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Stereotypy : Literature review

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Abstract

Stereotypies have been defined in a variety of ways, but are generally accepted to be involuntary movements that occur repeatedly in the same patterned. These movements are seen in a variety of neurological and psychological conditions but are perhaps less well recognised than other types of movement disorder. Various aspects of stereotypies including pathophysiology, differential diagnosis and treatment have been reviewed.

1. Introduction

Stereotypies have been described for more than one hundred years, initially as part of tic disorders and in dementia praecox. Originally, it was noted as one of psychotic symptoms in dementia praecox, and as a feature of some patients with tics but it has become clear that stereotypy is not restricted to only these conditions.

Stereotypies have also been described in amphetamine addicts [1] and a number of behavioural conditions especially in autism and mental retardation. Recently, numerous other conditions associated with stereotypies have emerged, for example Rett syndrome, Neuroacanthocystosis, Drug-induced (e.g. Levodopa) and recently, NMDA Antibody encephalitis.

2. Definitions of Stereotypy

There are a number of definitions of stereotypy. One of these is proposed by Jankovic. He defined stereotypy as "involuntary or unvoluntary, coordinated, patterned, repetitive, rhythmic, purposeless but seemingly purposeful or ritualistic movement, posture or utterance"[2]. Another definition was derived from American Psychiatric Association which defined stereotypy as "repetitive, non-functional motor behaviour". They also stated that the movements should be repeated in the monotonous pattern without conscious control and occurred in normal level of consciousness.

Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) defined stereotypic movement disorder as "Motor behavior that is repetitive, often seemingly driven, and nonfunctional. This behavior markedly interferes with normal activities or results in severe bodily self-injury. The behavior is not due to the direct physiological effects of a substance or a general medical condition"[3]. Basically, behavioral characteristic of stereotypy includes repetitive, unvarying and non-functional behavior[4]. Definitions of stereotypy are therefore variable, complicated and diverse.

Likewise, there is no consensus on the classification of stereotypies but from some authorities, stereotypies can be divided into either normal (physiological) stereotypy or pathological stereotypy, simple or complex and sometimes by which body parts are involved.

Stereotypy has not been well-recognised when compared to other movement disorder. It can be presented in variety of diseases and caused by a number of aetiology. Stereotypies can be presented in either neurology or psychiatry clinics. At first, stereotypy

was described as a symptom of schizophrenia. Subsequently, stereotypies were observed in amphetamine addicts which defined this behaviour as "Punding"[1]. At present, stereotypies were frequently reported in autism and mental retardation. Recently, substantial conditions that associated with stereotypies have been emerged for example Rett syndrome, Hallervorden-Spatz syndrome, Neuroacanthocystosis, Drug-induced (e.g. Levodopa) and NMDA Ab encephalitis etc. Even though, there are plenty of developing knowledge in stereotypy but there are a few reviews on this topic. This literature review includes pathophysiology, proposed classification including associated conditions and treatment in stereotypy.

3. Objectives

This literature review aims for update the knowledge of Stereotypy, particularly motor stereotypy by divided into

1. Pathophysiology of stereotypy

2. Causes of stereotypy (stereotypy associated conditions)

3. Treatments of stereotypy

4. Methods

4.1 Search strategy

This literature review was undertaken from electrical databases search including MEDLINE (Pubmed), EMBASE, Cochrane and Trip database.

We searched for articles which were published using key words including "Stereotypy" and "Stereotypic movement disorder", in combination with "Pathophysiology", "Causes" and "Therapy". We excluded non-English language articles and review articles. In order to cover all important sources of data, manual search techniques (Cross-references) were also used from the reference in defined publications.

4.1.1 Stereotypy and Pathophysiology

Inclusion criteria: Pubmed, EMBASE, Cochrane, Trip databases were searched for pathophysiology of stereotypy.

Exclusion criteria: We selected only "English" articles

Key words: Stereotypy; Stereotypic movement disorder; Pathophysiology to identify relevant articles in this objective.

We searched in Pubmed using words "pathophysiology" and "stereotypic movement disorder". 61 articles were found from Pubmed in this subject. We excluded 55 studies because they were not useful or relevant to pathophysiology of stereotypy. There were 6 articles left from Pubmed database.

When searching relevant articles in Embase database in last 10 years (1998-2008), we used "Stereotypy" as key words instead of "stereotypic movement disorder" and combined with "pathophysiology", we found 65 articles in English from these key words. Of these articles, there were no additional articles that relevant and have useful data.

Cochrane and Trip database did not retrieve any additional studies while Cross-References retrieved 10 articles related to pathophysiology of stereotypy.

Results: 16 articles were obtained for review, 6 articles from database search and another 10 studies from cross-reference.

4.1.2 Stereotypy and Causes

Inclusion criteria: Pubmed, EMBASE, Cochrane, Trip databases were searched for causes of stereotypy.

