The structure and neurobiology of repetitive and restricted behavior in the autism spectrum

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Thesis outline

The goal of this thesis is to investigate in what way improved characterization of restricted and repetitive behaviors can aid different fields of research and contribute to the diagnosis and treatment of patients in the autism spectrum. It will start by giving a short overview of autism spectrum disorder, with a focus on definition. This is followed by a short summary of the role of restricted and repetitive behaviors in autism spectrum disorder. The biology of these behaviors is then reviewed, followed by a discussion focused on the thesis goal.

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Abstract

Autism Autism spectrum disorder (ASD) is a pervasive and relatively common childhood disorder. It is currently understood that it is a spectrum of disorder, characterized by a very heterogeneous etiology. ***Restricted and repetitive behaviors in autism spectrum disorders*** One of the core components of ASD is restricted and repetitive behaviors (RRBs). This is a broad class of behaviors characterized by repetition and rigidity and is separable from social and communication deficits in ASD. A wide variety of instruments are currently being used to measure RRBs and various models are employed to characterize this heterogeneous category of behavior. ***Biology*** Research on the neurobiology of RRBs has revealed a cortico-basal ganglia system. In this system, direct and indirect pathways involved in sensorimotor, associative and limbic loops, balance different behaviors. This balance can be perturbed by a wide variety of genes and neurotransmitters, resulting in various RRBs. ***Discussion*** Studying RRB has already revealed much in various areas of research, and has led to novel ASD candidate genes and information on the neurobiology of ASD. The possible impact of improved characterization of RRB on ASD research, diagnosis and treatment is discussed.

Autism

Autism is a highly heritable pervasive developmental disorder with a largely unknown etiology. It is characterized by impaired social skills and verbal and nonverbal communication, and repetitive and restricted behaviors (RRB). The following paragraphs will give a short overview of autism spectrum disorder (ASD) with a specific focus on definition.

Prognosis

The long-term prognosis of children diagnosed with ASD is poor. While early and intensive behavioral therapy is relatively effective, less than 30% of all ASD patients ever reach independent status (Billstedt, Gillberg, & Gillberg, 2005; Cederlund, Hagberg, Billstedt, Gillberg, & Gillberg, 2008). The only drug currently approved for ASD is risperidone, which does not target the core symptoms, but rather certain maladaptive behaviors such as aggression and irritability (Matson & Hess, 2011).

Prevalence

Early prevalence studies performed in the 1970's indicated a very rare disorder, with a prevalence of about 4 cases in 10,000 children. Over time, and as ASD became a broader and more well-known category, this estimate increased to a widely accepted and replicated figure of 60/10,000 in 2003 (Fombonne, 2003). The latest reports conclude that the current prevalence of ASD could very well be even higher, reporting prevalence numbers of 90/10,000 and 116/10,000 (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2006 Principal Investigators, 2009; Baird et al., 2006). This has changed autism from a very rare disorder to one of the most common childhood disorders. The increase in prevalence is in large part due to the evolution of the definition from a narrow "infantile autism" towards a more inclusive ASD (see: **Definition**), as well as the greatly increased awareness of the disorder.

Environmental factors

The increase in prevalence could also be partly due to a real increase in incidence, and environmental factors contributing to developing autism have been cause for concern. Many possible environmental risk factors for autism have been researched. Some, most notably vaccinations that supposedly caused autism, have been extensively reported in the media. While it is still considered likely that undetermined environmental factors do play a role, significant environmental risk factors have so far not been found (Newschaffer et al., 2007), and the absence of any link between vaccinations and autism has been conclusively demonstrated (Doja & Roberts, 2006; Madsen et al., 2002).

Definition

History

In 1943, Leo Kanner described eight boys and three girls who were suffering from very similar and pervasive problems. He described them as suffering from "autism" (meaning to be removed from the world, at that time used as an aspect of schizophrenia), obsessiveness, repetitive motor behaviors (RMB) and echolalia. Kanner argued that these children were suffering from a disorder that was markedly different from schizophrenia: instead of withdrawing from reality, as was the case in schizophrenia, the children he describes had never fully been part of that reality. He concludes by labeling the disorder he observes in these children "inborn autistic disturbances of affective contact". Contrary to this label and his conclusion that the disorder should be seen as an innate handicap, the following decades focused more on his observations about the *parents* of the children. Kanner's observation that the parents were intelligent and successful, obsessive, lacking interest in people and emotionally

