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Title: The Neural Circuitry of Restricted Repetitive Behavior: Magnetic Resonance Imaging in Neurodevelopmental Disorders and Animal Models

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PII: S0149-7634(17)30553-5
DOI: https://doi.org/10.1016/j.neubiorev.2018.05.022
Reference: NBR 3131

To appear in:

Received date: 11-8-2017
Revised date: 18-4-2018
Accepted date: 20-5-2018

Please cite this article as: Wilkes BJ, Lewis MH, The Neural Circuitry of Restricted Repetitive Behavior: Magnetic Resonance Imaging in Neurodevelopmental Disorders and Animal Models, *Neuroscience and Biobehavioral Reviews* (2018), https://doi.org/10.1016/j.neubiorev.2018.05.022

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The Neural Circuitry of Restricted Repetitive Behavior: Magnetic Resonance Imaging in Neurodevelopmental Disorders and Animal Models

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Highlights

- Mapping the neural circuitry of RRB is in its early stages
- MRI provides needed translational studies of the network connectivity mediating RRB
- MRI findings implicate cortico-basal ganglia and cerebellar circuits in RRB
- MRI studies of animal models of RRB are lacking and sorely needed
- Advanced MRI with *in vitro* neuroscience methods are needed to confirm RRB circuitry

Abstract

Restricted, repetitive behaviors (RRBs) are patterns of behavior that exhibit little variation in form and have no obvious function. RRBs although transdiagonstic are a particularly prominent feature of certain neurodevelopmental disorders, yet relatively little is known about the neural circuitry of RRBs. Past work in this area has focused on isolated brain regions and neurotransmitter systems, but implementing a neural circuit approach has the potential to greatly improve understanding of RRBs. Magnetic resonance imaging (MRI) is well-suited to studying the structural and functional connectivity of the nervous system, and is a highly translational research tool. In this review, we synthesize MRI research from both neurodevelopmental disorders and relevant animal models that informs the neural circuitry of RRB. Together, these studies implicate distributed neural circuits between the cortex, basal ganglia, and cerebellum. Despite progress in

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neuroimaging of RRB, there are many opportunities for conceptual and methodological improvement. We conclude by suggesting future directions for MRI research in RRB, and how such studies can benefit from complementary approaches in neuroscience.

Keywords: Repetitive behavior; autism; developmental disorders; translational; neural networks; brain connectivity; diffusion tensor imaging; functional magnetic resonance imaging; basal ganglia; cerebellum

1. Introduction

Restricted, repetitive behaviors (RRBs) are seemingly purposeless patterns of behavior that exhibit little variation in form, interfere with appropriate behavior, and in some cases may even cause direct harm (e.g., self-injury). RRBs encompass a broad variety of behaviors, including motor stereotypies (e.g., hand-flapping or body-rocking), compulsions, rituals, and circumscribed interests (e.g., fixation on trains or electronic devices). RRBs are often categorized as either "lower-order" repetitive motor behaviors, or "higher-order" repetitive behaviors that are associated with insistence on sameness or resistance to change (Turner, 1999). RRBs are present in a number of human conditions and disorders but the broad range of these behaviors are diagnostic for Autism Spectrum Disorder (ASD) and highly prevalent in syndromic and non-syndromic intellectual and developmental disability (IDD; Flores et al., 2011; Mount et al., 2002; Oakes et al., 2016). It is these disorders of development that will be the focus of this review. As the prevalence of neurodevelopmental disorders, particularly ASD, has dramatically increased over the past two decades (Boyle et al., 2011), RRBs impact a larger portion of clinical populations than ever before. For example, diagnoses of ASD have grown from one in 150 children in the year 2000 to one in 68 children as of 2012 (Christensen et al., 2016). Although behavioral interventions

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have some degree of success in treating RRB (Boyd et al., 2012; Rapp & Vollmer, 2005a; Rapp & Vollmer, 2005b), pharmacological interventions are currently aimed at treating associated problems (e.g., aggressive behavior) and have no demonstrated efficacy for RRB in ASD and IDD (Carrasco et al., 2012; King et al., 2013). This shortcoming is largely due to an incomplete understanding of the neural circuitry mediating RRB.

A great deal of previous research directed toward understanding the etiology and pathophysiology of neurodevelopmental disorders has focused on alterations in specific brain regions, targeted neurotransmitter systems, and/or select genes. Although these efforts have made important contributions toward the current state of the science, much is yet to be learned about mechanisms that mediate RRB in neurodevelopmental disorders. As highlighted by Gunaydin & Kreitzer (2016), recent advances in neuroscience have fostered a shift in thinking as to how various clinical disorders and behaviors are mediated, with evidence pointing to subtle alterations across multiple brain regions, neurotransmitter systems, and synaptic processes that converge as neural circuits. ASD, for example, has been conceptualized by some as a brain network connectivity disorder (Just et al., 2004**)** where the integrated activity of large-scale neuronal networks are impaired. Adopting a neural circuit approach has resulted in great progress in other research areas such as drug-addiction, where convergent circuitry is affected by drugs acting through multiple molecular mechanisms (Kalivas et al., 2006). Similarly, a circuit-oriented approach is likely to provide great utility towards understanding the complex and heterogeneous phenomena of RRB appearing in ASD and related neurodevelopmental disorders. Although little is currently known about how RRB is mediated at the level of neural circuits, previous research in neurodevelopmental disorders (Langen et al., 2011b; Leekham et al.,

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2011; Lewis & Kim, 2009) and animal models of RRB (Ahmari et al., 2016; Bechard & Lewis, 2012; Langen et al., 2011a), suggests a critical role for networks involving the basal ganglia. Previous efforts dedicated to understanding the pathophysiology of RRB in animal models through investigating components of basal ganglia circuitry (e.g., Bechard et al., 2016; Presti & Lewis, 2005; Tanimura et al., 2008, 2010, 2011), have added much to our understanding of this phenomenon, but little work has been done to place these findings in the broader context of large-scale brain networks. The basal ganglia are a point of convergence for multiple large-scale brain networks, but there are also opportunities for basal ganglia and cerebellar networks to interact at the level of cortex, thalamus, and pontine nuclei (see Fig. 1). The complexity of such networks are further evidenced by the existence of multiple functionally distinct cortico-basal ganglia macro-circuits (see Fig. 2).

Magnetic resonance imaging (MRI) provides the best method for non-invasive evaluation of the structure and function of neural circuits in clinical disorders, and has enabled great progress in many areas of clinical research. Moreover, neuroimaging is being increasingly applied to the study of animal models of psychiatric conditions and neurodevelopmental disorders (Lythgoe et al., 2003; Oguz et al., 2012). Prior neuroimaging reviews have described brain alterations in ASD, but did not focus on how these alterations map onto specific behavioral domains such as RRB (e.g., Dichter, 2012; Ecker et al., 2015; Mahajan & Mostofsky, 2015; Müller et al., 2011; Rane et al., 2015). Similarly, although neuroimaging findings from animal models relevant to ASD and IDD have been described (Ellegood et al., 2015; Ellegood & Crawley, 2015), there has been almost no exploration of how these findings pertain to RRB, or other abnormal behaviors, in such models.

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Although a small body of neuroimaging findings related to RRB in ASD has been previously reviewed (Traynor & Hall, 2015), there has been no attempt to synthesize these findings with what is presently known in the literature about the neural circuitry of RRB from other clinical disorders and from relevant animal models. Thus, there is a pressing need for synthesis of findings from multiple neurodevelopmental disorders and corresponding animal models in order to move the field forward. In this review we aim to (1) critically review and synthesize neuroimaging findings from RRB in ASD and IDD and corresponding relevant animal models, (2) determine what these findings, taken together, inform us about the specific neural circuitry of RRB, and (3) suggest future directions for neuroimaging investigations of RRB that have been effectively employed in other areas within neuroscience. Although RRBs are observed in clinical populations other than ASD and IDD (e.g., Tourette syndrome [TS], obsessive compulsive disorder [OCD], drug addiction, frontotemporal dementia), it is beyond the scope of this review to evaluate neuroimaging findings pertinent to RRB in such disorders.

2. Studying Neural Circuitry with Magnetic Resonance Imaging

The use of MRI in neuroscience was initially focused on gross neuroanatomy (e.g., volumetrics) and tissue contrast (e.g., neuro-oncology). Specialized applications of MRI, such as functional and diffusion-weighted MRI, have enabled the study of the interconnected organization of the central nervous system (CNS) and have since become essential tools in neuroimaging. Moreover, the same approaches used for imaging in human populations can be applied to animal models research, enabling a highly translational research environment. Approaches used to acquire and analyze neuroimaging data, including those most

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relevant to studying neural circuitry have been reviewed elsewhere (e.g., Malhi & Lagopoulos, 2007; Yang et al., 2011). Thus, the remainder of this section will only briefly review common imaging modalities and how they are used to study neural circuitry.

2.1. Volumetric MRI

T_1 or T_2 weighted images are often used for volumetric assessment of brain tissue. Regions of interest (ROIs) can be defined using either manual segmentation with a reference atlas, or registration software to apply previously defined ROIs from an MRI segmentation atlas. Alternatively, statistical assessments of relative volumes across all voxels in the brain may be performed independently of neuroanatomical labeling schemas. In deformation-based morphometry (DBM), images are transformed into a common stereotactic space and averaged to generate a study-specific template. Each subject's structural scan is then registered to the study-specific template in order to generate the deformation-field necessary to transform the brain from the subject's native space onto the study-specific template. These deformation fields, which have been demonstrated to correspond with volumetric expansion and contraction, are used as input data for voxelwise statistical analyses of brain volume across groups or conditions (Ashburner et al., 1998). Because statistical comparisons are performed for every voxel, an important component of voxelwise analyses is correction for multiple comparisons (e.g., family-wise error rate, false discovery rate). This approach does not require *a priori* hypotheses about how tissue may differ between groups, and may reveal subtle or unexpected differences that would not be discernable through assessment of specific pre-defined regions of interest (ROIs).

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2.2. Diffusion-weighted MRI

Diffusion-weighted MRI relies upon principles of molecular diffusion, whereby molecules move through space in a temperature-dependent fashion. In biological tissue, diffusion-weighted MRI measures the rate of diffusion of water molecules and provides contrast in tissue with different rates of diffusion, mediated by its microstructural composition. For example, water diffuses at a faster rate along the length of an axon than perpendicular to it. This is due to the presence of barriers to diffusion in the perpendicular plane, such as the surrounding myelin sheath, but also the cellular membrane and microtubules along the length of the axonal process (Beaulieu, 2002).

Diffusion weighting is achieved by applying magnetic field gradients across many different orientations and this has the effect of "sensitizing" the image acquisition to displacements of water in each of these directions. The strength of the applied diffusion gradient and time over which it is applied are described with a scalar unit, *b*, and "*b*-values" are part of common terminology in describing diffusion MRI acquisition parameters (for greater detail, see Yang et al., 2011). Although a minimum of six uniformly distributed diffusion-weighted directions and one low-diffusion weighted (b_0) image are required to estimate diffusion parameters, greater precision is attained with acquisition schemes of at least 20 diffusion weighted images (Jones, 2004).

Diffusion in the brain may be represented as geometric tensors that describe the direction and magnitude of net water diffusion in three orthogonal planes. This use of diffusion-weighted MRI to assess brain tissue is commonly referred to as diffusion tensor imaging (DTI). As indicated above, estimating diffusion tensors benefits greatly from acquisitions with 20 or more diffusion-

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sensitizing directions. For example, High Angular Resolution Diffusion Imaging (HARDI) uses at least 60 diffusion directions, with both high and low diffusion weightings (i.e., b-values). Although imaging times are increased, developments in multichannel radiofrequency coils have reduced scan time significantly for HARDI acquisitions, keeping these within a reasonable time frame for obtaining data quickly in study subjects (e.g., 5-10 minutes with a 32-channel coil). Diffusion tractography allows for assessment of WM fiber bundles that are not evident through gross neuroanatomy, such as parsing of WM fibers in the corona radiata based on their origin and efferent targets (Smith et al., 2004). Tractography improves as spatial resolution increases (i.e., smaller slice thickness) and with better estimates of diffusion parameters, achieved through a larger number of diffusion directions and/or higher magnitude of gradient pulses (b-values).

Two of the most common metrics from diffusion-weighted MRI are mean diffusivity (MD) and fractional anisotropy (FA). MD provides a quantification of the average rate of water diffusion across all three orthogonal planes, and is often further broken into axial diffusivity, describing rate of diffusion along the length of the fiber bundle, and radial diffusivity, an aggregate of diffusion in the two minor planes of the fiber bundle. FA describes how much the tensor ellipsoid deviates from a sphere (isotropic diffusion). Whereas measures of MD and FA are direction independent, the directional components of diffusion tensors (eigenvectors) can be used to make inferences about continuous fiber bundles between adjacent voxels if the tensors are in alignment. These fibers bundles have been demonstrated to correspond with WM bundles in the brain, as water diffusion occurs more freely along the length of axons, whereas cellular membranes and myelination limit diffusion perpendicular to the length of axons (Moseley et al., 1990).