Exclusion criteria: We selected only "English" and "Human" articles

Key words: Stereotypy; Stereotypic movement disorder; Causes; Aetiology to identify relevant articles in each objective.

We searched in Pubmed using words "nervous system diseases" and "stereotypic movement disorder". 134 articles were found from Pubmed for these keywords. We excluded 109 studies because they were not useful or relevant to causes of stereotypy. There were 23 articles left from Pubmed database.

In order to cover articles about stereotypy and mental diseases. We used other keywords which are "mental disorders" and "stereotypic movement disorder" 197 articles were found and we excluded the same articles that we found from "nervous system diseases" and stereotypic movement disorder". There were additional 8 articles from these keywords.

When searching relevant articles in Embase database in last 29 years (1980-2008), we used the same keywords with Pubmed, we found 65 articles in English from these key words. Of these articles, there were additional 2 articles that relevant and have useful data.

Cochrane and Trip database did not retrieve any additional new studies while Cross-References retrieved 37 articles related to neurological and psychological conditions related to stereotypy.

Results: 70 articles were obtained for review, 33 articles from database search and another 37 studies from cross-reference.

4.1.3 Stereotypy and Treatment

Inclusion criteria: Pubmed, EMBASE, Cochrane and Trip databases were searched for treatment in stereotypy.

Exclusion criteria: We selected only "English" and "Human" articles

Key words: Stereotypy; Stereotypic movement disorder; Therapy to identify relevant articles in this objective.

We searched in Pubmed using words "Stereotypic movement disorder" and "therapy". 83 articles were found from Pubmed in this subject. We excluded 73 studies

because they were not useful or relevant to treatment of stereotypy. There were 10 articles left from Pubmed database.

When searching relevant articles in Embase database in last 29 years (1980-2008), we used "Stereotypy" and "therapy", we found 16 articles from these key words. Of these articles, there was no additional article that has useful data.

Cochrane database and Trip database did not retrieve any additional studies

Cross-References retrieved 5 articles related to treatment in stereotypy.

Results: 15 articles were obtained for review, 10 articles from database search and another 5 studies from cross-reference.

4.2 Limitation of the methodology

There were important problems during literature searching, which can be summarized here;

1. Stereotypy has variable phenomenologies. Some article use "repetitive behaviour", "compulsive –like behavior", instead of stereotypy or stereotypic movement disorder. We manually select only articles that related to motor stereotypy which is subgroup of repetitive behaviours and excluded compulsive-like behaviours because they are classified in Obsessive-Compulsive Spectrum Disorder (OCSD)

2. A number of articles were reported before 1971 which could not be retrieved from database. The standard textbooks which refer in articles were also used in order to complete data.

3. From literature searching, a lot of conditions causing stereotypy were reported but only few conditions for instance, physiological stereotypies can be compared in each study

because other conditions did not have enough subjects to report and have different methodologies.

4. In some aetiologies, for instance stereotypies from structural lesions and NMDA Ab encephalitis, there were only a few reports causing stereotypy. Therefore, we compared case report in each articles for comparing characteristic in each cases.

Other sources of data

References from the chapters in textbooks had also been reviewed and scrutinized. There were reviews from different movement disorder textbooks as following;

- Movement disorder 3; Chapter 25 (Stereotypies); Joseph Jankovic

- Tics and Related disorders; Andrew J. Lees

  o Chapter 9 (Disorders of movement in the mentally retarded)

  o Chapter 10 (Disorders of movement in schizophrenics)

- Higher-order motor disorders: From neuroanatomy and neurobiology to clinical neurology; Chapter 21 (Tics and stereotypies); Joseph Jankovic

- Parkinson's disease and Movement disorders 5th edition; Chapter 35 (Stereotypy and Catatonia); Joseph H. Friedman

- Movement disorders in neurology and neuropsychiatry 2nd edition

  o Chapter 22 (Crack Dancing and Other Movement Disorders related to cocaine use)

  o Chapter 58 (Movement disorders in Schizophrenia)

  o Chapter 87 (Motor dysfunction in Autism)

  o Chapter 89 (Rett syndrome: A clinical and neurobiologic overview)

  o Chapter 90 (Motor disorders in persons with mental retardation or developmental disabilities)

5. Results

5.1. Pathophysiology of Stereotypy

Pathophysiology of stereotypies are variety and inconclusive. The evidence from literature searching can be summarized in Appendix A1

Stereotypy has been a topic of interest for researchers for several decades. Although substantial knowledge about stereotypy has emerged from this process, pathogenesis of stereotypy is still unclear. Most pathophysiological evidence concerning stereotypy came from animal models. Previous studies about pathogenesis of stereotypies focused on psychological aspects and neurochemical substances.

