD can address. For instance, in order to better characterize the role of development on flexible choice behavior, studies with larger samples of ASD individuals across a wide range of ages are needed. The inclusion of more impaired and clinically heterogeneous groups will help to identify whether symptoms are related to altered brain function.

To better understand the relationship of brain deficits to behavior, tasks that are more likely to elicit performance differences, such as probabilistic reversal learning, are needed alongside simpler reversal learning paradigms. An important trade-off in all imaging studies of clinical populations, and especially those involving particularly young or impaired patients, is significantly modulating task difficulty whilst still ensuring that patients with a range of cognitive and functional impairments are able to adequately perform the test. Although this presents a challenge again from a scanning standpoint, improvements in methodologies, such as motion correction algorithms and better signal-to-noise ratio, will make these studies more feasible.

Finally, the current reversal learning study yielded not only important neurocognitive findings but also necessitated the development of a novel methodology for assessing behavioral flexibility. Translating these studies to other clinical populations in which rigid behavior and cognition is a hallmark, such as OCD, will help to clarify the specificity of impairments in components of frontostriatal circuitry to ASD or their generizability across disorders (D'Cruz et al., 2011).

4.9. Concluding Remarks

In sum, this is the first study to identify specific functional alterations in brain circuitry during response shifting in ASD, and to suggest mechanisms by which these deficits may contribute to clinical manifestations of behavioral rigidity and Insistence on Sameness. The results suggest that in ASD, there is an impairment in the interaction of limbic, cognitive, and motor systems that respond to changes in environmental contingencies and adapt behavior accordingly. Reduced performance-related error

signals in ventrostriatal feedback processing systems could fail to provide bottom-up drive to attention and motor planning areas, and impede the flexible selection and planning of future behavior. This could manifest clinically as rigid patterns of behavior that are not contextually adaptive which contributes to the profile of Insistence on Sameness characteristic of ASD. Studies of reversal learning can also be readily conducted in rodent models, and thus represent a useful translational strategy for testing mechanistic hypotheses about the neurobiology of behavioral rigidity and its pharmacologic treatment. As such, our findings inform understanding of a clinical dimension of ASD for which effective treatments are not yet available, and suggest important new approaches and targets for clinical assessment and intervention.

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PUBLICATIONS

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