"cold" (Kanner, 1943) led to the idea that "refrigerator mothers" were to blame for their children's disorder, and this idea remained prevalent for decades. When more systematic research was done comparing families of autistic children to those of healthy children, the view that parenting could be a factor in developing autism was eventually abandoned (Cantwell, Baker, & Rutter, 1979). In the 1970's and 1980's, advancing research into heritability (Folstein & Rutter, 1977; E. R. Ritvo, Freeman, Mason-Brothers, Mo, & Ritvo, 1985) firmly established autism as a developmental disorder with biomedical origin. In 1980, "infantile autism", closely modeled on the description of Leo Kanner, was officially recognized in the Diagnostic and Statistical Manual of Mental Disorders III (American Psychiatric Association, 1980). Criteria included onset before the age of 30 months, lack of responsiveness to other human beings, gross impairments in communication and language, and bizarre responses to the environment. However, in the year before official recognition of autism in the DSM-III, the usefulness of regarding Kanner's autism as a unitary disorder was already strongly challenged in a seminal article by Wing and Gould (Wing & Gould, 1979). In this epidemiological investigation, 132 children impaired in one or more of the three domains of autism (social interaction, language and repetitive and stereotyped behaviors) were examined in detail. After careful analysis, the authors described a very heterogeneous group of children suffering from social, verbal and behavioral impairments, of which those that could be diagnosed with Kanner's autism formed a clear but not absolutely differentiated subgroup. They noted that investigating only a particular subgroup, such as Kanner's autism, would limit usefulness and generalizability of research. What Wing and Gould suggested was a system of classification based on the full range of impairments, not limited to criteria such as delineated by Kanner (Wing & Gould, 1979). The following DSM revision (DSM-III-R, American Psychiatric Association, 1987) replaced "infantile autism" with a much broader definition of "autistic disorder", reflecting this idea of a broader spectrum of disorder.

Current definition

The broad definition of autistic disorder in the DSM-III-R is now replaced with a narrower description in the currently used revision of the DSM-IV (DSM-IV-TR, American Psychiatric Association, 2000) to be more in line with clinical practice and the widely used International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10, World Health Organization, 1992). Autistic disorder is classified as a type of pervasive developmental disorder (PDD). This category also includes Asperger syndrome, childhood disintegrative disorder, Rett syndrome and a relatively broad category of PDD-not otherwise specified (PDD-NOS) which allows for diagnosis of children not meeting full autistic disorder criteria. The DSM-IV-TR criteria for autistic disorder include severe dysfunction before the age of three in language and communication and social interaction, and the presence of restricted and repetitive behaviors (RRBs) and interests.

Future direction

The current draft version of the DSM-V includes proposed changes to this classification. Proposed is a new category: ASD. This would include autism, Asperger's disorder, childhood disintegrative disorder and PDD-NOS. Also, the domains of language and communication and social interaction would be merged into one social/communication domain. To be included in this proposed new diagnostic category of ASD, four criteria must be met: (a) persistent deficits in social communication and interaction, (b) restricted and repetitive patterns of behavior, interests or activities, (c)

symptoms must be present in early childhood, (d) symptoms together must limit and impair everyday functioning (www.dsm5.org, December 2011).

Dysfunction within these domains is not absolute, and patients with ASD can differ greatly even though they have the same diagnosis. Also, since an ASD diagnosis is based on behavior and not etiology or pathophysiology, it should not be seen as a unitary condition but rather as a clinical syndrome. The conceptualization as a spectrum of disorder captures this broad scope and is recognized in the DSM-V plans.

The current view of ASD as a broad spectrum of diverse etiologies converging on similar cognitive and behavioral phenotypes is supported by genetic studies. Although there is a 70-90% concordance rate for autistic disorder in monozygotic twins, linkage and association studies have been relatively unsuccessful in finding specific risk factors, likely due to a heterogeneous etiology (Abrahams & Geschwind, 2008).

A large twin study has shown that in the general population, social, communication and RRB traits were only moderately correlated. This supports the idea that these components are separable in ASD (Ronald, Happé, & Plomin, 2005; Ronald, Happé, Price, Baron-Cohen, & Plomin, 2006). Separating these components would allow for much more pathophysiologically homogeneous groups and thereby greatly aid research into the etiology of ASD.

Restricted and repetitive behaviors in autism spectrum disorders

Kanner in his 1943 study of 11 children already noted the children's "monotonously repetitious" noises, motions and performances, their lack of spontaneous activity and an "anxiously obsessive desire for the maintenance of sameness" (Kanner, 1943). Restricted and repetitive behaviors (RRBs) are now considered one of the three core components of autism, the others being deficits in communication and social interaction. Some form of RRB needs to be present before the age of three for an autism diagnosis (American Psychiatric Association, 2000; World Health Organization, 1992). Current DSM-IV-TR criteria for autism include four RRB subtypes based on clinical observation of patients (table 1). The ICD-10 criteria are very similar (American Psychiatric Association, 2000; World Health Organization, 1992).

A) Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
B) Apparently inflexible adherence to specific, nonfunctional routines or rituals
C) Stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements)
D) Persistent preoccupation with parts of objects

Table 1 DSM-IV definition of restricted and repetitive behaviors (American Psychiatric Association, 2000)

RRBs are a broad and heterogeneous class of behaviors linked by repetition, rigidity, invariance and inappropriateness. Restrictedness refers to the narrowness of focus, inflexibility and perseveration in interests and activities, specific object attachments and insistence that aspects of the environment stay the same. Repetition is the manifestation of rhythmic motor behavior, repetitive speech, repetitive manipulation of objects, routines and rituals (Leekam, Prior, & Uljarevic, 2011; Turner, 1999).