In view of psychological aspects, they have focused on environmental causes of stereotypy, particularly confinement and deprivation. Confinement was linked with stereotypies due to evidence from captive animals [5]. Previous studies showed that repetitive behaviour could develop in confinement. Similarly, deprivation could also generate stereotypy in animals reared alone and sometimes cause self-damaging and aggressive behaviours. These hypotheses were supported by humans with congenital blindness and deafness who have high prevalence of stereotypies.

Neurochemical substances were also intensively studied in animals. Stereotypic behaviours including sniffing, licking, gnawing, biting and grooming after amphetamine injections in rodents has been observed since 1963 by Randrup[6]. Intrastriatal or systemic injection of indirect dopamine agonists (ie. amphetamine and cocaine) and dopamine agonists (ie. apomorphine) also generates these behaviours in animal models.

In previous study by Kelly[7], 6-Hydroxydopamine (6-OHDA) intracranial injection was used to induce dopamine depletion in amphetamine induced stereotypy rat. In

Nucleus Accumben (NAc) lesion, they failed to induce locomotion response after low dose amphetamine injection but it could be induced in caudate lesion. On contrary, stereotypies induced by high dose amphetamine were inhibited with caudate lesion but not NAc lesion. These results confirmed that stereotypies were mainly mediated by nigrostriatal dopaminergic pathway and locomotor activities were controlled by NAc

Costall and colleague [8] observed varieties of stereotypy behaviours in different lesion in Dopamine(DA) system. They generated lesion structure in DA system including caudate/putamen (CP), globus pallidus (GP) and substantia nigra (SN), mesolimbic nucleus accumbens (ACB), tuberculum olfactorium (TUO) and central amygdaloid nucleus (ACE) by 6-OHDA and observed changing steretoypies including sniffing, biting and locomotor activity in rats. Authors concluded that various types of stereotypy were not mediated by the same sites and each stereotypy involves more than one DA structure area.

In order to explore the role of dopamine receptors and stereotypy, Chipkin and colleague[9] observed up-regulation number of D1 /D2 binding receptors in rat brains. Changing of stereotypies in rats was also compared between Sprague-Dawley rats which were pre-treated with a dopamine antagonist (Haloperidol or SCH 23390) and those which induced to be supersensitive by reserpine. Stereotypies were induced by apomorphine and rats were scored on the severity of stereotypy then striatal D1 and D2 binding sites were determined. They found that the number of striatal D1 and D2 receptors were increased in haloperidol pre-treatment rats but only D2 were significantly increased. They also concluded that apomorphine induced stereotypy was related to both of D1 and D2 but D2 has more important role on stereotypy.

Non-dopaminergic neurotransmitters abnormalities were thought to contribute for causing stereotypies. Glutamate system was proved to be another system involving stereotypies by Karler and colleague. They used CPP, NMDA-type glutamate antagonist,

inhibit amphetamine induced stereotypies [10]. They also demonstrated that stereotypies were able to be generated by an NMDA agonist which had similar effect as amphetamine. These stereotypies were blocked by CPP but not by dopamine antagonist, Sulpiride. This effect suggested that glutaminergic system contribute to generating stereotypies, apart from dopaminergic system. This group also conducted another study using an NMDA-type glutamate antagonist, selective GABAa antagonists inject to amphetamine and cocaine induced stereotypy mice [11]. They found that both agents could block stereotypy. These emphasized that Dopaminergic, Glutaminergic and GABA system involved in stereotypy.

Furthermore, neuropeptides were also considered to contribute in pathogenesis of stereotypies. Blumstein et al. demonstrated by microinjections many kinds of neuropeptide into the medial nucleus accumbens after apomorphine induced stereotypies. Stereotypies were increased by cholecystokinin, neurotensin while met-enkephalin reduced stereotypies. These results confirmed that stereotypies were also modulated by neuropeptides.

Recently, excessive dopaminergic action was proposed to be other factor that can induce stereotypy after dopamine-dependent stereotypies had been reported. It was considered to have the similar mechanism between punding induced by dopamine replacement therapy and psychostimulant. Patch-matrix organization of striatum was discovered by Gerfen [12]. He found that striatum was divided into two compartments, striosomes and extrastriosomal matrix. Limbic system send signals to neurons in the striasome subsequently transmit them to substantia nigra pars compacta. Gene induction assay was used to determine activation of neurons in each compartment in stereotypy induced rodent models. They found that striatal activating function can predict motor stereotypy [13]. Graybiel et al. also found that repetitive stimulation by a dopamine agonist lead to intense expression of c-fos (intermediate early genes) in the striasome associated with induction of stereotypy [14].

5.2. Causes of stereotypies

Most of researches on stereotypies were studied in normal infant (physiological stereotypy), mental retardation and autistic spectrum disorder particularly autism and Rett's syndrome.