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Segmentation approaches allow for quantification of diffusion parameters in particular ROIs, but is most commonly used for WM structures as the interpretation of diffusion parameters in GM is less clear due to its inherently complex fiber and neuronal organization (e.g., neuronal density, degree of arborization, membrane integrity). Diffusion-weighted imaging can permit inferences about axonal connectivity and WM integrity. Technical limitations currently prevent mapping of axonal processes at the level of single cells in the mammalian nervous system, but single cells have been imaged in *Aplysia* (Grant et al., 2001), and efforts have been made to corroborate diffusion tensor tractography with WM histology at microscopic resolutions in the human spinal cord (Hansen et al., 2011). For large WM fasciculi (e.g., corona radiata, corpus callosum, internal capsule), assessment of diffusion parameters may be performed after segmentation. A voxelwise approach for assessing large WM fasciculi throughout the brain is referred to as tract-based spatial statistics (TBSS; Smith et al., 2006). This approach uses non-linear registration to align images from multiple individuals into a common coordinate space, followed by derivation of a "mean FA skeleton" of major WM projections using tissue contrast from FA weighted images. Statistical parametric mapping is then performed throughout the mean FA skeleton, allowing for groupwise comparisons. One advantage of TBSS is that limiting analyses to major WM pathways in the brain reduces of the number of voxels that statistical comparisons are performed on, partially alleviating concerns about multiple comparisons. As with DBM, TBSS may reveal subtle differences between groups that would not be discernable through assessment of specific pre-defined ROIs.

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2.3. Functional MRI

MRI can also be used to indirectly assess brain function by means of detecting differences in signal resulting from the degree of blood oxygenation in neural tissue. This approach, referred to as functional magnetic resonance imaging (fMRI), depends upon the difference in magnetic susceptibility for oxygenated and deoxygenated blood. Oxyhemoglobin is paramagnetic and has little interaction with magnetic fields, whereas deoxyhemoglobin is diamagnetic and highly susceptible to influence from magnetic fields. Because the brain is highly vascularized, the signal resulting from neural tissue with different proportions of oxygenated and deoxygenated blood is distinct and can provide contrast in time-series MRI images. After further accounting for changes in cerebral metabolic rates for oxygen, cerebral blood flow and blood volume, this signal is described as the blood oxygenation level dependent (BOLD) signal (Ogawa et al., 1992). Typically, fMRI paradigms involve BOLD signal measurement during a resting baseline with subsequent measurements during a particular task or state. The BOLD signal differences from baseline can be analyzed for particular regions of interest, or across the whole brain in a voxelwise fashion, to identify areas that are interpreted as having increased or decreased neuronal activation during a particular task or state. Multiple statistical contrasts between different task/state paradigms then allows for assessing selective BOLD activations relevant to *a priori* hypotheses. An alternate approach for analyzing fMRI data uses BOLD signal coherence between different brain regions during resting state (resting state fMRI; rs-fMRI) or during a specified task, in order to infer *functional connectivity* between brain regions. During a resting state, BOLD signal coherence is typically strongest between regions that comprise the *default mode network* (DMN). The exact role of

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the DMN has not been elucidated, but it has been hypothesized to mediate a "self-centered predictive model of the world" (Raichle, 2015). Although the DMN represents brain regions with the most robust BOLD coherence during a resting state, rs-fMRI can reveal functional connectivity alterations between other regions or circuitry, provided sufficient image resolution.

3. Magnetic resonance imaging of repetitive behavior in ASD and IDD

Neuroimaging investigations relevant to RRB have only been performed in ASD, Fragile X syndrome (FXS) and Prader-Willi syndrome (PWS). Only a single study has reported findings of individuals actively engaging in RRB (skin picking in PWS) during neuroimaging (Klabunde et al., 2015). The remaining imaging findings reviewed here were correlated with a clinical or behavioral metric for RRB, or an event-related fMRI task where aberrant performance may have commonalities with RRB. For a review of neuroimaging findings related to RRB in other clinical disorders (e.g., OCD, TS, Parkinson's disease, Huntington's disease), please see Langen et al. (2011b). For a review of RRB in syndromic IDD that has *not* been studied with MRI, see Moss et al. (2009).

Literature searches were conducted for publications that included the following search parameters: neurodevelopmental disorders with RRB (e.g., ASD, FXS, PWS), relevant neuroimaging terminology (e.g., MRI, DTI, fMRI, tractography, resting state functional connectivity), terms relevant to RRB (e.g., repetitive behavior, stereotypy, self-injury), and publication date between the years of 1990 and 2017. The resulting publications were screened to ensure that they met the criteria of correlating imaging findings to a clinical or behavioral metric for RRB, or fMRI during a task where aberrant performance may have commonalities

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with RRB (e.g., Go/No-go). References in these publications yielded additional studies that met inclusion criteria and so are reviewed here.

3.1. Summary and Interpretation of Literature

Imaging studies that have focused on RRB in ASD and IDD exhibit a large degree of methodological and participant heterogeneity, including dissimilar age groups and imaging protocols. Moreover, there are multiple metrics for characterizing type and severity of RRB. For example, The Autism Diagnostic Interview – Revised (ADI-R) and Repetitive Behavior Scale – Revised (RBS-R) are parent reports, whereas the Autism Diagnostic Observation Schedule (ADOS) is an observational assessment performed by a clinician. Much of this work has involved volumetric comparisons, but recently investigations with DTI and rs-fMRI have provided significant contributions to this field. Table 1 accompanies the findings reviewed here and includes: the names of studies that observed a correlation between imaging findings and RRB, the sample studied, imaging modality, behavioral task (if relevant), primary neuroimaging findings, correlated measure of RRB and direction of that correlation.

Neuroimaging studies in ASD and IDD link structural and functional alterations in a broad range of brain regions and functional networks to RRB. At first glance, it may appear unclear how these systems could all be implicated with regard to one behavioral domain. Considering the heterogeneity of RRB (i.e., motor stereotypies, compulsions, insistence on sameness) and experimental methodologies used (e.g. population, metric of RRB, imaging parameters, and analytic techniques), it is less surprising that such a broad range of findings has been reported.

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Alterations to frontal and temporal cortices are the most varied and difficult to interpret in relation to RRB, as these regions are also implicated in social and/or communication deficits. Superior frontal gyrus alterations have only been linked to RRB in children and adolescents with ASD, including two rs-fMRI studies (Uddin et al., 2013; Weng et al., 2010) and a single diffusion weighted imaging study (Cheung et al., 2009). These studies suggest aberrant connectivity between superior frontal gyrus and cingulate cortex, with increased connectivity to the anterior cingulate cortex (ACC) and reduced connectivity to the posterior cingulate. The superior frontal gyrus is thought to be closely linked to self-awareness and interoception, including sensorimotor processing (Goldberg et al. 2006). In the DSM-V, abnormal sensorimotor processing constitutes part of the RRB diagnostic domain for ASD, and altered function of the superior frontal gyrus in RRB may relate to altered sensorimotor processing in this population. Alternatively, involvement of the superior frontal gyrus in RRB may be a secondary effect of impaired social skills in ASD, as this region is linked with self-awareness and impaired social skills, which may be viewed as an improper balance between self-awareness versus awareness of others. In support of this notion, the insular cortex, which is also thought to mediate interoception (Critchley et al., 2004), has been repeatedly implicated in neuroimaging of RRB in ASD and FXS (Cascio et al., 2014; Kana et al., 2007; Menon et al., 2004;; Uddin et al., 2013; Zhou et al., 2016).

Middle frontal gyrus alterations related to RRB have been observed in children and adults with ASD (Delmonte et al., 2013; Cheung et al., 2009) and PWS (Klabunde et al., 2013). The middle frontal gyrus has been implicated in self-referential processing, but is also thought to be a site of convergence between dorsal and ventral attention networks, mediating shifts in attentional control between exogenous and endogenous stimuli (Japee et al., 2015). Klabunde et al.

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(2015) showed increased activity of the middle frontal gyrus during self-injurious skin picking in PWS. Considered alongside other work that showed reduced activity of the middle frontal gyrus during task switching (Woodcock et al., 2010), findings from Klabunde et al. (2015) may suggest that the middle frontal gyrus is not appropriately contributing to attentional switching for relevant exogenous stimuli and instead contributes toward maintenance of attentional focus on the self. In ASD, positive correlation of ADI-R RRB scores with functional connectivity between the middle frontal gyrus and caudate (Delmonte et al., 2013) may be similarly interpreted.

The inferior frontal gyrus, superior temporal gyrus, and middle temporal gyrus have been related to RRB in ASD and FXS using structural MRI (Rojas et al., 2006; Gothelf et al., 2008), event-related fMRI (Kana et al., 2007; Menon et al., 2004; Schmitz et al., 2006), and rs-fMRI (Di Martino et al., 2011). These cortical regions contribute to various aspects of language and communication, typically lateralized to the left hemisphere (Ardila et al. 2016). The right inferior frontal gyrus, however, has been demonstrated to play a critical role in response inhibition, particularly during Go/No-go tasks (Aron et al., 2004), and findings from Kana et al. (2007) showed reduced activation of the right inferior frontal gyrus during a Go/No-go task in adults with ASD. Nonetheless, many of the studies discussed here have implicated left lateralized alterations to these brain regions in neurodevelopmental disorders with RRB. As social and communication deficits are diagnostic for ASD and common in FXS, it may be that correlations with RRB observed in these studies could also be driven by greater global symptom severity in these neurodevelopmental disorders. In fact, many of these studies also found a similar brain-behavior correlation for measures of social and communication deficits (e.g. Rojas et al., 2006). An alternate viewpoint, however, that some forms

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of RRB may drive social and communication deficits, has been supported in a longitudinal study by Larkin et al. (2016) on RRB and its relation to language and cognitive development in young typically developing (TD) children. Their findings showed that young children who showed greater sensorimotor RRB at 26 months of age had poorer theory of mind and receptive verbal ability at 51 months of age. This relationship was not evident for higher-order RRBs such as restricted interests or insistence on sameness. Thus, in ASD, it may be that correlations observed between measures of RRB and altered structure/function of these cortical regions is strongly influenced by items pertaining to lower-order RRBs.

No volumetric alterations of the cingulate cortex have been found in relation to RRB. However, RRBs have been found to correlate with reduced FA in WM near the ACC in ASD (Cheung et al., 2009; Thakkar et al., 2008) and reduced functional connectivity in both the anterior (Uddin et al., 2013; Zhou et al., 2016) and posterior (Monk et al., 2009) cingulate, ,suggesting that the cingulate is aberrantly connected within larger circuits. Using a sparse regression algorithm, repetitive scores on the ADI-R in children with ASD were predicted by the degree of functional connectivity within the ACC circuit known as the 'salience-network' (i.e., ACC, frontal cortex, insula, thalamus). These connectivity differences were further used to train a classification algorithm to identify a participant's diagnostic group with 78% accuracy (Uddin et al., 2013). The functional consequences of such altered connectivity are evident in many event-related fMRI studies pertinent to RRB (Klabunde et al., 2015; Menon et al., 2004). The ACC is a node within DMN circuitry, and evidence supports its critical role in response-monitoring and outcome expectation (Hoffmann & Falkenstein, 2012). The structural and functional neuroanatomy of the ACC, particularly its caudal aspects, place it as a likely contributor to the regulation of motor commands and/or cognitively salient

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information issued to the basal ganglia, which these studies suggest may be improperly mediated in neurodevelopmental disorders with RRB.

By far the most frequently reported brain alterations linked to RRB in ASD and IDD involve nuclei of the basal ganglia. Enlargement of caudate volume, or greater caudate growth rate in younger individuals, are the most consistently reported findings linked to clinical metrics of RRB in ASD and FXS (Estes et al., 2011; Hollander et al., 2005; Gothelf et al., 2008; Langen et al., 2007; Langen et al., 2014; Qiu et al., 2016; Rojas et al., 2006; Sears et al., 1999). These studies mostly indicate that larger caudate volume is associated with greater RRB severity (Hollander et al., 2005; Gothelf et al., 2008; Langen et al., 2014; Rojas et al., 2006; Sears et al., 1999), but some studies provide contrary evidence of no correlation (Langen et al., 2007) or that greater caudate volume/growth rate is linked to lower RRB severity (Estes et al., 2011; Qiu et al., 2016). This apparent contradiction may be explained through a developmental perspective, as studies that found a negative correlation between caudate volume/growth rate and RRB were carried out in young children (Estes et al., 2011; Qiu et al., 2016), whereas positive correlations with RRB were found in adolescents and/or adults (Hollander et al., 2005; Gothelf et al., 2008; Langen et al., 2014; Rojas et al., 2006; Sears et al., 1999).

fMRI studies using the Go/No-go paradigm indicated reduced task-related activation of the caudate in participants with FXS, and that better task performance was positively correlated with degree of caudate activity (Hoeft et al., 2007). Studies using rs-fMRI further indicate altered function of the caudate in the form of reduced cortico-striatal functional connectivity in ASD (Delmonte et al., 2013) and PWS (Pujol et al., 2015). The direction of correlations identified in these studies, however, does not correspond. As these rs-fMRI studies were performed in

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different neurodevelopmental disorders (i.e., ASD, FXS, PWS), different age groups, and using different RRB metrics (i.e., ADI-R, Social Communication Questionnaire, Child Behavior Checklist), it is difficult to determine which factor might explain between-study variability for this behavioral relationship.