RRBs are observed in both clinical and nonclinical populations and normally developing children often display RRBs that are also associated with ASD patients of all ages (Evans et al., 1997; Leekam et

al., 2007; Thelen, 1979, 1981). RRBs in normally developing children seem to play an adaptive role (Evans et al., 1997; Iverson & Wozniak, 2007; Thelen, 1981) and are difficult to distinguish from abnormal RRBs that might signify a child at risk for ASD. Differences between normally developing children and children that develop ASD are subtle, and in very young children diagnosis of dysfunctional RRB remains complicated (Cox et al., 1999; Moore & Goodson, 2003; Stone et al., 1999; Ventola et al., 2006). In older children, the differences are mostly quantitative and vary in severity, frequency and developmental course rather than category. (Iverson & Wozniak, 2007; Leekam et al., 2007; Matson, Dempsey, & Fodstad, 2009; Ozonoff et al., 2008; Richler, Bishop, Kleinke, & Lord, 2007; Richler, Huerta, Bishop, & Lord, 2010; South, Ozonoff, & McMahon, 2005).

Many of the RRBs observed in ASD is also found in other disorders, such as Parkinson's disease (PD), obsessive compulsive disorder (OCD) and Tourette's syndrome (TS). Many of these behaviors are very similar across disorders, showing mostly quantitative differences. A categorical difference was noted in rituals and restricted interests, which are more pronounced in ASD patients compared to other diagnostic groups (Bodfish, Symons, Parker, & Lewis, 2000; Lam, Bodfish, & Piven, 2008; Lewis & Kim, 2009; Moss, Oliver, Arron, Burbidge, & Berg, 2009).

Research

Many different measurement tools are currently being employed to study normal and abnormal RRB development. A recent review of RRB questionnaires and interviews in ASD revealed that in the 45 articles reviewed, 16 different questionnaires/interviews were used (Honey, Rodgers, & McConachie, 2012).

Most studies that investigate RRB employ questionnaire/interview based methods, mainly the Autism Diagnostic Interview-Revised (ADI-R) and the Repetitive Behavior Scale-Revised (RBS-R) (Honey et al., 2012; Leekam et al., 2011). These questionnaires can give accurate reports on RRBs in different situations (Barrett, Prior, & Manjiviona, 2004; Leekam et al., 2011), give quantifiable data, and are standardized and have been methodologically reviewed (Honey et al., 2012).

The ADI-R is a parent interview based on clinical descriptions of autism patients and the DSM-IV criteria (see table 1) (Le Couteur, Lord, & Rutter, 2003; Lord, Rutter, & Le Couteur, 1994). It contains 14 items rating the impact of RRBs and is commonly used in RRB research. Since the ADI-R is developed as a diagnostic tool to evaluate the presence of the DSM-IV subtypes, its use in studying the patients that are diagnosed by its own criteria introduces a risk of circularity in reasoning.

The RBS-R is a parental questionnaire developed to assess a wider range of RRBs independent of diagnosis (Bodfish, Symons, & Lewis, 1999; Bodfish et al., 2000). It consists of 43 items to assess the severity of six categories of RRBs: stereotyped behavior, self-injurious behavior, compulsive behavior, ritualistic behavior, sameness behavior and restricted behavior.

An interesting example of diagnostic overlap can be found in the use of the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) (Goodman et al., 1989). This questionnaire developed to rate obsessive-compulsive behavior has been found to provide useful information about RRBs in ASD with some modifications (Scahill et al., 2006).

Comparing the results of studies employing these different measurement techniques and definitions of RRBs is problematic. A single accurate and reliable classification and measurement system for RRBs in normal as well as in cross-diagnosis abnormal development would greatly aid research into normal

and abnormal RRB development in children (Bodfish et al., 2000; Leekam et al., 2011; Symons, Sperry, Dropik, & Bodfish, 2005).

Subtypes

Identification of neuropathological processes and contributing genes in ASD has been complicated greatly by the large phenotypic heterogeneity of the disorder. To study more homogenous groups, researchers focus on specific phenotypes such as RRBs (Geschwind, 2009; Lam et al., 2008). Within ASD, RRB is a familial factor, and likely modulated by genes that are mostly independent of those that affect the social and communication domains (Abrahams & Geschwind, 2008; Happé & Ronald, 2008; Ronald, Happé, Bolton, et al., 2006).

The category of RRB itself is also not a unitary entity and contains a wide variety of behaviors. However, there is a lack of consensus on the categorization of RRBs. Many different models are proposed, with 2, 3, 4, 5 or 6 factors (Honey et al., 2012). Results from both ADI-R and RBS-R are in greatest agreement with a 2 or 3 factor model, which are related to the DSM-IV subtypes (see table 1). Items C and D relate to the "low level" (motor behavior) factor of repetitive motor behaviors (RMB), and items A and B to the "high level" (cognitive behavior) factor insistence on sameness (IS) and circumscribed interests (CI), which can be seen as one unitary or as two separate categories. (Bishop, Richler, & Lord, 2006; Cuccaro et al., 2003; Honey, McConachie, Randle, Shearer, & Le Couteur, 2008; Honey et al., 2012; Lam et al., 2008; Mooney, Gray, Tonge, Sweeney, & Taffe, 2009; Richler et al., 2007, 2010; Szatmari et al., 2006; Turner, 1999). An illustration of ordering RRBs along an axis from lower to higher level can be seen in **figure 1**.