Stereotypies have also been observed in tic disorders, obsessive compulsive disorder and unmedicated-schizophrenia without prevalence study. Particular neurodegerative disorders that can cause stereotypies were only reported in view of case study and case series. Stroke, postinfectious (Encephalic lethargica) and autoimmune disorder (Antibasal ganglion antibody associated disorder) are other examples of secondary process that can sometimes affect basal ganglia and their pathway causing stereotypies. Psychostimulants and antipsychotic agents have been known to be important causes of stereotypies but prevalence of stereotypies are unknown.

From literature searching, there were several conditions associated with stereotypies which can be summarized in Appendix A2

Stereotypies associated conditions

- Physiological stereotypy and Primary stereotypy

- Secondary stereotypy

1. Associated with developmental delay

    a. Mental retardation and intellectual disabilities

    b. Autistic spectrum disorders (including autism, pervasive developmental disorder-not otherwise specified (PDD-NOS), Rett's syndrome and Asperger's syndrome)

2. Neurodegenerative disorders

    a. Neuroacanthocytosis

    b. Wilson's disease

    c. Pantothenate kinase-associated neurodegeneration (PKAN)

    d. Lesch-Nyhan syndrome

    e. Frontotemporal dementia

3. Tic disorders and Tourette's syndrome

4. Psychiatric disorder

    a. Obsessive compulsive disorder

    b. Schizophrenia and Catatonia

5. Post infectious and autoimmune disorder

    a. Encephalitis lethargica

    b. Movement disorders associated with Antibasal ganglion antibody

6. Paraneoplastic syndrome (Anti-NMDA Ab encephalitis)

7. Secondary to basal ganglia lesions (Stroke)

8. Drug induced stereotypies

    a. Psychostimulants

    b. Dopamine replacement therapy

    c. Tardive dyskinesia

9. Associated with sensory deprivation (Blindness, Deafness and Confinement)

Physiological stereotypy and Primary stereotypy

Physiological stereotypy was described as "repetitive of movements seen in normal individual". Common physiological stereotypies are finger/hand sucking, foot kicking, lip sucking/lip biting, body rocking, head rolling etc. Physiological stereotypy has been frequently observed in children and was studied by Kravitz and Boehm[15]. In this study, they divided infants into groups. First group included 140 normal infants, 25 normal birth weight infant (>2500 g) with perinatal disease, 22 low birth weight infants (<2500 g) with

perinatal disease and 32 low birth weight infants without perinatal disease. Hand sucking was found in all 140 normal birth weights infant in hours after children birth. Other types of stereotypies including foot kicking, lip biting, body rocking, head rolling and banging were also common. Head rolling and head banging were uncommon (10% and 7%, respectively). Furthermore, infants with low Apgar scores and having history of perinal disease had prolonged hand-sucking times compared to those with high Apgar score.

The second group observed stereotypies in 140 normal developing infant compared to 12 cerebral palsy infants and 22 Down's syndrome infants. All infants were followed from 1 month to 1 year old. The pattern, age of onset and frequency of stereotypies were observed monthly after one month to one year old. In age-matched infant, they found that onset of stereotypies were delayed in Down's syndrome when compared to normal infant. Author suggested in conclusion that the onset of each stereotypies in infant could be used as the marker for early developmental retardation.

The effects of perinatal disease and maturation age on stereotypies were studied for a second time by Field et al.[16]. They compared the onset of stereotypies in 20 infants in each groups; normal term, preterm with respiratory distress syndrome (RDS) and postterm infants with the symptoms of the postmaturity syndrome. The onset of stereotypies in RDS group was delayed but there was no difference from other groups when corrected with the prematurity. These results concluded that stereotypies were not affected by perinatal complication.

Thelen conducted longitudinal study in 20 normal infants in the first year of life[17]. He observed onset, quantity and variety of stereotypies in these children. The results showed that the onset of stereotypies correlated with motor development. Author concluded that stereotypies were normal process in neuromuscular developing.

Another stereotypy study in normal children focused on common types of stereotypy; body rocking, head banging and head rolling [18]. They included 525 normal children who had aged between 3 months to 6 years. In the results, body rocking was observed in 19.1% of all children. Head rolling and head banging were less prevalent (6.3% and 5.1%, respectively). They also noted that stereotypies were not persistent, children displayed stereotypies about 15 minutes in each episode. Body rocking often presented when children were listening to music. Head banging was common when they were tired and head rolling usually presented while they were left alone. In addition, developmental milestones in children who had body rocking and head banging were delayed when compared to those without these stereotypies.

Troster conducted the prevalence study of stereotyped behaviours in non handicapped children[19]. He included children 142 children from 9 residential care institutions. From this study, about 58% of children reported at least one type of stereotypy once a week. Thumbsucking, hair twisting and body rocking occured frequently in children aged 10 months to 3 years and thumbsucking prevalence was decreased inversely with age. In contrast, nail biting or chewing were common among preschool-age children.

Since there were many reports of stereotypies without underlying pathology, we use term "Primary stereotypy" to define as stereotypy which is not associated with other medical and psychological conditions for example mental retardation, autistic spectrum disorder, neurodegenerative diseases etc.