Enlargement of the putamen (Hollander et al., 2005; Sears et al., 1999) and greater putamen growth rate (Langen et al., 2014) were both related to greater RRB severity, as was covariance of volume of the putamen with other limbic structures (Eisenberg et al., 2015). A single DTI study using tractography identified a negative correlation between FA of fiber bundles originating in the putamen with performance on a Go/No-go task in ASD (Langen et al., 2012). Event-related functional alterations of the putamen pertinent to RRB include reduced activity of the putamen during a Go/No-go task in FXS (Menon et al., 2004). Greater cortico-putamen functional connectivity was linked to higher RRB severity in ASD (Di Martino et al., 2011), whereas reduced functional connectivity of the putamen to globus pallidus (GP) was correlated with greater self-picking behaviors in PWS (Pujol et al., 2015). Pujol et al. (2015) did not distinguish between internal and external portions of the GP, however. Thus it is unclear whether such findings support the hypothesis of reduced activity of the indirect pathway in the expression of RRB (Bechard et al., 2016; Bechard & Lewis, 2012; Lewis & Kim, 2009; Tanimura et al., 2008, 2010, 2011).

Volume of the GP was negatively correlated with higher-order RRB in ASD (Estes et al., 2011), but this finding was not significant after accounting for total brain volume. A large multi-site investigation of subcortical volumes in ASD by Turner et al. (2016) also found no relationship between GP volume and RRB. As discussed above, functional connectivity between the putamen and GP were negatively correlated with self-picking behaviors in PWS (Pujol et al., 2015).

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Cheung et al. (2009) observed that higher FA of the internal capsule, a white matter tract proximal to the GP, was associated with higher RRB scores. Other than these studies, there have been no specific findings linking the GP to RRB in neuroimaging studies of neurodevelopmental disorders. Moreover, none of these studies has distinguished internal and external portions of the GP. Although whole-brain analytic approaches (e.g., DBM) have the capacity to identify such brain-behavior relationships in the GP and its subdivisions, insufficient image resolution may contribute to lack of findings in this area and will be discussed further in *Section 3.2*.

Despite being one of the most consistently reported anatomical abnormalities related to ASD (see review by Mosconi et al., 2015), the cerebellum has only been linked to RRB in a small number of human neuroimaging studies of ASD (Cheung et al., 2009; D'mello et al., 2015; Rojas et al., 2006; Wolff et al., 2017). These studies showed that GM smaller volumes within lobules I-IV and crus of the cerebellum corresponded to higher RRB, whereas greater volume of the vermis (lobules VIIB and VIIIA) corresponded to higher RRB (D'mello et al., 2015; Rojas et al., 2006). Of relevance to these studies, reduced volume of the cerebellar vermis in children with ASD was found to be correlated with greater RRB as measured by an observer during children's exploration of a novel environment, although neuroimaging and behavioral assessments were performed over a year apart (Pierce & Courchesne, 2001). This study did not, however, find a significant relationship between vermis volume and RRB scores from the ADI or ADOS. Regarding cerebellar WM, Cheung et al. (2009) reported that greater RRB was associated with reduced FA intra-cerebellar WM, whereas Wolff et al. (2017) reported that young children with ASD showed increased FA in the MCP and SCP.

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The cerebellum receives inputs from a large variety of regions in the cortex and thalamus (see Dum & Strick, 2003), so it is difficult to conjecture whether cerebellar pathology is primarily related to RRB, or whether these effects are secondary to alterations in other brain systems. Findings from Wolff et al. (2017), however, suggest that cerebellar pathology (i.e., increased FA of the SCP) in children later diagnosed with ASD may be present as early as 6 months. Interestingly, a recent HARDI tractography study in healthy adults found evidence of fiber bundles projecting from the subthalamic nucleus (STN) to cerebellar cortex, as well as fiber bundles from the dentate nucleus to substantia nigra (SNr; Milardi et al., 2016). This poses the interesting idea that in addition to canonical projections from STN to SNr, that there may be a parallel loop through the cerebellum (i.e., STN → cerebellar cortex → dentate nucleus → SNr). These tractography findings are supported by viral tracing work in non-human primates that demonstrated disynaptic connections between STN and cerebellar cortex (Bostan et al., 2010) as well as the striatum and dentate nucleus of the cerebellum. Although neuroimaging studies have not yet implicated STN alterations in relation to RRB in neurodevelopmental disorders, STN abnormalities have been implicated in animal models of RRB (Bechard et al., 2016; Grabli et al., 2004; Tanimura et al., 2008, 2010, 2011). Furthermore, high frequency stimulation of the STN has effectively reduced stereotypy in rodents (Aliane et al., 2012), non-human primates (Baup et al., 2008), and in severe obsessive-compulsive disorder (OCD; Mallet et al., 2008). These pathways provide a potential mechanism through which basal ganglia and cerebellar alterations linked to RRB may be related.

Although a majority of the studies discussed here reported lateralized findings in relation to RRB in ASD and IDD (e.g., D'mello et al., 2015; Hollander et al., 2005; Rojas et al., 2006; Pujol et al., 2015; Qiu et al., 2016; Sears et al., 1999),

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it is unclear how these findings map onto the topography of RRB. Generally speaking, the investigations covered in this review have found that in the cortex there are both left and right lateralized alterations that correlated with RRB. Subcortically, however, there is a predominance of right lateralized alterations that correlate with RRB (Di Martino et al., 2011; Hoeft et al., 2007; Hollander et al., 2005; Pujol et al., 2015; Qiu et al., 2016; Sears et al., 1999).

There has been little distinction regarding brain regions involved in higher-order versus lower-order RRB. Most studies have correlated brain alterations with total RRB scores from the ADI-R, ADOS, or RBS-R, without further subdividing those scales. Studies that further distinguished between higher and lower-order RRB primarily found correlations with higher-order constructs (e.g., insistence on sameness, ritualistic behavior), but not those pertaining to lower-order RRB (Hollander et al., 2005; Langen et al., 2014; Qiu et al., 2016; Sears et al., 1999). Although tasks of response inhibition, such as Go/No-go, may appear closer in construct to lower-order RRBs, they should not be considered as equivalent. Parallel cortico-basal ganglia macro-circuits (motor, associative, and limbic) are topographically organized in structures of the basal ganglia (Alexander et al., 1986; Groenewegen et al., 2003; Karachi et al., 2005), and although it is reasonable to conjecture that higher and lower-order RRBs may correlate more strongly with particular macro-circuits, there has been no attempt to elucidate this distinction.

Investigations of repetitive behavior in neurological and psychiatric conditions corroborate similar neural circuitry to that implicated in ASD and IDD. Diffusion imaging studies in pediatric OCD have revealed significant correlations of symptom severity with global WM integrity and regional WM integrity of the superior longitudinal fasciculus, internal capsule, and corpus callosum (for a review see Koch et al., 2014). Greater functional connectivity in portions of cortico-basal

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ganglia circuitry has also been found in both pediatric (Tian et al., 2016) and adult (Beucke et al., 2013) populations with OCD. Furthermore, over-connectivity of cortico-striatal circuitry was associated with greater tic severity in Tourette syndrome (Worbe et al., 2015).

The brain-behavior relationships described in this section reflect that RRB scores can account for approximately 10 to 15 percent of the variance in regional volume for structures like the caudate and putamen. RRB scores appear to have a stronger relationship with measures of brain connectivity captured in rs-fMRI and diffusion imaging experiments, where they account for between 12 to 47 percent of total variance in these imaging metrics. It is worth nothing that the strength of these brain-behavior relationships further support the notion that the structure and function of broader neural circuits may provide greater insights into RRB than the study of isolated brain regions.

Together these neuroimaging findings provide evidence of structural and functional alterations relating to RRB. These alterations differ across disorders, involve multiple cortical sub-regions and the cerebellum, but converge on structures of the basal ganglia. The convergence of neuroimaging findings on structures of the basal ganglia makes sense considering the neuroanatomical convergence in the basal ganglia of broader circuits involving the cortex and cerebellum. The ACC, which was most frequently tied to RRB through event-related fMRI studies pertinent to RRB (i.e., response inhibition), is also neuroanatomically situated to modulate cortico-basal ganglia inputs, and likely plays a meaningful role in the mediation of RRB. As will be discussed in *section 4*, these findings with RRB corroborate similar investigations in animal models of RRB.

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3.2. Advantages and Limitations

The use of MRI provides the most direct and feasible approach for studying neuroanatomy and neural circuitry in human populations. Relatively few investigations, however, have correlated brain alterations in neurodevelopmental disorders to behavioral and clinical metrics pertinent to RRB, and even fewer have adopted a circuit-oriented approach. The use of functional and diffusion weighted MRI has expanded the scope of neuroimaging investigations of RRB in neurodevelopmental disorders beyond isolated brain regions and morphology, enabling the study of structure and function in complex neural circuits. These investigations have identified multiple brain regions and neural circuits that appear to play a role in the expression of RRB in neurodevelopmental disorders, but there is still much work to be done to identify the specificity of such alterations across disorders, ages, and different topographies of RRB.

One important opportunity afforded by neuroimaging paradigms is longitudinal study designs, as multiple scans can be performed on the same individual with no known detrimental effects. The previously described longitudinal investigations by Langen et al. (2014) and Qiu et al. (2016) on striatal development in children with ASD and their findings of increased striatal growth rate correlated with clinical metrics of RRB would not have been revealed with cross sectional study designs. Despite these two important studies, additional longitudinal investigations in neurodevelopmental disorders with RRB are critically needed, as they have the potential to identify sensitive periods in brain growth and development in relation to behavior.

There are additional limitations inherent in human neuroimaging. One of these limitations relates to noise artifacts produced by motion, ranging from

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respiration to larger movements, such as shifting the body for comfort. Fortunately, this difficulty has been long-recognized by the neuroimaging community and there are numerous approaches for motion correction (Maclaren et al. 2013) for both structural and functional imaging paradigms. Motion correction approaches have not sufficiently advanced to enable correction of very large movements, however, prohibiting activity-dependent investigations of some lower-order motor RRBs (e.g., body-rocking). The inability to correct for large movements has also limited inclusion of low-functioning individuals in MRI investigations, as they are unlikely to comply with instructions to remain motionless for extended periods of time. MRI investigations of RRB in ASD focus almost exclusively on high-functioning individuals and severely limit the generalizability of findings. Nonetheless, appropriate considerations in study-design, largely drawing from the field of behavior analysis, can enable successful neuroimaging of individuals with more pronounced intellectuality disability. For example, Nordahl et al. (2016) outlined an effective protocol for acquiring quality MRI data from low-functioning children with ASD by utilizing a pre-scan parent interview, video modeling of the intended procedures, a pediatric friendly environment (i.e., space-theme), and practice sessions in a mock-scanner.

Another limitation of neuroimaging in neurodevelopmental disorders with RRB relates to image resolution, which is directly proportional to both magnetic field strength and acquisition time. Although image resolution has been improved by increasing the field strength of magnets used for human MRI devices and improvements in transmit/receive radio frequency (RF) coil systems, acquisition times for scans used in both research and clinical settings can limit the upper boundaries of image resolution. Scans with longer durations may become uncomfortable for participants and are typically not used in research settings as

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participant attrition or more severe motion artifacts may occur. Additional consideration regarding acquisition time must be given for diffusion weighted scans, as a minimum of 6 diffusion weighted directions are required to resolve diffusion parameters for each voxel, causing scan time to be at least 6 times longer than for a non-diffusion weighted image with comparable acquisition parameters. In practice, a minimum of 45 diffusion weighted directions has been suggested to appropriately characterize diffusion parameters in tissue with complex microstructural organization, such as crossing fibers (Tournier et al., 2013). Consequently, diffusion weighted sequences typically have lower spatial resolution than non-diffusion weighted sequences in order to maintain practical acquisition times. Nevertheless, diffusion imaging methods are improving rapidly due to developments in gradient and RF coil hardware, sequence design, and analysis software (Tournier et al., 2011).

Despite improvements in image resolution, characterizing the structure and function of smaller subcortical nuclei can remain challenging. This has been a particularly salient limitation in the study of RRB in neurodevelopmental disorders, for which cortico-basal ganglia circuitry is strongly implicated. For example, a recent investigation found that functional imaging of the STN during a stop-signal reaction task produced discernible activation patterns using a specialized sequence on a 7T system, but not with a comparable sequence performed on a 3T system or commonly used sequences for cortical fMRI at 7T (de Hollander et al., 2017). A recent diffusion weighted imaging investigation on a 7T system also successfully characterized neural circuits in the basal ganglia and thalamus at high resolution with a large number of diffusion directions and feasible acquisition times in neurotypical individuals (Lenglet et al., 2012). Less detailed assessments of cortico-striatal connectivity in ASD (Langen et al. 2012), cortico-striato-pallido-

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thalamic connectivity in Tourette syndrome (Worbe et al. 2015), and globus pallidus interna (GPi) connectivity in dystonia (Rozanski et al., 2013), however, demonstrate the feasibility of basal ganglia tractography in relevant clinical populations on 3T MRI systems. Detailed tractography of basal ganglia circuits in the context of RRB in ASD and IDD has not been performed, and such studies are greatly needed.