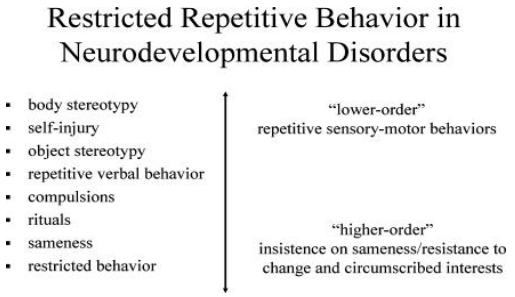

Figure 1 Specific categories of restricted repetitive behavior ranging from "lower order" or motor behavior to "higher order" or cognitive behavior based on Turner (Turner, 1999). From: (Lewis & Kim, 2009).

Despite these issues of definition and grouping, researching RRBs instead has already provided interesting new insights into the pathophysiology of ASD, which will be discussed in the following section.

Biology

Introduction

The relatively scarce research into RRBs has provided novel insights into the pathophysiology of ASD. A model based on interaction between environmental and developmental factors and the cortico-basal ganglia circuitry has emerged, with possible implications for diagnosis and treatment of ASD. In this section, animal and human studies relevant to the neuropathology of RRBs in ASD will be briefly discussed. The reviews by Lewis and Kim (Lewis & Kim, 2009) and Langen et al (Langen, Durston, Kas, van Engeland, & Staal, 2011; Langen, Kas, Staal, van Engeland, & Durston, 2011) are highly recommended for a more in-depth discussion.

Since the RRBs typically found in ASD are not unique to ASD and do not correlate very strongly with other ASD factors, research from other disorders such as OCD can prove to be applicable to specific RRBs in ASD and provide valuable insights into possible etiologies for RRBs in ASD. Special consideration is given to converging evidence from other disorders or mouse models.

Genes

The number of genes that can potentially affect pathological repetitive behavior is large and research into the genetics of RRBs sparse. Here is a short overview of the most commonly referenced RRB related genes.

Genes that are thought to play a role in RRB are mainly neurotransmitter transporter genes. Association studies have linked GABA receptor subunit beta-3 (GABRB3) to autism, serotonin receptor 2c (HTR_{2C}) to autism and OCD, and SAP90/PSD95-associated protein (SAPAP3) to trichotillomania and OCD (Langen, Kas, et al., 2011). Since the $gabrb3^{-/-}$ (DeLorey et al., 1998; Homanics et al., 1997), $5\text{-}HT_{2c}^{-/-}$ (Chou-Green, Holscher, Dallman, & Akana, 2003) and $sapap3^{-/-}$ (Welch et al., 2007) mice are all used in animal models of repetitive behavior, these genes link animal and human studies. When genes are associated with a neuropsychiatric disorder involving repetitive behavior and knockout mouse models of these genes generate repetitive behavior, the converging evidence becomes compelling and more likely to provide valuable insights into the neurobiology underlying RRBs in ASD.

The q11-q13 locus on chromosome 15 has been of foremost interest in autism and RRB. Inherited duplications in this area is the most common genetic abnormality found in ASD (1-2% of all cases). The 15q11-q13 region is also affected in Prader Willi, Rett and Angelman syndromes, which show phenotypic overlap with ASD. GABRB3, located in this region and used in animal models of RRB, is implicated in linkage and association studies of ASD (Abrahams & Geschwind, 2008; DeLorey et al., 1998; Homanics et al., 1997; Lewis & Kim, 2009). When using a measure of insistence on sameness instead of ASD as a grouping factor, much stronger linkage was observed, demonstrating the utility of defining more homogeneous ASD subgroups in genetic research (Shao et al., 2003).

The effectivity of SSRIs in attenuating RRBs in OCD and in certain cases of ASD might point to the involvement of abnormalities in serotonin genes. Indeed, abnormalities in the serotonin-transporter-linked polymorphic region (5-HTTLPR) have been found to be associated with rigid-compulsive behaviors and ASD risk (Sutcliffe et al., 2005). A possible genotype-phenotype relationship has been found regarding variants of 5-HTTLPR, where phenotypic differences, including intensity of stereotyped and repetitive behavior, could be linked to variations of this gene (Brune et al., 2006). The serotonin system is also implicated in the $5\text{-}HT_{2c}$ mouse model, where a knockout of this serotonin receptor gene leads to spontaneous development of repetitive and compulsive behavior (Chou-Green et al., 2003). Knocking out sapap3 in mice, while not specifically targeting the serotonin system, does result in animals displaying compulsive grooming behaviors that are treatable with selective serotonin reuptake inhibitors (SSRIs) (Welch et al., 2007).