Primary stereotypies were often studied. Stereotypic movement disorder in normal adults were first examined by Castellanos et al. [20]. Of 52 enrolled patients, 32 were excluded because they had been previously diagnosed with psychiatric conditions. 20 remaining subjects were interviewed and analysed in this study. Only 12 patients met DSM-IV diagnostic criteria for stereotypic movement disorder. The results demonstrated

that affective or non-OCD anxiety disorders were common among stereotypic movement disorder patients. Body-rocking is the most common stereotypy (67%) followed by thumb-sucking. Almost all of patient (11/12), the onset of stereotypies started by the aged of 7 and Self-injurious behaviours were found in half of these patients.

Stereotypies in college students have also been studied. It was originally described by Hansen et al that stereotypy were common among this group despite normal intellectual function. Niehaus et al. assessed stereotypies in college students and also linked with compulsive and impulsive symptoms. They included 649 students using questionnaire. The results showed that almost all of students had stereotypic behaviours. Face touching was the most common (75%). Playing with pens and hair were also common in these students (68.2 and 67%, respectively). In addition, a number of stereotypies correlated with higher obsessive-compulsive symptoms score.

In order to examine stereotypies in specific group, nonautistic children stereotypies were studied by Tan et al.[21] They excluded mental retarded patients which were well-known associated condition with stereotypies and included children aged of 2 to 7.5 years. Although there were only 10 children in this study, half of patients had hyperactivity and attention-deficit problems. Arm flapping and hand posturing were common in these children and stereotypies were stopped in two children without prescribing drug. Nonetheless, they all had intelligence and no mental retardation.

Mahone et al studied sterotypies in larger cohort of normal developing children who had neither metal retardation nor pervasive developmental disorders[22]. They did review medical record in 40 children which included from aged 9 months to 17 years. They found that age of onset typically started before 2 years old (75%) and nearly all stopped with cueing (98%). They also noted that stereotypies are more likely to occur more than once a day (90%) and were precipitated by being excited (70%). Flapping was the most common

type stereotypy (48%) and arms were usually involved (70%). Interestingly, ADHD were found to be the commonest condition which associated to stereotypies in this study (25%) and a history of motor or vocal tics before stereotypy were also common in this cohort (18%).

More recently, 100 normal developing children and motor stereotypies have been studied by Harris et al, they conducted longitudinal follow-up study[23]. The average of follow-up duration was about 7 years. In this study, 94% of patients were continued having stereotypy during follow-up while only 6 patients had remission. Most of them had head nodding stereotypies. They found about half of stereotypy patients have underlying conditions such as attention-deficit-hyperactivity disorder, tics disorder and obsessive-compulsive disorder. These emphasized that it was important to recognise these underlying conditions, before simply diagnosing such children with primary stereotypy.

Secondary stereotypy

1. Associated with developmental delay

Mental retardation and Intellectual disabilities

Stereotypies have been frequently observed in children with mental retardation and intellectual disability. Head nodding, head banging, body rocking and self-injurious behaviour are regularly seen in mental retarded patients. Greater stereotypies correlated with lower IQ[24].

Stereotypies are common in the mentally retarded. Prevalence ranges from 34-60.9% in institutionalized patients with mental retardation [25, 26] whilst lower prevalence in those who live in the community [27].

A long-term observational study was conducted by Baumeister. Multiple stereotyped movements were observed in 7 preschool mentally retarded children. They repeatedly examined stereotypies of each child during different in school activities. The results showed that specific activities changed the frequency of stereotypies and concluded that stereotypies could be affected by environmental conditions.

Schwartz et al. analysed topographic of stereotypies between mental retardation and normal infants. They compared characteristic of hand gazing and body rocking in each groups. This study demonstrated that there were topographic differences between retarded and non-retarded infants. These results supported hypothesis that stereotypies in retarded children might not extend from physiological stereotypy in normal developing infants.

Stereotypies were investigated in three groups of preambulatory children; Down syndrome (n=7), motor impairments (n=11) and non-disabled children (n=10). Chronological age ranged from 2.8-38.3 months. Subtype of stereotypies, frequency and duration had been observed in each group for 9-14 months biweekly. This study found that stereotypies were less prevalence in motor impairments group compared to those with Down syndrome and non-disabled children. This study supported hypothesis that stereotypies is essential for preambulatory motor development.

Since the aetiology of mental retardation is variable, Haw et al conducted a study observing movement disorder only in Down's syndrome [28]. They included 145 subjects and compared between patients from hospital and community. Of these patients, 22 patients had received neuroleptic treatment. Movement disorders particularly orofacial dyskinesia were common (>90%) in this patients. Stereotypies were observed in 39% of all patients. When focusing on body parts, stereotypies were most common in upper extremities (40%). trunk and face and tongue were less common (34% and 20% respectively).