Limitations relating to study populations and clinical or behavior metrics relevant to RRB also need to be recognized. There is a strong population bias in investigations of RRB in neurodevelopmental disorders. The majority of these investigations have been in ASD, and moreover, in high-functioning individuals. This bias may be partially explained by the population distribution of neurodevelopmental disorders with RRB, with ASD being most prevalent. Although the implicated neural circuitry appears to have some degree of overlap across disorders, the population bias toward high-functioning ASD limits the generalizability of findings. Some investigators suggest that alterations to neural circuitry may depend on the particular topography of RRB (Eisenberg et al., 2015), which partially account for variability of findings observed within ASD, as individuals with ASD can display multiple subtypes of RRB (e.g., motor stereotypy, resistance to change).

Another important consideration in this body of work are population demographics, including gender and age of research participants. Although some of the investigations discussed in this review have included female participants, there are currently no neuroimaging studies of RRB in ASD that have specifically targeted gender differences. Related to age, whereas some studies specifically focused on either child or adult populations, many included a broader range of ages that spanned across multiple developmental stages. Those studies that

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included participants of broader age ranges often did not have the statistical power to determine age-related effects, and as a result may have failed to identify brain alterations pertinent to RRB in their study population. Significant developmental heterogeneities have been identified in the expression of RRB in ASD, including age-related effects on the expression of RRB subtypes (e.g., sensorimotor vs insistence on sameness; Richler et al., 2010). As such, more rigorous control of age in experimental populations may serve to benefit future neuroimaging investigations of RRB in neurodevelopmental disorders.

Some neuroimaging findings that were correlated with RRB were also correlated with social and/or communication deficits in individuals with ASD, such as functional connectivity of the superior frontal gyrus with posterior cingulate cortex (Weng et al., 2010). Although the overlap of these correlations may make interpretation of such brain-behavior relationships difficult in the context of those experiments, they were not specifically designed to parse out the relative contribution of RRB to the observed neuroimaging measures while controlling for social and/or communication deficits. It is certainly possible to utilize statistical methods to critically investigate the relationship between brain alterations and RRB, while controlling for other factors such as social and/or communication deficits.

In terms of clinical metrics of RRB, a majority of the studies discussed here have correlated their findings with section C of the ADI-R (Restricted, Repetitive, and Stereotyped Patterns of Behavior). Although this clinical scale is useful as a diagnostic tool, its specificity for ASD limits its application to other neurodevelopmental disorders with RRB. The RBS-R has also been has been successfully used to characterize RRB in other neurodevelopmental disorders (Bodfish et al., 2000; Flores et al. 2011; Oakes et al., 2016), and has capacity to

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distinguish subtypes of RRB. Neuroimaging studies have found significant brain-behavior relationships using both RBS-R total scores (Eisenberg et al., 2015; Wolff et al., 2013, 2015, 2017), as well as particular subtypes of RRB (Wolff et al., 2013, 2017). In addition to brain-behavior relationships with RRB described in neurodevelopmental disorders, neuroimaging correlations with scales relevant to RRB have been described in other conditions. For example, scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) showed positive correlation with functional connectivity of the putamen in individuals with OCD (Beucke et al., 2013).

Several scales that have been used to characterize RRB in neurodevelopmental disorders have not yet been used in neuroimaging studies of RRB. The Social Communication Questionnaire (SCQ; Rutter et al., 2003), Diagnostic Interview for Social and Communication Disorders (DISCO; Wing et al., 2002), and Repetitive Behavior Questionnaire (RBQ; Turner, 1995) all contain items relevant for characterizing RRB and have been used in populations with neurodevelopmental disorders. Use of these measures alongside neuroimaging may enable more comprehensive explorations of brain-behavior relationships with RRB, as well as greater generalizability across neurodevelopmental disorders.

The Go/No-go paradigm of response-inhibition used as a stand-in for RRB during fMRI investigations accounts for a large portion of neuroimaging research on RRB. Although performance on such tasks have been shown to correlate with RRB severity in ASD (Mostert-Kerckhoffs et al., 2015), a meta-analysis of fMRI studies on response inhibition suggests that many brain networks that are observed to show greater activity during Go/No-go tasks may actually correspond to cognitive constructs (e.g., working memory, attentional shifts) that are engaged by more complex implementations of the Go/No-go task (see Criaud & Boulinguez,

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2013). Moreover, there are commonly used behavioral tasks of response inhibition that have not been studied with fMRI in neurodevelopmental disorders. For example, fMRI experiments using the stop-signal reaction task have not been performed in neurodevelopmental disorders, despite evidence that children with ASD show behavioral deficits on it (de Vries & Geurts, 2014). Inclusion of a broader range of behavioral tasks in fMRI research may help disentangle the complex involvement of a wide-variety of brain regions in RRB.

Lastly, despite the unparalleled advantages of directly characterizing brain alterations and their relationship with RRB in neurodevelopmental disorders, findings from these studies in humans cannot be followed up with more detailed characterizations and manipulations of the affected neural circuitry at cellular, molecular, and genetic levels of analysis. Fortunately, neuroimaging in combination with other techniques for manipulating and characterizing neural circuitry in animal models of neurodevelopmental disorders (e.g., optogenetics, viral tracers) provides the possibility for more rigorous experimental control in the study of RRB.

4. Magnetic resonance imaging in animal models with repetitive behavior

Animal models of RRB can be induced through a variety of insults to the central nervous system (e.g., lesion or genetic mutants), pharmacological manipulations (e.g., psychostimulants), impoverishment of early environment/experience, and use of particular inbred mouse strains (for a review, see Bechard & Lewis, 2012). As in human neurodevelopmental disorders, presentation of RRB is not uniform across animal models. Some animal models primarily display lower-order RRBs, such as motor stereotypies, as in the

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excessive self-grooming in multiple lines of *Shank3* mutant mice (Wang et al., 2011). Other animal models also display behaviors that reflect higher-order RRB, such as reversal learning deficits in C58/J mice (Whitehouse et al., 2017), which may serve as a model for 'insistence on sameness' behavior. This discussion will center on animal models with RRB and MRI findings in those models. We will forego discussion of animal models with RRB that have not been investigated with MRI.

There has been little work aimed toward understanding common or disparate mechanisms mediating RRB among these animal models. Although the targeted genetic and molecular alterations used to generate some of these animal models were based on genetic studies of human neurodevelopmental disorders (e.g., *Shank3*, *15q11-13*), there is an incomplete understanding of how these isolated manipulations converge at cellular and neural circuit levels to mediate RRB. MRI is well-suited to the task of characterizing alterations of brain structure and function that mediate RRB across these animal models, as well as translational research to human disorders. Furthermore, MRI findings in animal models with RRB provide a useful foundation for targeted cellular, molecular, and genetic level investigations using other research methodologies.

The field of preclinical neuroimaging research in RRB is in its infancy, however. Only two of the neuroimaging studies animal models with RRB have correlated imaging and a behavioral measurement of RRB (Allemang-Grand et al., 2017; Ellegood et al., 2013). This lack of specificity is reflected by the fact that many these animal models were not investigated with the goal of understanding the pathophysiology of RRB per se, but rather to understand how genetic mutations associated with neurodevelopmental disorders alter brain morphology. This severely restricts interpretation of brain alterations described in many of these

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models, as they cannot be conclusively linked to RRB expression or severity. Due to this limitation and the limited scope of neuroimaging work performed in these models, neuroimaging studies in animal models with RRB will be discussed even in the absence of specific correlations with behavioral measures of RRB. The findings discussed in this section will not be presented in tabular format, however, as the majority of experiments only implemented volumetric comparisons and have no behavioral data to correlate with imaging findings.

4.1. Summary and Interpretation of Literature

The predominant approach for studying animal models with RRB with MRI has been through *ex vivo* structural assessments using regional volumetrics or DBM. A large amount of evidence regarding neuroanatomical alterations in animal models with RRB comes from a study of 26 mouse models of ASD (Ellegood et al., 2015), although not all models included in that study exhibit an RRB phenotype. As many of the models discussed subsequently include findings from Ellegood et al. (2015), it should be noted that some of these findings were gleaned from figures included in that paper, and were not explicitly stated by the authors as statistically significant.

DTI experiments, including those utilizing tractography, have only been performed in BTBR and *Fmr1* mouse models of RRB (Dodero et al., 2013; Ellegood et al., 2010; Ellegood et al., 2013; Sforazinni et al., 2016). There are a small number of studies that have used fMRI in an animal model with RRB (Allemang-Grand et al. 2017; Dodero et al., 2013; Haberl et al., 2015; Sforazzini et al. 2016; Squillace et al., 2014;), only one of which includes a behavioral measure in relation to imaging findings (Allemang-Grand et al. 2017). A majority of this work has been carried out in animal models with RRB resulting from targeted

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genetic mutations, with more recent work emerging from inbred strains with RRB. Neither animal models with RRB induced pharmacologically or by specific early environmental insults have been investigated with MRI.

Mice with mutations to the *Mecp2* gene have been used as a model of Rett syndrome and display forelimb stereotypies (Moretti et al. 2005). Compared to control mice with normal *Mecp2* expression, male mice with hemizygous *Mecp2* truncation (-/Y) had larger relative volume in the cerebellar vermis (Steadman et al., 2014). Female mice with heterozygous *Mecp2* truncation (-/+) had greater volume in the vermis and cerebellar cortex (lobules IV – VII), whereas female mice with homozygous *Mecp2* truncation (-/-) showed more widespread volumetric enlargements in the cerebellum, including vermis and a greater number of regions in the cerebellar cortex (lobules III – X). Subsequent investigation of *Mecp2* hemizygous male (-/Y) mice confirmed prior findings of increased volumes in the cerebellum, but also showed other volumetric differences, including greater volumes in the brainstem and smaller volumes in frontal cortex, striatum, stria terminalis, corpus callosum, and thalamus (Ellegood et al., 2015).

An investigation of the relationship between *Mecp2* mutations, the functional severity of those mutations, and corresponding neuroanatomical alterations was performed by Allemang-Grand et al. (2017). Compared to wild-type mice, all *Mecp2* mutant mice showed reduced volumes in the cortex (frontal, motor, somatosensory, and cingulate), striatum, globus pallidus, and thalamus. Effects on the cerebellum were dependent on the type of mutation, where mice with fewer functional *Mecp2* alleles had progressively greater volumes in the cerebellum. Moreover, linear models relating neuroanatomy to the severity of functional impairment found a negative correlation between functional impairment rating and volume in the cingulate, motor cortex, somatosensory cortex, striatum, globus

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pallidus, and basal forebrain. These findings correspond well with morphological alterations in human imaging studies of Rett syndrome (Reiss et al, 1993; Carter et al., 2008; Dunn et al., 2002; Naidu et al., 2001), and provide preliminary evidence that such alterations may relate to RRB in this population.

Mice with a knockout (KO) of the *Fmr1* gene, the causal factor of FXS, display increased self-grooming when expressed on the C57BL/6 genetic background but not on the FVB background (Pietropaolo et al., 2011). *Fmr1* KOs on the C57BL/6 background showed reduced volume of cerebellar WM and deep cerebellar nuclei, with a notable trend toward reduced volume of the striatum (Ellegood et al., 2010), although no differences were observed in DTI metrics from the same study. One study performed DTI and rs-fMRI to examine structural and functional connectivity in *Fmr1* KO mice on the C57BL/6 background (Haberl et al., 2015). Their findings showed reduced structural connectivity (i.e., FA) in the corpus callosum and brain-wide reductions in functional connectivity, including connections among cortical association regions (i.e., visual, auditory, motor, somatosensory), as well as between striatum and primary somatosensory cortex. These findings are consistent with the notion of dysfunctional cortico-striatal circuits in animal models that display RRB.

Mice with only one copy of the *16p11.2* gene, deletions of which have been found in individuals with ASD, display increased locomotion and stereotypic climbing behaviors (Horev et al., 2011). Portman et al. (2014) showed that juvenile mice with only one copy of the *16p11.2* gene (*16p11.2* +/-) have smaller absolute volumes of the striatum, but this difference did not remain after controlling for total brain volume. Controlling for total brain volume, *16p11.2* +/- mice showed smaller volume in the GP, nucleus accumbens, and several regions of frontal cortex that project to the basal ganglia. A separate investigation in adult *16p11.2*

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heterozygous mice showed significant neuroanatomical differences for 11 of 62 of the brain regions measured, controlling for total brain volume (Ellegood et al., 2015). These included smaller volume of striatum and larger volumes of the midbrain, fornix, hypothalamus, periaqueductal grey, and superior colliculus

Two models with RRB phenotypes result from mutations of the gene coding for the β3 subunit of the $GABA_A$ receptor on the q11-13 region of chromosome 15, which has been associated with ASD, PWS, and Angelman syndrome. Homozygous *15q11-13* KOs display repetitive circling behaviors (DeLorey et al., 1998), whereas mice with *15q11-13* duplication show behavioral inflexibility (Nakatani et al., 2009). Although *15q11-13* homozygous KO mice have not been studied with MRI, mice with a *15q11-13* duplication showed significant neuroanatomical differences for 15 of 62 brain regions, including smaller relative volumes for thalamus, hypothalamus, midbrain, basal forebrain, medial septum, superior cerebellar peduncle, and inferior and superior colliculi (Ellegood et al., 2015).