Glutamate has been implicated in ASD RRB since the glutamate transporter gene solute carrier family 1 (SLC1A1) is both a susceptibility gene for OCD, as well as being under the highest linkage peak of a recent ASD genome study (P. D. Arnold, Sicard, Burroughs, Richter, & Kennedy, 2006; Dickel et al., 2006; Szatmari et al., 2007). A more specific relationship to RRB in ASD is still unclear (Brune et al., 2008).

While dopamine has an important function in the regulation of RRBs (as will be discussed later, for an illustration see **figure 3**), there is currently no evidence for dopamine genes playing a role in RRBs in ASD (Lewis & Kim, 2009). A possible mechanism by which dopamine can influence RRB is through Delta FBJ murine osteosarcoma viral oncogene homolog B

(ΔFosB). ΔFosB is associated with drug addiction and habit forming (Kelz et al., 1999), and has been demonstrated to selectively affect excessive wheel running. Transgenic animals that overexpress ΔFosB in striatonigral projection neurons (direct pathway) exhibit excessive wheel running, while wheel running is inhibited in animals with ΔFosB overexpression in striatopallidal projection neurons (indirect pathway). Since it is known that striatal ΔFosB expression is modulated by dopamine, this could be a possible avenue for treatment of specific RRBs (Werme et al., 2002). These pathways will be described in more detail in a following section on neurobiology.

Environment

Environmental restriction is one of the most established causes of repetitive behavior in animals of all kinds. In standard laboratory housing of rats and mice, stereotyped behavior is often observed (Garner & Mason, 2002; Würbel, 2001). Environmental enrichment, especially when introduced early in development, can have profound influence on the development of RMB. It has been found to significantly reduce the development of RMB in deer mice and striped mice. Selective changes in cortico-basal ganglia circuitry were associated with this behavioral difference in deer mice (Jones, Mason, & Pillay, 2011; Lewis, 2004). Environmental enrichment is in general associated with reduced stereotyped behavior as well as increased cognitive flexibility. This relationship is likely due to the influence of common cortico-basal ganglia pathways (Lewis & Kim, 2009).

The prenatal environment can also influence development of ASD symptoms, including RRBs. Pregnant rhesus monkeys exposed to immunoglobulin g (IgG) from mothers who had children with ASD had offspring that displayed persistant RMB, while prenatal exposure to IgG from mothers who had normally developing children had no effect (Martin et al., 2008). Prenatal exposure to valproic acid has also been shown to cause symptoms related to ASD in rats, such as RRBs and reduced social behaviors. These behaviors have been shown to be reduced or reversed by enriching the environment the rats live in (Schneider, Turczak, & Przewłocki, 2006)

Since deprivation induced RMB are more common in apes and monkeys than in lower animals, it follows that humans are at an increased risk (Ridley, 1994). Severe behavioral and cognitive problems, many similar to ASD, have indeed been observed in environmentally deprived children from Romanian institutions. However, specific environmental effects on the development of RRB behavior in these children could not be disentangled from other possible contributing factors (Beckett et al., 2002; Rutter et al., 1999, 2007).

Neurobiology

As in genetic studies, neuroimaging studies aimed specifically at RRBs are scarce. Much information has been gained from findings in studies on ASD, OCD, PD, HD and TS however, and many findings correlate with animal studies implicating cortico-basal ganglia circuitry. Genetic studies and the persistence of induced RRBs indicate neurobiological abnormalities to be fundamental to RRBs. Environmental deprivation and enrichment studies have shown that early development is of great importance to the development of RMB. Selective brain changes associated with these stereotyped behaviors are observed in the basal ganglia (Lewis, 2004; Lewis & Kim, 2009; Tanimura, Vaziri, & Lewis, 2010).

Many studies point to a critical role for the basal ganglia in RRB in animals. Experiments have shown a selective attenuation of stereotyped behavior following modulation of striatal dopamine, glutamate and adenosine receptors (Presti, Gibney, & Lewis, 2004;

Presti, Mikes, & Lewis, 2003; Tanimura et al., 2010; Welch et al., 2007).

Broadly speaking, activation of the direct, striatonigral, pathway stimulates the thalamus, enhances behavior and leads to a general increase in activity, not specifically RRB. Inhibition of this pathway suppresses all behavior. Activation of the indirect, striatopallidal, pathway suppresses the thalamus, and reduces RMB. Inhibition of this pathway induces RMB (Langen, Kas, et al., 2011).

Corticostriatal loops can be subdivided into three macro-circuits, based on the primary cortical input location: sensorimotor (motor and oculomotor loops), associative (dorsolateral prefrontal loop) and limbic (orbitofrontal and ACC loops). Repetitive behavior then, is a disruption of any of these circuits. The type and location of disruption would determine the type of RRB. While this is a simplified representation of cortico-basal ganglia circuitry structure and function, the location of disruption in different loops has proven to result in different RRBs (Langen, Kas, et al., 2011). **Figure 2** is an illustration of these loops.