Thompson and Reid conducted a longitudinal follow-up study in 100 people with severe intellectual disabilities [29]. Stereotypies tended to persist over the 26 year follow up in comparison to many other behavioural symptoms which resolved.

Self-injurious behaviours (SIB) have been frequently reported with stereotypy in autism and mental retardation. SIB can also be seen as a symptom of complex disease for instance Tourette's syndrome, neuroacanthocytosis, Lesch-Nyhan syndrome etc. Prevalence of SIB was about 10-15% in institutionalized retarded patients. Moreover, the prevalence of SIBs in retarded patient and autism were higher.

Autism spectrum disorders

Autism is the most common disorder in Autism spectrum disorders (ASDs). It was generally characterised by "restricted , repetitive and stereotyped patterns of behaviour, impairment in social interaction and communication which onset typically start before the aged of three"[30]. Prevalence of autism was variable reported ranging from 1/1000 up to about 1/150 children from recent study with male gender preponderance [31]. Several clinical features were found to be associated with autism, for instance cognitive disability, seizure, persistent primitive reflexes. Definite pathogenesis of autism is still inconclusive but substantial theories were proposed including abnormal brain neurochemistry (high peripheral sereotonin concentrations), neuroanatomy abnormalities, environmental factors and genetic factors.

Even though language developmental abnormalities were frequently described as prominent clinical features, autistic children have impairments in motor function for instance delayed walking ability. Clumsiness and impaired motor integration were also observed with symptoms of irritability and hyperactivity. Apart from these symptoms, repetitive behaviour disorders including stereotypic movements were regularly seen in

autism and have been widely studied. Body rocking, foot tapping, flapping of upper extremities and flicking fingers at the eyes were common in autism.

There were some differences between autistic stereotypies and nonautistic stereotypies. Firstly, the rate of stereotypies seems to be correlated to mental age in nonautistic group, additionally, the severity in autistic stereotypy is more relentless than those with nonautistic children and appears to be more common than among age and ability matched control.

Stereotypies in autism were compared to mental retardation by Bodfish et al.[32]. They observed repetitive behaviour in 32 adult mentally retarded persons with autism compared to 34 mentally retarded subjects without autism. The results suggested that stereotypies were more common in adult mentally retarded person with autism than those without autism (aged, gender and intellectual level-matched). Moreover, autism severity could be predicted by severity scores for stereotypy in a previous study. Recent study from Matson and Dempsey[33] confirmed the same result.

Age is other factors associated with stereotypies in autism. MacDonald et al. [34] studied stereotypies comparing between autistic spectrum children and normal developing children in the aged match (2,3 and 4 year-old). 30 subjects participated in autistic spectrum children and normal children. Results suggested that autistic groups had greater stereotypy than normal control in all age-matched group (2, 3 and 4 year-old) with increasing intensity in older groups.

Prevalence and risk factors for self-injurious behaviours in autism was also studied[35]. Baghdadli et al. enrolled 222 autistic children who had aged between 2-7 years. The data collected from medical records and interviews with their parents. Of these patients, they divided in sample into 2 groups which were autism with SIBs and autism without SIBs. The results showed that prevalence of SIB was 53%. A logistic regression

analysis demonstrated that history of perinatal diseases and higher degree of autism was risk factors of SIBs in autistic children.

Rett's syndrome (RTT) was first described in 1966 by Rett [36]. RTT was classified in autistic spectrum disorder. RTT typically affects females, although males can have RTT [37]. Most of Classic RTT is caused by mutation in Methyl-CpG-binding protein 2 (MECP2) gene [38]on X-Chromosome. Girls with RTT are normal until 18 months and subsequently develop a range of behavioural and motor abnormalities. The early signs of RTT are microcephaly and growth retardation that present before the age of 2 [39]. Classically, autistic features, hand stereotypies (hand wringing or washing and clapping) and mental retardation become apparent later in most patients. Hand stereotypies normally develop after age 2 years. As the syndrome progresses, RTT patients can have seizures, scoliosis, autonomic dysfunction and anxiety after 3 years old. They lose the ability to walk and become wheelchair-dependent as adolescents. Parkinsonian feature are also reported in RTT after aged 20 [40, 41].

Rett syndrome and stereotypic movements has been frequently reported in previous articles. FitzGerald et al. studied associated movement disorders in 32 patients aged between 30 months to 28 years old who had Rett syndrome [42]. Stereotypic movements and gait disturbance were the most common motor abnormalities in Rett syndrome. They also found that hyperkinetic movements were more commonly seen in young patients while the older patients tended to be bradykinetic.

Hand stereotypies were commonly seen in RTT. There had been defined in various way including "repeated, quite simple and essentially clumsy movements with incorporated tapping, rubbing and clasping or squeezing, washing, wringing/wriggling, twiddling, twisting the fingers and clapping" [43-45]. Stereotypic hand movements tended to be performed in mid-line position [45].