Mice with a deletion of the *Shank3* gene, which encodes a synaptic scaffolding protein associated with ASD, show reduced social behaviors, engage in excessive self-grooming, and have dysfunctional glutamatergic synapses (Peça et al., 2011; Yang et al., 2012; Wang et al., 2011). *Shank3* KO mice on a C57BL/6 background show significantly reduced total brain volume, but after controlling for multiple comparisons none of the observed differences in relative brain volume remained for the 62 brain regions investigated (Ellegood et al., 2015). Mice with a KO of the *neurexin-1α* gene, a presynaptic cell adhesion protein associated with ASD, exhibit excessive self-grooming and impaired pre-pulse inhibition, a measure of sensorimotor gating (Etherton et al., 2009). Data figures from Ellegood et al. (2015), although not explicitely discussed in text, show that heterozygous

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neurexin-1α KOs have enlarged striatal volume, whereas homozygous *neurexin-1α* KOs have reduced striatal volume, and both manipulations result in reduced volume of the superior cerebellar peduncle.

Mice with a deletion of the integrin β3receptor (*Itgβ3*) gene, which has been linked to increased 5-HT levels in ASD, display increased self-grooming and reduced preference for novel social interactions (Carter et al., 2011). Compared to control mice with normal *Itgβ3* expression, homozygous *Itgβ3* KO mice show significant neuroanatomical differences in 39 out of 62 brain regions, including larger relative volume of amygdala and parieto-temporal lobe, as well as smaller relative volume of frontal lobe, striatum, GP, internal capsule, thalamus, corpus callosum, cerebellar cortex and deep nuclei (Steadman et al., 2014; Ellegood et al., 2015).

Parvalbumin is a calcium binding protein, and individuals with ASD show reductions in parvalbumin containing interneurons in the medial prefrontal cortex (Hashemi et al., 2016). *Parvalbumin* KO mice have deficits in social interactions and ultrasonic vocalizations, which are used to mimic the communication deficits diagnostic for ASD. *Parvalbumin* KO mice also show deficits in reversal learning, another measure of “higher-order” RRB (Wöhr et al., 2015). MRI in *Parvalbumin* KO mice showed that they had smaller neocortical volume and greater cerebellar volume as juveniles, but that these differences did not persist into adulthood (Wöhr et al., 2015). Volumetric comparisons with more detailed neuroanatomical distinctions have yet to be performed in this model.

Specific teratogens known to induce CNS damage have also been implicated as causal factors in a sub-population of ASD. Rats that have been exposed to valproic acid (VPA) *in utero* display locomotor stereotypy, reduced acoustic prepulse inhibition, and decreased number of social behaviors (Schneider

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& Przewlocki, 2005). Frisch et al. (2009) showed that rats that have been exposed to VPA *in utero* show reduced total brain volume, as well as reduced relative brain volumes of cortex and brainstem. A separate investigation of rats exposed to VPA *in utero* demonstrated reduced volume of the hippocampus, as well as greater T_2 relaxation time for hippocampus, thalamus, amygdala, and striatum (Petrenko et al., 2013).

The animal model of RRB most rigorously characterized through MRI is the inbred BTBR mouse strain. The BTBR strain, which exhibits agenesis of the corpus callosum, recapitulates many features of ASD, including impaired social behavior and RRB in the form of intense bouts of spontaneous self-grooming (McFarlane et al., 2008; Ellegood et al., 2013), as well as deficits in reversal learning during operant tasks (Amodeo et al., 2012). Ellegood et al. (2013) demonstrated that relative to total brain volume, inbred BTBR mice have significant volumetric differences for 20 out of 62 brain regions as compared to control strains with low incidence of repetitive behaviors (C57BL/6 and FVB). BTBR mice showed smaller cerebral white matter and ventricular volumes than either control strain, reduced cerebral grey matter compared to B6 mice, but increased brainstem and olfactory volumes compared to both control strains. The cerebellum of BTBR mice was smaller than FVB controls, but larger than B6 controls. DTI was used to assess FA differences in a voxelwise fashion. As expected due to callosal agenesis in BTBR mice, there was reduced FA in regions where the corpus callosum would be, but also reduced FA of the external capsule and increased FA in hippocampal white matter, although these findings were not correlated with self-grooming.

Moreover, whole-brain DBM was used to assess voxel clusters where volume differences significantly correlated with higher self-grooming behaviors, *but not reduced sociability*, across all animals included in the study. The authors

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note that this analytic strategy did not result in a “barbell” effect driven purely by volume differences between strains (Ellegood et al., 2013). Clusters with relatively reduced volume were found within the striatum, GP, thalamus, hippocampus (dentate gyrus), entorhinal cortex, internal capsule, and stria medullaris. In contrast, voxel clusters with enlarged volume correlated with higher self-grooming behaviors, but not reduced sociability, were found within the hippocampus (CA3), cerebellar cortex, and arbor vita of the cerebellum. These findings provide robust evidence of brain alterations specific to RRB, rather than non-specific strain differences of the BTBR model.

Dodero et al. (2013) used TBSS, tractography, and rs-fMRI to investigate BTBR neuropathology. They confirmed previous evidence of callosal agenesis and abnormal hippocampal commissure, but also revealed the presence of large rostro-caudal WM “Probst” bundles. This study selected seed regions for deterministic tractography that were first revealed by TBSS, which is limited to the large-scale WM “skeleton” of the brain. It remains unclear whether BTBR mice have abnormal connectivity between structures that have been identified as having volumetric differences, such as fiber bundles arriving at or projecting from GP. rs-fMRI revealed that BTBR mice have reduced basal cerebral blood volume in thalamus, nucleus accumbens, cingulate, and somatosensory cortex, and increased activity in the hypothalamus and dorsal hippocampus.

In a similar investigation in BTBR mice and C57BL/6 controls, Sforazzini et al. (2016) performed DTI and rs-fMRI in order to perform tractography and resting state functional connectivity analyses, respectively. Tractography verified callosal agenesis and rostro-caudal “Probst” bundles in BTBR mice. Interhemispheric functional connectivity analyses revealed that BTBR mice had reduced interhemispheric connectivity for striatum, cingulate, insular, frontal association

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regions, primary and secondary motor cortex, but greater interhemispheric connectivity within hippocampal, occipital and temporal regions. Immunohistochemistry with a viral tracer was also performed and supported interhemispheric connectivity abnormalities found with rs-fMRI. There was also evidence of bilateral differences in functional connectivity, particularly underconnectivity of striato-thalamo-cortical circuits in BTBR mice, but histochemical approaches were not used to verify this subset of findings.

One additional study to utilize fMRI in BTBR mice was a targeted fMRI investigation of dopaminergic function. BTBR mice were shown to lack the fMRI BOLD response seen in control mice in response to the dopamine transporter blocker GBR 12909 (Squillace et al., 2014). This experiment, however, was targeted toward better understanding of altered reward-processing seen in ASD, and had no specific relation to the RRB phenotype seen in BTBR mice.

Cortical aberrations in animal models of RRB differ across models, but alterations in volume and function were often localized to frontal and temporal cortical regions (Ellegood et al., 2015; Haberl et al., 2015; Portman et al., 2014). In addition, clustering analysis carried out by Ellegood et al. (2015) on neuroanatomical differences across ASD-relevant mouse models, many of which show RRB, revealed that cortical changes were closely linked to basal ganglia changes. Altered structure and function of frontal and temporal cortices were similarly implicated in neuroimaging studies of neurodevelopmental disorders with RRB (see section *3.1*). As in human neurodevelopmental disorders, some of these animal models also display abnormal social and/or communication phenotypes in addition to RRB. In the absence of behavioral correlations, it is impossible to determine whether these frontal and temporal cortical alterations in animal models with RRB specifically relate to their RRB phenotype. Parsing how these alterations

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relate to behavior for these cortical regions will be difficult, considering the less comprehensive mapping of structure-function relationships in the rodent cortex.

Analogous to human neurodevelopmental disorders with RRB, the most frequently reported findings in animal models with RRB were alterations of structures within the basal ganglia. The most consistent finding in animal models with RRB was reduced volume of the striatum (Ellegood et al., 2010; Ellegood et al., 2015; Portman et al., 2014), which was also negatively correlated with self-grooming behavior in BTBR mice (Ellegood et al., 2013). The direction of this volume difference is, however, opposite of that observed in neurodevelopmental disorders (i.e., enlargement of the striatum). It is difficult to speculate how opposite effects on volume might result in similar behavioral outcomes between human neurodevelopmental disorders and animals models with RRB, as such a volumetric divergence has not been documented between other human disorders and corresponding animal models.

Reduced volume of the GP was also demonstrated in animal models with RRB (Ellegood et al., 2015; Portman et al., 2014; Steadman et al., 2014) and in BTBR mice was negatively correlated with self-grooming behavior (Ellegood et al., 2013). This finding is consistent with human neuroimaging data from a large multi-site investigation in ASD, which showed reduced volume of the GP, despite no observed correlation with RRB (Turner et al., 2016). It is possible that the GP plays a different role in the expression of RRB in human neurodevelopmental disorders and animal models. These species-related differences in GP function are evidenced by the fact that high frequency stimulation of the entopeduncular nucleus (rodent equivalent to human GPi) did not attenuate Parkinsonian symptoms in a rodent model (Fischer et al., 2015), yet the GPi is one of the major sites for deep brain stimulation used to improve motor symptoms of Parkinson's

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disease in humans. Further neuroimaging investigations are needed to confirm this correlation in BTBR mice, as well as possible correlations of RRB with GP volume in other relevant animal models of RRB.

Differences in cerebellar anatomy have been repeatedly associated with animal models that include RRB, but the direction of these findings has been inconsistent across models. A number of relevant animal models showed clusters of reduced volume within the cerebellum, including *Fmr1*, *15q11-13*, *Shank3*, and *Itgβ3* mice (Ellegood et al., 2010, 2015). *Mecp2* and *Parvalbumin* KO mice, however, showed enlargement within the cerebellum (Ellegood et al., 2015; Steadman et al., 2014; Wöhr et al., 2015). BTBR mice were shown to have volumetric enlargement of the cerebellar cortex and arbor vita, correlated with greater self-grooming behaviors (Ellegood et al., 2013). The cerebellum is often implicated in MRI studies of neurodevelopmental disorders, especially in ASD, and these studies suggest that RRB corresponds to smaller volumes within cerebellar GM or reduced FA of cerebellar WM (Cheung et al., 2009; D'mello et al., 2015; Rojas et al., 2006; Wolff et al., 2017). Considering animal and human studies together, there is greater correspondence for the notion of reduced cerebellar volumes in relation to RRB.

4.2. Advantages and Limitations

In animal models, RRB results from a variety of genetic manipulations, administration of pharmacological agents (e.g., amphetamine, cocaine), impoverishment of early environment/experience (Mason & Rushen, 2006), and generation of specific inbred mouse strains. Some of these models represent highly salient features of RRB in human neurodevelopmental disorders (e.g., *Mecp2* mice). Other models, however, display RRBs that do not align well with

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RRBs observed in corresponding human neurodevelopmental disorders (e.g., *Fmr1* mice). A majority of these animal models center around sensorimotor, or lower-order RRBs, but there are select animal models of RRB that also display analogs for higher-order RRB, such as reversal learning deficits. A critical shortcoming of neuroimaging investigations of animal model with RRB has been the lack of correlation between brain alterations and behavioral indices of RRB. Only two studies have correlated their neuroimaging findings with behavioral indices of RRB in an animal model (Allemang-Grand et al. 2017; Ellegood et al., 2013), and no study thus far has explored the relationship between brain alterations and analogs of higher-order RRB. Although the animal imaging studies discussed in this review have contributed an important early step toward understanding brain changes in neurodevelopmental disorders with RRB, this critical gap severely limits interpretation of findings. The current state of animal model research and parallel investigations in clinical populations warrant more detailed and rigorous neuroimaging investigations of RRB in these animal models.

It is also important to note that many of the animal models with RRB discussed in this review were investigated with the aim of understanding ASD pathology in general. Thus, these models display abnormal social behaviors in addition to RRB. In the absence of behavioral correlations, some of the neuroimaging findings from these models may relate to abnormal social behaviors. There are a number of animal models of RRB which have not yet been investigated with neuroimaging approaches, such as *Sapap3* KO mice (Welch et al., 2007), the inbred C58 mouse strain (Muehlmann et al., 2012), or the outbred deer mouse (*Peromyscus maniculatus)* (Muehlmann et al., 2015). MRI investigations are needed for these models, as they have been demonstrated to display robust and specific RRB phenotypes.