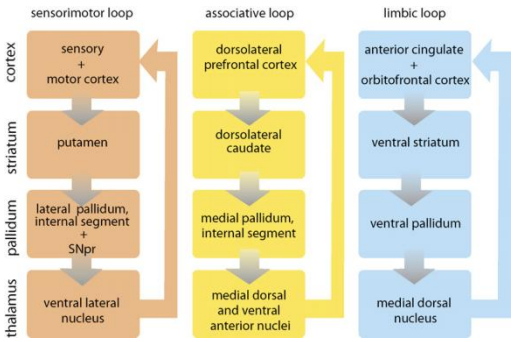

Figure 2 Corticostriatal loops involved in repetitive and restricted behavior. From: (Langen, Kas, et al., 2011).

Imbalance in these cortico-basal ganglia systems has been seen to modulate RRBs. Most attention has been given to how an imbalance between direct and indirect pathways can lead to specific RRBs, based on the location of the imbalance in different loops. An assay of neuropeptides specific to the direct, excitatory striatonigral pathway and the indirect, inhibitory striatopallidal pathway has suggested a more detailed role of the basal ganglia in RMB. Spontaneous RMB in deer mice can be related to a relatively hyperactive direct pathway, which is a consequence of a disturbed and relatively hypoactive indirect pathway (Presti & Lewis, 2005; Tanimura, King, Williams, & Lewis, 2011). Specific pharmacological intervention in the indirect pathway has been shown to reduce stereotyped behavior in deer mice (Tanimura et al., 2010). This is possibly related to the genetic finding that the relative expression of ΔFosB in direct versus indirect pathways is related to excessive wheel running and is associated with habit forming (Kelz et al., 1999).

Lesions in the amgydala and hippocampus have been observed to lead to delayed development of RRBs as well. This has been observed both in macaque monkeys and rats (Bauman, Toscano, Babineau, Mason, & Amaral, 2008; Daenen, Wolterink, Gerrits, & Van Ree, 2002). In macaque monkeys, it was observed that these lesions affected the medial prefrontal cortex, which in turn influenced cortical-striatal connections and striatal dopaminergic functioning.

Structural MRI studies of ASD patients have produced conflicting results regarding the basal ganglia, with larger, smaller and similar volumes being reported (Brambilla et al., 2003; Langen, Durston, et al., 2011; Stanfield et al., 2008). When RRB was used as the grouping variable instead of RRB, a stable and replicated correlation was demonstrated between striatal, mainly caudate nucleus, volume and repetitive behavior (Hollander et al., 2005; Langen et al., 2009; Rojas et al., 2006; Sears et al., 1999).

The anterior cingulate cortex (ACC), an important part of the motivational/limbic cortico-basal ganglia loop, has also been implicated in neuroimaging studies on

ASD and RRBs. Structural, functional and connectivity abnormalities in the ACC and connecting white matter have been related to rigid and repetitive behavior in ASD (Thakkar et al., 2008). In a test of response and cognitive flexibility, the severity of RRB in ASD patients was strongly negatively correlated with ACC activity (Shafritz, Dichter, Baranek, & Belger, 2008).

Neuroimaging studies have shown structural and functional changes in frontostriatal circuits in patients with Tourette's syndrome. While results have not been consistent, dopaminergic modulation of frontostriatal circuits is thought to play a major role in TS (Albin & Mink, 2006).

A corticostriatal model (specifically the motivational, orbitofrontal circuit) with a large role for serotonin dysfunction is currently central to OCD (Abramowitz, Taylor, & McKay, 2009). OCD symptomatology is significantly correlated with cortico-basal ganglia circuit activation, in particular orbitofrontal and caudate activation (Adler et al., 2000). A loss of striatal D_2 receptors in OCD patients is also in line with the cortico-basal ganglia circuit involvement in RRB, specifically indirect pathway disturbance (Denys, van der Wee, Janssen, De Geus, & Westenberg, 2004). While the distal etiology of OCD behaviors remains largely unknown, it appears that they are in large part mediated by the same circuits that are implicated in ASD RRBs.

Neurotransmitters

There are several indicators for the roles of different neurotransmitters in RRB, coming from genetic studies and studies on behaviors in various other disorders and pharmacological studies of risperidone and SSRIs. Various neurotransmitters play a role in the cortico-basal ganglia circuits that form the center of most neurobiological models of RRB. GABA and glutamate agonist and antagonist administration to various areas of the basal ganglia has shown to modulate RMB in animals. In general, increased striatal neuronal activity is seen to disinhibit feedback to the cortex, inducing stereotypic behavior, while reducing striatal activity reduces stereotypic behavior.

Glutamate appears to have a strong link to RRB, due to its specific role in the cortico-basal ganglia circuitry and data from animal studies. Furthermore, SLC1A1, a glutamate transporter gene, has been identified as a susceptibility gene for OCD and is close to the highest linkage peak of a ASD genome scan (P. D. Arnold et al., 2006; Dickel et al., 2006; Szatmari et al., 2007). Several other glutamate related genes (such as neurexin 1 (NRXN1), glutamate receptor iononotropic kainite 2 (GRIK2), tuberous sclerosis 1 and 2 (TSC1&TSC2), and SH3 and multiple ankyrin repeat domains 3 (SHANK3)) are also associated with ASD (Abrahams & Geschwind, 2008; Szatmari et al., 2007).