Although hand stereotypies are a classical feature and one of the diagnosic criteria in RTT[46] , other types of stereotypies are also very important according to the largest study of stereotypies in RTT which conducted in 2007. Temudo et al. reported stereotypies in 83 patients comparing between RTT with MECP2 mutation and those without mutation [47]. They found that MECP2 mutation in 63.9% of patients. Overall, the most prominent hand stereotypies were wringing and washing by both hands in mid-line. Bruxisms were also very common in this cohort. In MECP2 mutation group, they had more mixture and number of stereotypies, without hand gaze stereotypies. Furthermore, hand stereotypies (without hand gaze), bruxism and 2 or more types of stereotypies were found to be associated with MECP2 mutation. Atypical stereotypies in RTT have often been reported in previous case studies [41, 48, 49].

2. Neurodegenerative disorders

Neuroacanthocytosis

Neuroacanthocytosis is a group of hereditary neurodegenerative disorder which includes Chorea-acanthocytosis (ChAc), McLeod syndrome (MLS) and Abetalipoproteinaemia. Only ChAc and MLS typically present with involuntary movements. They normally present in the third to fourth decade. Chorea and facial hyperkinesias were most common features from previous study [50]. Dystonia and vocal-motor tics are commonly found. Parkinsonism and gait abnormalities were also reported. Cognitive impairment, personality changes, and dysarthria are clues of diagnosis. Seizures were fairly common. Distal muscle weakness and atrophy with depression of deep tendon reflexes are essential signs for diagnosis. In terms of stereotypies, self-injurious behaviour for instance lip-tongue biting and head banging were occasionally reported with more prevalence in ChAc than MLS.

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A fresh blood smear for acanthocytes is important for diagnosis but the quantity of acanthocytes in the blood smear does not correspond to severity. Serum creatinine kinase (CK) is generally mildly elevated. Mutation of VPS13A is diagnostic test for ChAc while specific antibodies to Kell phenotype or XK gene mutation use for diagnose MLS

Pantothenate kinase-associated neurodegeneration (PKAN)

PKAN is one of the neurodegeneration with brain iron accumulation (NBIA) diseases with autosomal recessive inheritance pattern. Presenting clinical features are broadly divided by the age of onset. Early-presenting PKAN patients usually present with dystonia, dysarthria and pyramidal abnormality leading to gait difficulties whilst late-presenting PKAN are more likely to have parkinsonian symptoms in initial presentation [51]. Early-presenting PKAN usually develop symptoms before age 6 years with rapid progressive deterioration and has more aggressive clinical course.

Stereotypic movement disorders have been reported in two cases of Hallervorden-Spatz syndrome which thereafter has been renamed as PKAN. The first case was reported in 16-year-old boy who initially presented with gait dystonia and frequent falls. Obsessions and compulsions were also noted at the beginning. Complex motor tics, generalized dystonia and stereotypies developed within one year after on onset. The second case was 40 year-old female who developed had severe lower extremities dystonia and stuttering speech at the aged of 16. Obsessions and stereotypic movements developed later and persisted into adulthood. Two mutations on PANK2 gene were detected in the second case.

Lesch-Nyhan syndrome

Lesch-Nyhan syndrome (LND) is an inborn error of purine metabolism caused by mutations of hypoxanthine-guanine phosphoribosyltransferase (HPRT). Absent HPRT

activity leads to failure in recycling of hypoxanthine and guanine, consequently, the overproduction of hyperuricemia. LND is X-linked recessive disorder so it usually affects males. Heterozygous females are typically asymptomatic carriers.

LND patients are normal at birth but psychomotor delay (ie. hypotonia) becomes apparent before 6 months old. Hyperuricemia can cause gouty arthritis and nephrolithiasis. Neurological deficits divided into three categories which are motor disorders, cognitive impairment and self injurious behaviour. Abnormal movements are normally observed after delayed development for 18 months. Dystonia is very common while choreoathetosis are less common (about 50%) [52, 53]. Generalized action dystonia with hypotonia at rest was commonly seen in motor disorders. Chorea and ballism associated with voluntary movements were also noted. Ocular examinations were abnormal in LND patients [54].

Anderson and Ernst conducted study focusing on self-injurious behaviours (SIB) in 40 LND patients aged between 2 to 32 years. Biting lips and fingers are the most common forms of SIB. Onset of SIB ranged from 1 to 10 years and SIB were variable in daily activities. Stressful event particularly removal of restraints for bathing aggravated SIB worse (71.1%) while "enjoy himself" were associated with decreasing SIB (94.9%) [55, 56].

Wilson's disease

Wilson's disease (WD) is autosomal recessive disorder which is caused by ATP7B gene mutations on chromosome 13 [57-60]. These result in defective of ATP7B protein leading to copper accumulation in liver because of failure excretion copper into biliary system. Copper deposit can be seen in specific structures in extrahepatic organ for instance, proximal renal tubular cells, Descemet's membrane in cornea and the brain. MRI brain can demonstrate basal ganglia, thalamus, midbrain, pons and cerebellum abnormalities due to

copper deposit. Cortical atrophy and widespread white matter change were observed in some patients [61, 62]. These cause a variety of neurological symptoms and signs.