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Although use of MRI to study animal models of RRB provides opportunities for experimental manipulations that are not possible in human clinical populations, there are some fundamental limitations in this area of research. The most salient of these limitations is that rodent brains (for mice, ~450 mm^3) are dramatically smaller than human brains (~1300 cm^3). The use of higher field strength magnets and longer scan times in animal neuroimaging, however, allow for much greater spatial resolution than is common in human neuroimaging. Despite greater spatial resolution afforded by methodologies used in animal neuroimaging, the smaller total volume of rodent brains makes the relative resolution of animal and human neuroimaging data comparable. Fortunately, high-resolution animal neuroimaging is approaching the spatial resolution common among histological assays, as evidenced by Johnson et al. (2008), who performed *ex vivo* imaging of C57BL/6 brains at isotropic resolutions of 21.5 µm. Although high-resolution structural scans afford similar resolution to histological approaches, diffusion-weighted MRI and tractography provide the unparalleled utility for simultaneous characterizations of microstructural organization across multiple brain regions and the connections between them. Importantly, assessment with MRI and/or DTI does not preclude histological analyses, which may subsequently be performed on the same tissue. Although the use of neuroimaging in concert with histological approaches for studying neural circuitry in animal models has not been applied to RRB, these complementary approaches have been effectively demonstrated in the study of traumatic brain injury, drug addiction, and brain development (Laitinen et al., 2015; Narayana et al., 2014; Takahashi et al., 2012).

Related to image resolution, a number of mouse neuroimaging atlases group together numerous small subcortical structures, some of which are critical components of cortico-basal ganglia circuitry. For example, the high resolution (32

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μm) C57BL/6 atlas established by Dorr et al. (2008), which has been utilized by a number of subsequent studies of animal models of RRB, does not include individual segmentations for STN or SNr, both of which are critical components of the cortico-basal ganglia circuitry implicated in RRB. Mouse atlases generated by the Australian Mouse Brain Mapping Consortium (Ullmann et al., 2014; Watson et al., 2017), however, do include segmentation of these structures. Similarly, a C57BL/6 atlas at comparable resolution (21.5 μm) established by Johnson et al. (2010) also includes segmentation of the SNr. These atlases demonstrate that assessment of small basal ganglia nuclei (e.g., STN and SNr) in the mouse brain can be performed with neuroimaging methodologies currently in practice, although no neuroimaging studies have yet investigated these structures in animal models with RRB.

Exploratory analyses, such as DBM or whole-brain volumetrics using pre-defined neuroimaging atlases, comprise a bulk of the neuroimaging investigations in animal models of RRB. Although exploratory neuroimaging investigations are an important component toward understanding the neural circuitry mediating RRB, there is a strong need for hypothesis based investigations in this area of research. White-matter alterations have been repeatedly implicated in neurodevelopmental disorders, such as ASD (Ben Bashat et al., 2007; Billeci et al., 2012; Bode et al., 2012; Langen et al., 2014), but comparable experiments have not been performed in animal models of RRB. It is likely alterations in white-matter integrity and microstructure contribute to development and expression of RRB, and this relationship could be explored in greater detail with animal models.

There are only three currently published DTI investigations in an animal model with RRB, all using BTBR mice (Dodero et al. 2013; Ellegood et al., 2013; Sforazzini et al., 2016). DTI studies in other animal models of RRB are sorely

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needed, as well as tractography analyses. Including behavioral measures and/or histology would also greatly benefit DTI studies in animal models of RRB. Furthermore, although research lacking *a priori* hypotheses can provide a useful starting point for identifying pathology in animal models of RRB, hypothesis-driven investigations into specific components of the neural circuitry implicated in RRB are needed. Hypothesis-based queries are especially critical for tractography analyses, as 'seed' and /or 'target' regions are necessary.

fMRI has not been widely used to study animal models of RRB, with the exception of BTBR (Dodero et al., 2013; Sforazzini et al., 2016; Squillace et al., 2014) and *Fmr1* mice (Haberl et al., 2015). Importantly, no fMRI study in an animal model of RRB has correlated brain alterations with behavior. As fMRI investigations are often related to specific behaviors or response patterns, it is not surprising that this neuroimaging approach has not been as widely utilized in animal models of RRB. Motion artifacts preclude the possibility of acquiring quality fMRI data from an animal engaging in lower-order RRB, and there are currently no appropriate analogs to high-order RRB in animal models that are suitable to investigation with fMRI. Surprisingly, there are relatively few rs-fMRI studies that have assessed functional connectivity in an animal model with RRB (Dodero et al., Haberl et al., 2015; Sforazinni et al., 2016). Assessment of functional connectivity with rs-fMRI is well-suited to the study of RRB in animal models, and more such investigations using this approach are needed.

One of the major advantages of studying neurobiology of RRB with MRI in animal models is the capacity to perform targeted histological analyses to investigate mechanistic underpinnings of MRI findings in those models. Furthermore, histological studies using neuronal tracers, such as biotinylated dextran amines or modified viral vectors, provide the capacity to look at specific

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neuronal projections between structures of interest, and can be compared to tractography data from neuroimaging. This approach has been elegantly demonstrated in BTBR (Sforazzini et al., 2016) and C57BL/6J control mice (Calabrese et al., 2015).

A number of nonhuman primate models of RRB have been described (Lutz, 2014), and these models have added to our understanding of the neural circuitry of RRB (Bauman et al., 2008; Baup et al., 2008; Grabli et al., 2004; Martin et al., 2008; Saka et al., 2004). To our knowledge, however, MRI has only been used in nonhuman primate models of RRB as a tool to identify stereotactic coordinates for targeted chemical lesions (Bauman et al., 2008). Nonhuman primate models are an important intermediate in translational research between rodent models and humans (Watson and Platt, 2012). Neuroimaging in nonhuman primate models of RRB is needed to better understand neural circuitry of RRB, especially with regard to neural circuits that share a greater degree of homology to humans than mice, such as the frontal cortex.

Lastly, compared to other approaches for studying brain morphology and circuitry, MRI methodologies are the most highly translational to human research. MRI has set the stage for bidirectional translational research, where findings from clinical populations can also be more thoroughly investigated in corresponding animal models. The bidirectional translational utility of MRI is especially evident in the area of stroke research. Dijkhuizen et al. (2012) described how loss of interhemispheric functional connectivity following ischemic stroke in humans has been replicated in rats with experimentally induced stroke, and mechanistic details of this process were further investigated with manganese enhanced MRI (van Meer et al., 2010), an *in vivo* tract-tracing agent not used in human due to potential adverse effects.

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5. Conclusions

RRBs appear across a number of neurodevelopmental disorders, but effective treatments are limited by inadequate understanding of the neural circuitry mediating such behaviors. Neuroimaging investigations are particularly well-suited to the translational study of neural circuitry and have provided insights into altered brain morphology, connectivity, and function that mediate RRB in neurodevelopmental disorders and corresponding animal models.

In ASD and IDD, alterations of the frontal and temporal cortices have been repeatedly correlated with RRB, but were often not unique to RRB. Many of these same frontotemporal regions were also implicated in social and communication deficits, often within the same studies. The goal of these investigations was to relate neuroimaging findings to general ASD symptomatology, rather than targeting brain-behavior relationships for RRB while controlling for social or communication deficits. The ACC, which has been consistently implicated in fMRI tasks pertinent to RRB, is thought to be involved in the regulation of motor commands and/or cognitively salient information to the basal ganglia (Hoffmann & Falkenstein, 2012).

Alterations in structures of the basal ganglia are by far the most consistently reported imaging findings correlated with RRB among multiple neurodevelopmental disorders. Enlargement of the caudate and putamen, as well as aberrant cortico-striatal connectivity, implicate widespread alterations to a variety of brain networks. Currently there is lack of MRI research into the structure, connectivity, and function of smaller basal ganglia nuclei, and how alterations in these regions pertain to RRB in neurodevelopmental disorders. In particular, the STN has not yet been linked to RRB in imaging studies of neurodevelopmental

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disorders, despite its well-established role in animal models of RRB (Aliane et al., 2012; Bechard et al., 2016; Baup et al., 2008; Tanimura et al., 2008, 2010, 2011). This shortcoming is likely methodological in nature, and relates to use of insufficient image resolution or anatomical labeling practices.

A major role of the cerebellum and associated circuitry has begun to emerge from neuroimaging studies of RRB. Alterations to the cerebellum are also one of the most consistently reported pathological findings in post-mortem studies in ASD. The majority of these neuroimaging studies suggest that higher levels of RRB are associated with volumetric reductions in cerebellar GM or reduced WM integrity. Reduced volume of the cerebellar crus was correlated with higher RRB in multiple studies of children with ASD (Cheung et al., 2009; D'mello et al., 2015; Rojas et al., 2006; Wolff et al., 2017). The cerebellar crus has been shown to be functionally connected with regions of the frontal and temporal cortices (Buckner et al., 2011) that have been independently linked to RRB (Kana et al., 2007; Menon et al., 2004; Rojas et al., 2006). Moreover, novel pathways connecting the cerebellum and basal ganglia have recently been identified in human neuroimaging studies (Milardi et al., 2016) and support the notion that interactions between the cerebellum and basal ganglia may be important in the mediation of RRB.

Animal models with RRB show similar neuroanatomical alterations to those correlated with RRB in studies of neurodevelopmental disorders. In the only study linking imaging findings with behavior in an animal model of RRB (BTBR mice; Ellegood et al., 2013), higher rates of RRB were linked to reduced volumes in the striatum, GP, and thalamus, but greater volumes in the cerebellar GM and WM. Cortical alterations in animal models with RRB were typically localized to prefrontal and temporal regions, but the direction and magnitude of these changes differed

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considerably across models. The most frequent and consistently reported findings in animal models with RRB were alterations in structures of the basal ganglia, primarily reduced volumes of the striatum and GP. Alterations in the cerebellum were also frequently reported in animal models of RRB, and generally showed reduced volumes in both cerebellar GM and WM.

A majority of the brain regions whose morphology, connectivity, or function have been implicated in RRB are components of larger cortico-basal ganglia macro-circuits. Several cortical regions have been implicated in neuroimaging of RRB, but altered structure and function within the basal ganglia was more consistently reported. Alternate approaches to studying brain morphology and function corroborate the critical role of the basal ganglia in the mediation of RRB (Aliane et al., 2012; Bechard et al., 2016; Burguière et al., 2013; Baup et al., 2008; Grabli et al., 2004; Tanimura et al., 2008, 2010, 2011). The confluence of large scale brain networks within the basal ganglia makes these structures uniquely positioned, with the potential to moderate the initiation and termination of a broad range of cognitive and motor behaviors by functioning as a central hub among diverse neural networks.

Although many of the same structures are implicated from investigations in neurodevelopmental disorders and animal models of RRB, it is curious that opposite effects are observed for the volume of certain structures, particularly the striatum, between species. As direct relationships between brain volume and function are not fully understood, one possible explanation is that although network-level function of the basal ganglia result in similar behavioral outcomes between species, there are different cellular or molecular level pathologies that lead to structural and functional abnormalities observed in the striatum. An alternate explanation for the opposite effects on striatum volume between

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neurodevelopmental disorders and animal models with RRB, is that underlying pathology may result in compensatory changes to related structures or circuits in humans, whereas similar compensatory changes may not have occurred in these animal models. As the majority of the neuroimaging data in RRB are from higher-functioning individuals, it is possible that compensatory brain changes in these individuals may result in improved outcomes, relating to their higher level of intellectual functioning.

Most neuroimaging investigations of RRB have been in individuals with ASD, and findings in this population may not be recapitulated in other neurodevelopmental disorders with RRB, or broader clinical populations with RRB. For example, *decreased* volume of the caudate was reported in multiple neuroimaging studies of OCD (see review by Ahmari, 2016). Within ASD, the inconsistency of neuroimaging findings related to RRB may due, in part, to heterogeneity among study samples (e.g., age differences, gender distributions, comorbid conditions, medication status).

Differential involvement of cortical regions across studies in clinical populations may be due to both experimental design (i.e., different tasks used in fMRI investigations) and population heterogeneities. Similarly, differential cortical involvement across animal models of RRB is not surprising, as these models result from disruption of diverse genetic systems and display different topographies of RRB. Moreover, pathology in different components of these basal ganglia circuits, such as the STN or SNr, may exist in neurodevelopmental disorders but remain unobserved due methodological shortcomings (e.g., image resolution, labeling practices). The cerebellum has been clearly implicated in the pathophysiology of ASD, and neuroimaging evidence suggests that cerebellar pathology is also linked to RRB in this population (Cheung et al., 2009; D'Mello et al., 2015; Rojas et al.,

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2006). The extent to which the cerebellum may be involved in other neurodevelopmental disorders with RRB remains unknown.

There are currently no neuroimaging investigations in neurodevelopmental disorders with RRB that have assessed intra-basal ganglia connectivity using DTI tractography. As the pathophysiology of RRB appears to converge in the basal ganglia, this area of research is critically important. Specifically, one of the major theoretical frameworks for interpreting basal ganglia activity is the differential role of the direct and indirect pathway. As a result of the lack of studies investigating intra-basal ganglia connectivity, and studies which investigate STN and SNr morphology, there is currently no evidence from neuroimaging to suggest differential involvement of the direct and indirect basal ganglia pathways in neurodevelopmental disorders with RRB. Diffusion imaging investigations in OCD, which shares similar pathophysiology, demonstrate the feasibility of performing striato-pallidal tractography with current acquisition parameters (Worbe et al. 2015). Similarly, functional connectivity assessment of the STN have been demonstrated in Parkinson's disease (Baudrexel et al., 2011). Thus, there is a strong need for future investigations of intra-basal ganglia structural and functional connectivity in relation to RRB.