A modulatory role of dopamine on RRB is indicated in animal studies, and the influence of dopamine on direct and indirect pathway activity has been well described. However, no direct evidence of dopamine involvement in RRBs in ASD is available. In Lesch-Nyhan disease, characterized by severe repetitive self-injurious behavior, patients have a pervasive lack of dopaminergic nerve terminals and cell bodies (Ernst et al., 1996).

Serotonin is indicated due to its strong role in the basal ganglia and involvement in motor disorder (Di Giovanni, Di Matteo, Pierucci, Benigno, & Esposito, 2006). Also, genetic heterogeneity at the serotonin transporter locus (solute carrier family 6 member 4, SLC6A4) is linked to rigid-compulsive behaviors and autism (Sutcliffe et al., 2005). Tryptophan depletion has been associated with a significant increase in RRBs in autism patients (McDougle et al., 1996).

Serotonergic involvement has also been strongly indicated in a study where the severity of RRB in ASD patients was significantly affected by a 5-HT_{1D} agonist (Hollander et al., 2000).

A complex interplay between different neurotransmitters in RRB is likely. An example is the sapap3$^{-/-}$ model. Even though sapap3 is expressed in glutamatergic synapses, the phenotype can be rescued by continued systemic admission of an SSRI (Welch et al., 2007). Also, dopaminergic and serotonergic interventions have both been effective in reducing spontaneous RMB in deer mice (Korff, Stein, & Harvey, 2008). Dopamine induced RMB have been seen to be dependent on serotonin release and can in certain cases be alleviated by drugs that act on serotonin receptors (Langen, Kas, et al., 2011; Lewis & Kim, 2009). A schematic overview of the pathways and roles of dopamine, GABA, glutamate and serotonin can be seen in **figure 3**.

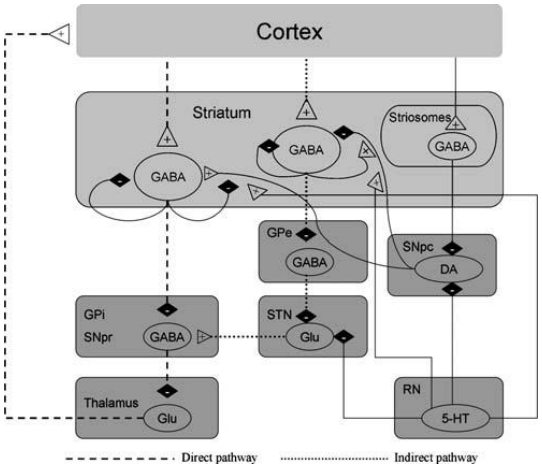

Figure 3 A schematic overview of the pathways and neurotransmitters involved in repetitive and restricted behavior. From: (Lewis & Kim, 2009)

Adenosine could prove to play an important part in this system. A dose dependent attenuation of spontaneous RMB was observed in deer mice that were co-administered adenosine A_{2a} and A_1 agonists. These receptors are selectively expressed in the indirect pathway, and the combination of these receptor agonists activated the indirect pathway, reducing stereotyped behaviors (Tanimura et al., 2010).

Treatment

There are two types of treatment for ASD patients: pharmacological and behavioral therapy. While both have shown some success in reduction of RRBs, neither has been designed specifically for this goal.

Risperidone, the only drug approved for ASD treatment, is a serotonin and dopamine antagonist. While pharmacological studies indicate risperidone can be effective at reducing RRBs in children and adolescents with ASD, the exact mechanism by which risperidone acts on RRBs is unknown and the main effects of risperidone in ASD patients are found more in other measures of behavior such as irritability and aggression (Matson & Hess, 2011; McPheeters et al., 2011; Soorya, Kiarashi, & Hollander, 2008; Wink, Erickson, & McDougle, 2010).

A second class of drugs often prescribed to ASD patients is SSRI, based on its effectiveness in OCD patients in reducing repetitive and obsessive behaviors. Results from studies on the efficacy of SSRIs in managing RRBs are mixed, and results generally show limited effect and some negative side effects (Matson & Hess, 2011; McPheeters et al., 2011; Soorya et al., 2008; Wink et al., 2010).

The National Autism Center concluded that behavioral therapy is relatively effective in treatment of RRBs in ASD patients (National Autism Center, 2009). One goal in behavioral intervention is to increase the repertoire of social and behavioral skills beyond restricted and repetitive behaviors, thereby loosening rigidity, facilitating more flexibility, and reducing repetitive behavior patterns. Early intensive behavioral intervention is one of the most used therapies for ASD, and one of the most effective, although it is not effective for all ASD patients (Reichow, 2011).