Diffusion imaging investigations, including TBSS and tractography, may reveal circuit pathologies that are not apparent from regional volumetric analyses, and have the potential to link seemingly disparate findings. For example, a recent diffusion imaging investigation performed tractography in healthy adult participants and showed fibers connecting the STN and cerebellar cortex, as well as fibers from the dentate nucleus of the cerebellum to the SNr (Milardi et al., 2016). Moreover, fibers of the cerebellothalamic fiber bundles running through the superior cerebellar peduncle may indirectly affect cortico-basal ganglia circuits via the

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thalamus, which has been implicated in neurodevelopmental disorders with RRB (Pujol et al. 2015) and animal models (Ellegood et al., 2015; Petrenko et al., 2013). Thus, there is a strong need for additional diffusion imaging investigations to assess structural connectivity in both neurodevelopmental disorders with RRB and corresponding animal models.

Beyond considerations related to neuroimaging paradigms and analytic approaches, there are other factors that are relevant to MRI research in RRB. Linking brain structure and function to RRB in humans entails the use of a behavioral index. The behavioral indices most frequently used to associate RRB severity with brain alterations were the ADI-R and ADOS. The ADI-R and ADOS are designed for use in ASD, and although a large portion of neuroimaging investigations of RRB are performed in this population, the use of behavioral assessments specific to one clinical population limits the generalizability of these findings to other neurodevelopmental disorders. Only five of the neuroimaging investigations discussed here have utilized an alternate behavioral index of RRB, the RBS-R (Dichter et al., 2012; Eisenberg et al., 2015; 2013; Wolff et al., 2013, 2015, 2017). Wolff et al. (2017) demonstrated that the type of behavioral index used to assess RRB can influence the identification of brain-behavior relationships, as significant relationships between cerebellar WM were only found with the RBS-R, whereas similar comparisons using RRB scores from the ADOS failed to find a relationship. Other work using the RBS-R has shown that some neuroanatomical alterations identified in ASD were linked to specific domains of RRB, such as self-injurious behavior or compulsions (Wolff et al., 2013).

An important consideration affecting the generalizability of findings from neuroimaging investigations of RRB in neurodevelopmental disorders is that of population bias. As there is a great degree of heterogeneity in intellectual function

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among neurodevelopmental disorders with RRB, research in these populations should attempt to recapitulate this diversity. Unfortunately, due to the necessity for minimal motion during MRI, lower-functioning individuals are often unable to participate in studies of this nature. A recent study by Nordahl et al. (2016), however, demonstrated that appropriate behavioral techniques (e.g., video-modeling, training in mock scans) can enable the acquisition of high-quality MRI data from low-functioning children with ASD.

6. Future Directions

As the majority of neuroimaging investigations specific to RRB in neurodevelopmental disorders have been performed in ASD, there is a critical need to expand investigations into the neural circuitry of RRB in other related neurodevelopmental disorders. Despite convergent findings related to basal ganglia circuitry, it is possible that RRB in different neurodevelopmental disorders may not be mediated by identical neural circuitry alterations. It is also possible that neural circuitry alterations related to RRB are dependent on the particular topography of RRB (Eisenberg et al., 2015; Wolff et al., 2013). Future investigations would be well-served by exploring the relationship of neural circuitry alterations with indices of repetitive behavior that have the capacity to parse out subdomains of RRB. Despite its relative brevity, the RBS-R is an assessment with the capacity to identify subtypes of RRB and would provide great utility for exploring relationships between RRB and neural circuitry. In addition to use in populations with ASD, the RBS-R has been used in FXS (Oakes et al., 2016), PWS (Flores et al. 2011), and non-syndromic intellectual disability (Bodfish et al., 2000). Thus, increased use of the RBS-R as an index of RRB can enable more detailed

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explorations of relationships between neuroanatomy and RRB, as well as greater generalizability across populations.

Females are dramatically under-represented in neuroimaging studies of RRB and evidence suggests that there are gender differences in brain connectivity in ASD (Irimia et al., 2017). Future neuroimaging investigations of RRB would benefit from inclusion of greater numbers of female participants, which can enable the study of possible gender differences in brain morphology and connectivity related to RRB. Individuals with more severe intellectual disability are also under-represented in neuroimaging study samples and future work should make efforts to include such individuals. The development of more complex motion correction algorithms in concert with improved approaches for tracking motion may improve the ability to collect usable MRI data from lower-functioning individuals. For example, Todd et al. (2015) used an optical camera to capture head movements and perform real-time changes to the image field of view during image acquisition, so that the same portion of the participant's brain remains in the same space of the acquired image despite head movements.

Neuroimaging investigations in animal models of RRB have mostly been restricted to volumetric comparisons and there has been minimal focus on how regional alterations associated with RRB might combine at the level of neural circuitry. For example, it is currently unknown how volumetric alterations in one brain region effects WM efferents, or the extent to which such alterations modify directly and indirectly connected brain regions. In order to understand the complex pathophysiology of RRB, it is critical to understand how regional alterations might affect structure and function of the larger neural circuits to which they contribute. In addition to DTI and rs-fMRI approaches, analyzing networks of anatomical

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covariance can lend to a better understanding of how volumetric differences can affect larger neural circuits (Evans, 2013).

Animal neuroimaging methodologies are well-developed in other lines of investigations, and the feasibility of neural circuit / network level investigations in an animal model of RRB has been demonstrated (Dodero et al., 2013; Sforazzini et al., 2016). Additional investigations of structural and functional connectivity in both animal models of RRB and neurodevelopmental disorders are needed to determine the extent to which such alterations are involved in the development and expression of RRB. Moreover, a neural circuit approach to the study of RRB in animal models can enable identification of candidates for targeted genetic and molecular level investigations.

Currently, neuroimaging studies from animal models of RRB have all been performed in animals housed in standard laboratory housing conditions. Mouse strains that display RRB when reared in a standard laboratory cage showed reduced RRB when reared in environmental enrichment (Bechard et al., 2016; Muehlmann et al., 2012), and a study unrelated to RRB showed that mice reared in environmental enrichment showed enlargement of striatum (Scholz et al., 2015). Thus, there is a strong need for neuroimaging investigations of the structural and functional brain changes that correspond with attenuation of RRB through environmental enrichment.

There is also a need to expand neuroimaging investigations to other models of RRB, such as C58 inbred mice and SAPAP3 knockouts. Additional neuroimaging investigations in mouse lines that exclusively display RRB without overlap with other phenotypes (e.g., social deficits), such as the SAPAP3 KO, may provide clarity as to which neuroanatomical and circuit pathologies are specific to RRB.

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A unique opportunity in the study of neural circuitry in animal models is that the same animal's brain may be imaged *in vivo, ex vivo*, and assessed via histology. Despite this opportunity, very few studies have incorporated these multiple levels of investigation. Only one investigation in an animal model of RRB has used histology in concert with neuroimaging metrics (BTBR; Sforazzini et al., 2016). There are a number of additional examples of this approach from other lines of investigation. Takahashi et al. (2011) compared tractography streamlines to histology (Luxol Fast Blue + Cresyl Violet) for cortical projection fibers in the cat brain, and found that the distribution and orientation of streamlines corresponded to those inferred from histology. Narayana et al. (2014) assessed WM differences resulting from chronic cocaine treatment and found that reduced FA in the splenium, fimbria, and internal capsule corresponded with reduced expression of multiple white-matter proteins. Hammelrath et al. (2016) utilized diffusion weighted images in combination with myelin staining (Black Gold II) to assess development of cortical WM in C57BL/6 mice and found that significant age dependent changes in myelin staining corresponded with T_2 in the regions analyzed. Calabrese et al. (2015) performed DTI scans at an isotropic resolution of 43 μm in a C57BL/6 mouse and compared probabilistic tractography to neuronal tracer data available from the Allen Brain Atlas mouse brain connectome, finding weak but significant correlations for 98% of the 976 generated fiber bundles. These studies demonstrate that investigations using neuroimaging in concert with other methodologies have the potential to greatly enhance our understanding of brain alterations and circuit pathologies.

This review has provided a critical summary of MRI investigations of RRB in ASD and IDD as well as corresponding animal models. Taken together these findings suggest that brain alterations mediating RRB in both neurodevelopmental

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disorders and animal models converge on circuits involving the basal ganglia and cerebellum. Lastly, we have suggested improvements for neuroimaging investigations in neurodevelopmental disorders and animal models with RRB. These include, but are not limited to, more detailed neuroanatomical labeling approaches, multimodal neuroimaging investigations (e.g., structural and functional connectivity), comparative neuroimaging investigations between clinical populations and corresponding animal models, and use of neuroimaging in concert with more traditional neuroscience techniques. These approaches have the potential to greatly enhance our understanding the brain alterations and circuit pathologies which mediate RRB, and provide promising targets for therapeutic interventions.

Acknowledgements

We would like to thank Marcelo Febo, Luis Colon-Perez, Lisa Curry-Pochy and David Vaillancourt for discussion and comments on this work. We would also like to thank Lisa Curry-Pochy for generating artwork used for figures in this work. This work was supported by the National Institutes of Health [R01MH080055, R21MH110911].

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Figure Captions

Fig. 1. Structures and connections of circuits implicated in RRB in the human (top) and mouse (bottom). Green dots indicate medium spiny neurons of the direct pathway, and red dots indicate medium spiny neurons of the indirect pathway. Solid lines indicate known synaptic connections. The dashed line from subthalamic nucleus to pontine nuclei in the human brain indicates synaptic connections inferred from viral tracer studies in nonhuman primates (Bostan et al., 2010). Lines ending with arrows indicate glutamatergic synapses, whereas lines with flat ends indicate GABA-ergic synapses. *Abbreviations*: **DN**, dentate nucleus of the cerebellum; **GPe**, globus pallidus externa; **GPi,** globus pallidus interna; **PN**, pontine nuclei; **STN**, subthalamic nucleus; **SNc**, substantia nigra pars compacta; **SNr**, substantia nigra pars reticulata.

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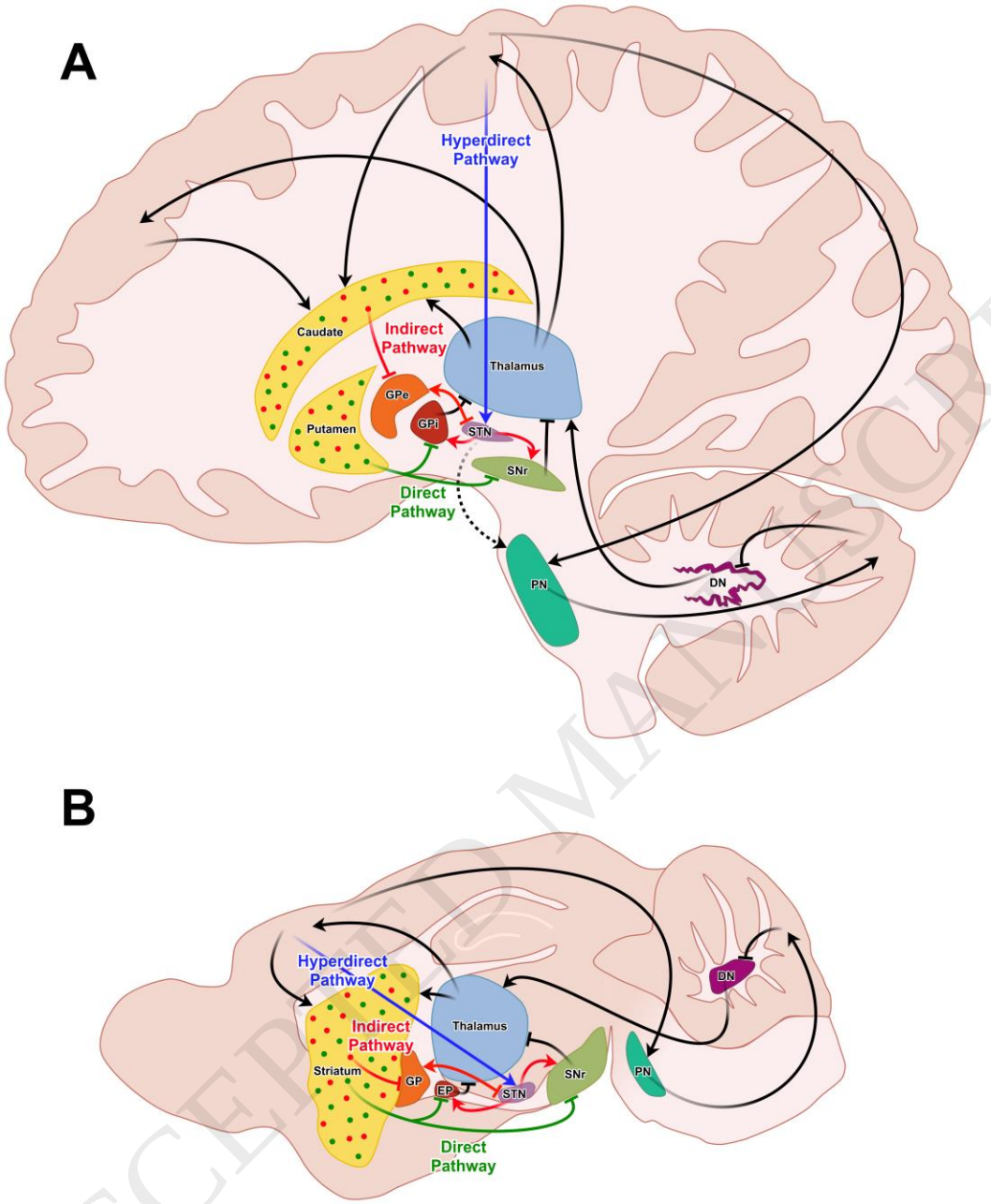