Discussion

The utility of a better characterization of RRB in ASD research will now be discussed. The focus will be on the progress that has been made by studying RRB, the improvements that can be made, and what the influence of improved RRB research can be.

Positive effects of studying RRBs have been found across the board. Novel genetic candidates influencing RRBs in ASD and OCD have been discovered that would have been missed had the disorder been used to define groups. Caudate neuroimaging findings had been extremely varied in ASD patients. When RRB was used as a variable instead of diagnosis, increased caudate volume was consistently found. Animal models of RRB have provided us with a well-defined model of cortico-basal limbic disturbances that is useful in guiding research to better understand and potentially treat specific behaviors found in ASD and other disorders.

However, a better and more homogeneous characterization of RRB is a central discussion point in many studies and reviews, across different fields. In neuroimaging, a wide array of different tools are currently being used, the most common one being the ADI-R, which is not intended for research use, and in comparison to other tools such as the RBS-R and CYBOCS, severely lacking in detailed description of RRB. The same ADI-R is also the only tool that has been employed to discover RRB related genes. While somewhat successful in discovering novel candidate genes, using more detailed measurement tools would greatly increase the potential of association and linkage studies, and allow for detection of genotype-specific phenotypes. In pharmacology and therapy, entirely different outcome measures are being employed, mainly the aberrant behavior questionnaire (ABC) and intelligence quotient (IQ) respectively. These measures do not provide detailed information on RRBs, which makes it difficult to interpret the effects of drugs and therapy on specific RRBs. The poor characterization of this central domain of ASD might be a large part of the reason there is currently no effective treatment. Widespread adoption of tools specifically designed to research RRBs, such as the RBS-R is essential to move research in all these fields forward.

Since risperidone is ineffective at treating any of the core domains of ASD, a search for better-targeted therapies for ASD is of high priority. In the case of RRB, there seem to be interesting neurobiological pathways that could be selectively targeted. It seems clear that different types of RRB have different underlying neurobiological substrates, and a detailed inventory of these types of RRB will allow their specific underlying neurobiological substrates to be mapped, and new drug targets for treatment found. A cortico-basal ganglia model has been developed that can account for many different RRB. Specific behaviors have been related to specific dysfunctions in different areas of this system. Detailed investigations of the neurobiological substrate of different RRBs could lead to a better understanding of the relationships between different behaviors across disorders, allow for a better grouping of behaviors on a neurobiological basis, and open an avenue for specific pharmacological interventions. Interesting targets in this system that have already been discovered include adenosine receptors and ΔFosB.

Early diagnosis of ASD in children is another important issue. We currently have little insight in the development of normal and abnormal RRBs, and the boundaries between them. Animal models, as well as clinical practice has demonstrated the importance of early intervention in ASD, and a more detailed understanding of RRBs could lead to improved tools to detect abnormal RRBs in children, and allow them to get earlier access to more specific treatment

options. Using alternatives to the ADI-R has already shown possible early detection of ASD by careful observation of RRBs in infants (Ozonoff et al., 2008).

It has been argued that children with ASD are in a self-imposed restricted environment due to deficits in social skills and communication. This might be a link between the different domains of ASD. It is known that RRBs are observed in animals as well as children that have been in a restricted environment. Since environmental enrichment is effective in mouse models to attenuate RRBs later in life, breaking through the self-imposed restricted environment could reduce RRBs in children as well. Indeed, some success in reducing RRBs has been observed in early behavioral intervention, which includes intensive contact with the child. However, little is still known about the effects of restricted environment on children, and we must be careful with drawing translational conclusions.

A better characterization of RRBs and their underlying neurobiology and genetics will also allow more detailed animal models for specific RRBs. As in humans, RRBs in animal models are often not well described, and many different measures are used. It has been shown that that different types of animal model (such as exposure to prenatal valproic acid, environmental restriction, chronic dopamine stimulation and lesioning) lead to relatively similar behaviors with different neurobiological substrates. It is likely that these models are modeling different kinds of RRBs, which in humans are more behaviorally differentiated than in animals with a more restricted behavioral repertoire. Only better differentiation between various RRBs and their related neurobiological substrates can lead to the discovery of similar substrates in animals. Indeed, careful differentiation of repetitive behaviors in mice has led to models of higher level behavior, related to insistence on sameness and rituals (Bissonette et al., 2008; Eilam, Zor, Szechtman, & Hermesh, 2006). Models such as these allow interspecies trait genetics (Kas, Fernandes, Schalkwyk, & Collier, 2007) of higher level RRBs, greatly broadening the scope of RRB research from simple RMB to much more advanced behaviors.

The potential influence of better-characterized RRBs is large, allowing for improved research in different fields, such as pharmacology, neuroscience and genetics across different disorders, such as ASD and OCD. A more careful and unified method of defining and describing RRBs would allow for studies of more homogeneous subjects and less variation between studies, leading to better defined and comparable conclusions on specific behaviors. This will in turn lead to better defined neurobiological substrates of these specific behaviors, and novel, more specific avenues for (pharmacological) interventions.

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