Fig. 2. Cortico-basal ganglia macro-circuits in the human brain, including motor (green), associative (blue), and limbic (red) loops. These regions are depicted as approximated schematics, rather than precise anatomical divisions. *Abbreviations*:

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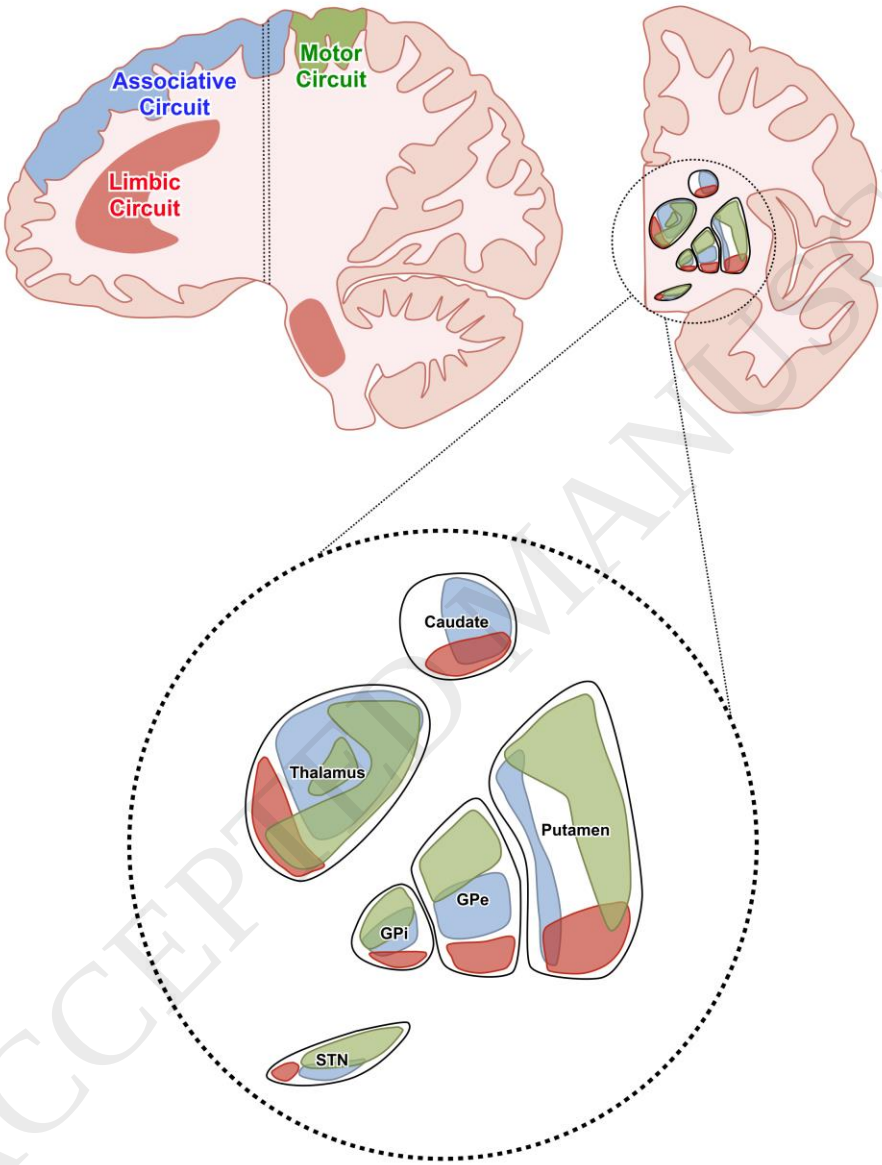
GPe, globus pallidus externa; **GPi,** globus pallidus interna; **STN**, subthalamic nucleus



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Tables

Table 1

Summary of studies that observed a correlation between neuroimaging findings and restricted, repetitive behavior (RRB) in neurodevelopmental disorders, organized by brain region. Each row includes the publication, population studied, imaging modality, behavioral task (if relevant), primary neuroimaging finding, and RRB correlation. Many of these studies also found between-group differences that did *not* correlate with RRB, but these negative findings are not reflected in Table 1. *Abbreviations:* **ASD,** Autism spectrum disorder; **PWS**, Prader-Willi syndrome; **FXS**, Fragile X syndrome; **FMRP**, Fragile X mental retardation protein; **MRI**, magnetic resonance imaging; **fMRI**, functional MRI; **BOLD**, blood oxygen level dependent signal; **rs-fMRI**, resting-state fMRI; **fc**, functional connectivity; **DTI**, diffusion tensor imaging; **FA**, fractional anisotropy; **ABC**, Aberrant Behavior Checklist; **ADI-R**, Autism Diagnostic Interview – Revised; **ADOS**, Autism Diagnostic Observation Schedule; **CBC**, Compulsive Behavior Checklist; **RBS-R**, Repetitive Behaviors Scale – Revised; **V**, ventral; **D**, dorsal; **L**, left; **R**, right.

Brain Region	Study	Population	Imaging Modality	Task (if fMRI)	Primary Finding	RRB Correlation	
Superior Frontal Gyrus (SFG)	Cheung et al., 2009	ASD / children	DTI	-	• Reduced SFG FA	(-)	ADI-R
	Uddin et al., 2013	ASD / children	rs-fMRI	-	• Increased fc between SFG and ACC	(+)	ADI-R
	Weng et al., 2010	ASD / adolescents	rs-fMRI	-	• Reduced fc between SFG and PCC	(-)	ADI-R
Middle Frontal Gyrus (MFG)	Cheung et al., 2009	ASD / children	DTI	-	• Reduced MFG FA	(-)	ADI-R

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	Delmonte et al., 2013	ASD / adults	rs-fMRI	-	• Increased fc between MFG and caudate	(+)	ADI-R
	Klabunde et al., 2015	PWS / children & adults	Task fMRI	Skin-picking behavior	• Increased MFG BOLD during skin-picking	(+)	Task inherent
Inferior Frontal Gyrus (IFG)	Rojas et al., 2006	ASD / children & adults	Structural MRI	-	• No group diff in IFG volume, but L-IFG volume correlated with ADI-R in ASD group	(-)	ADI-R
	Kana et al., 2007	ASD / adults	rs-fMRI	-	• Reduced fc between R-IFG and ACC, insula	(-)	Task inherent
			Task fMRI	Go/No-go	• Reduced R-IFG BOLD during Go/No-Go	(-)	
	Schmitz et al., 2006	ASD / adults	Task fMRI	Go/No-go	• Reduced L-IFG BOLD during successful No-go trials	(-)	Task inherent
Superior Temporal Gyrus (STG)	Rojas et al., 2006	ASD / children & adults	Structural MRI	-	• No group diff in volume, but bilateral STG volume correlated with ADI-R in ASD group	(+)	ADI-R
	Di Martino et al., 2011	ASD / children	rs-fMRI	-	• Higher fc between RV-Putamen and R-STG	(+)	ADI-R
					• Higher fc between LD-Putamen and R-pons	(-)	
Middle Temporal Gyrus (MTG)	Menon et al., 2004	FXS / adults	Task fMRI	Go/No-go	• Reduced R-MTG BOLD during Go/No-go, also + correlated with FMRP levels.	(-)	Task inherent

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Anterior Cingulate Cortex (ACC)	Cheung et al., 2009	ASD / children	DTI	-	• Reduced FA near ACC	(-)	ADI-R
	Thakkar et al., 2008	ASD / adults	DTI	-	• Reduced R-ACC FA	(-)	ADI-R
	Uddin et al., 2013	ASD / children	rs-fMRI	-	• Increased fc within Salience Network (ACC, SFG, thalamus, insula)	(+)	ADI-R
	Zhou et al., 2016	ASD / children & adults	rs-fMRI	-	• Reduced fc L-ACC to R-insula	(-)	ADOS
	Klabunde et al., 2015	PWS/ children & adults	Task fMRI	Skin-picking behavior	• Greater ACC BOLD during skin-picking	(+)	Task inherent
	Menon et al., 2004	FXS / adults	Task fMRI	Go/No-go	• Reduced ACC BOLD during Go/No-go	(-)	Task inherent
Insula	Uddin et al., 2013	ASD / children	rs-fMRI	-	• Increased fc in Salience Network (ACC, SFG, thalamus, insula)	(+)	ADI-R
	Zhou et al., 2016	ASD / children & adults	rs-fMRI	-	• Reduced fc between R-insula and L-ACC	(-)	ADOS
	Cascio et al., 2014	ASD / children & adolescents	Task fMRI	Visual stimuli related to circumscribed interests	• Greater L-insula BOLD for “Own” minus “Other” stimuli	(+)	Yale Special Interests Interview

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	Kana et al., 2007	ASD / adults	Task fMRI	Go/No-go	• Reduced insula BOLD during Go/No-go	(-)	Task inherent
	Menon et al., 2004	FXS / adults	Task fMRI	Go/No-go	• No group differences, but insula BOLD + correlated with FMRP levels in FXS group	(+)	Task with FMRP
Caudate	Estes et al., 2011	ASD / children	Structural MRI	-	• Enlarged striatum volume (Caudaute + Putamen)	(-)	ADOS
	Gothelf et al., 2008	FXS / children	Structural MRI	-	• Greater bilateral caudate volume	(+)	ABC
	Hollander et al., 2005	ASD / adults	Structural MRI	-	• Enlarged R-caudate volume	(+)	ADI-R
	Langen et al., 2014	ASD / children	Structural MRI	-	• No diff at two time points, but caudate greater growth rate	(+)	ADI-R
	Qiu et al., 2016	ASD / young children	Structural MRI	-	• Growth rate of R-caudate	(-)	ADI-R
	Rojas et al., 2006	ASD / children & adults	Structural MRI	-	• Enlarged R-Caudate volume	(+)	ADI-R
	Sears et al., 1999	ASD / adolescents & adults	Structural MRI	-	• Enlarged caudate volume, - correlated with ADI	(+)	ADI
	Hoeft et al., 2007	FXS / children	Task fMRI	Go/No-go	• Reduced R-caudate BOLD during Go/No-go	(+)	Task performance
	Menon et al., 2004	FXS / adults	Task fMRI	Go/No-go	• No group differences, but caudate BOLD + correlated with FMRP levels in FXS	(+)	Task with FMRP

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	Delmonte et al., 2013	ASD / adults	rs-fMRI	-	• Increased fc between R-caudate and R-MFG	(+)	ADI-R
	Pujol et al., 2015	PWS / adults	rs-fMRI	-	• Reduced fc between R-caudate and medial prefrontal cortex, correlated with ordering compulsions	(-)	CBC -
Putamen	Estes et al., 2011	ASD / children	Structural MRI	-	• No putamen group difference. Striatum volume (C+PU) correlated with ADOS	(-)	ADOS
	Hollander et al., 2005	ASD / adults	Structural MRI	-	• Enlarged bilateral putamen volume	(+)	ADI-R
	Langen et al., 2014	ASD / children	Structural MRI	-	• Growth rate of putamen in ASD group (although no between group differences)	(+)	ADI-R
	Eisenberg et al., 2015	ASD / adolescents & adults	Structural MRI	-	• Covariance of volume between putamen, pallidum, accumbens, amygdala,	(+)	RBS-R
	Langen et al., 2012	ASD / adults	DTI & fMRI	Go/No-go	• Trend for reduced FA of putamen tracts, correlated with Go/No-go performance	(-)	Task performance
	Menon et al., 2004	FXS / adults	Task fMRI	Go/No-go	• Reduced putamen BOLD during Go/No-go	(-)	Task inherent
	Di Martino et al., 2011	ASD / children	rs-fMRI	-	• Increased fc between R-putamen and R-STG	(+)	ADI-R
					• Increased fc between R-putamen and R-pons	(-)	

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	Pujol et al., 2015	PWS / adults	rs-fMRI	-	• Reduced fc R-putamen to L-GP and thalamus, correlated with self-picking behaviors	(-)	CBC
Globus Pallidus (GP) undifferentiated	Cheung et al., 2009	ASD / children	DTI	-	• Reduced FA in white matter near GP (internal capsule)	(-)	ADI-R
	Estes et al., 2011	ASD / adolescents & adults	Structural MRI	-	• Enlarged R-GP volume	(+)	ADI
	Pujol et al., 2015	PWS / adults	rs-fMRI	-	• Reduced fc R-putamen to L-GP and thalamus, correlated with self-picking behaviors	(-)	CBC
Cerebellum	Cheung et al., 2009	ASD / children	DTI	-	• Reduced FA in cerebellum	(-)	ADI-R
	Rojas et al., 2006	ASD / children & adults	Structural MRI	-	• Reduced L-cerebellum volume	(-)	ADI-R
	Wolff et al., 2017	ASD / young children	DTI	-	• Increased FA in SCP and MCP correlated with lower-order.	(+)	RBS-R
					• Increased FA in MCP correlated with higher-order.	(+)	