WD patients mainly present with either hepatic or neurological manifestations. Patients who present with neurological signs and psychiatric symptoms tend to be older than those with hepatic disease. Severities of hepatic manifestations range from asymptomatic hepatomegaly to fulminant hepatic failure. Hepatic manifestations usually present in late childhood or adolescence and onset after age of 40 is unusual.

In view of neurological presentation, the average onset is in second to third decade. Tremor is the most common sign of neurological features in WD. Other abnormal signs such as dystonia, cerebellar dysfunction and gait abnormalities were also common. Chorea, tics and myoclonus are not typical presentation. There was only one report which described stereotypies as a presenting sign of Wilson's disease[63].

Frontotemporal dementia (FTD)

FTD is a neurodegenerative condition which characterised by personality change and behavioural disturbance. FTD patients typically present between the ages of 45 and 65. Variety of neuropsychiatric symptoms such as social and personal conduct impairment, lack of emotion and loss of insight are main features in FTD. Stereotypic behaviours are one of supportive features in FTD and can differentiate from other types of dementia particularly Alzheimer's disease (AD) [64, 65].

However, stereotypic movements in FTD have been little studied. There were reported in a few articles[66].

The largest trial was conducted by Mendez[67]. 18 patients who met FTD criteria were studied and compared with 18 AD patients as a control group. There is no statistically significant difference between sex, age, education and dementia scores (MMSE and CDR).

Stereotypic behaviours were found in 8 FTD patients while only 1 patient was seen in AD group. Stereotypical movements included body rubbing (legs/arms, face and another part), clapping thighs, body rocking, eyebrows and mouth moving, lips pursing and fingertips picking. There was no difference in terms of involuntary movement in two groups when using the Abnormal Involuntary Movement Scale (AIMS). Interestingly, functional imaging (PET and SPECT scans) had abnormal orbitofrontal activity in all FTD patients who had stereotypical behaviours. Further larger studies are needed to confirm these findings.

3. Tics disorder and Tourette's syndrome

Tics disorder can be difficult to distinguish from stereotypies. Obsessive-compulsive disorder, Tics and Tourette's syndrome can sometimes associated with stereotypies [68] [22]. Premonitory urge is one of important clues that usually present in Tics disorder [69] while it is absent in stereotypy. Regarding pattern of disease, tics tend to be variable and fluctuating in severity[70] whereas stereotypies are generally fixed and having identical repetitive patterned. Furthermore, stereotyped movements in complex motor tics typically present with frequent eye blinking, shrugging shoulder, grimacing and head shaking whilst body rocking, foot tapping, hand waving and hair pulling-curling are more common in stereotypies [2, 71]. Adult onset of tics is uncommon and secondary tics should be considered. Obsessive and compulsive symptoms are phenomenon sharing between Tourette's syndrome and obsessive-compulsive disorder.

Although there was no prevalence study of stereotypies in Tics but these phenomenons were reported by Ringman and Jankovic [72]. They reported occurrence of symptom between tics and autistic spectrum disorder (Asperger's syndrome and autistic disorder) aged range from 3 to 32 years. All 12 patients met DSM-IV criteria for autistic

spectrum disorder and display variety of stereotypic movement disorders including body rocking, head banging etc. Of these patients, 7 patients had motor and vocal tics.

Stereotypic movement disorders can be another presenting in Tourette's syndrome. On occasion, mixture of tics and stereotypy are suggestive of specific syndromes for instance Autistic spectrum disorder, Rett's syndrome, Lesch-Nyhan syndrome etc.

4. Psychiatric disorders

Obsessive-compulsive spectrum disorders (OCSD)

Obsessive-compulsive disorder is the important neuropsychiatric disorder characterised by "intrusive thoughts or images (obsessions), which increase anxiety, and by repetitive or ritualistic actions (compulsions), which decrease anxiety". Typical symptoms are divided into "obsessive symptoms" and "compulsive symptoms". Obsessions typically present with concerning of contamination, harmful, saving and expenses and religious. OCD patients are regularly doing compulsive behaviours for instance, washing, bathing, checking, ordering and hoarding. OCD has been studied in substantial clinical researches. Abnormal anatomies, neurotransmitters, genetics and immunology have been observed in OCD patients and thought to be associated but exact pathogenesis is still unclear. OCD patient who had head of caudate lesion and putamen has also been reported.

Stereotypy can sometimes present with OCD and can be difficult to distinguish. Compulsions are different from stereotypy because these typically generate inner tension or anxiety and can be relieved by accomplishing the movement.

Repetitive behaviour in autism and obsessive compulsive disorder were compared in recent study from Zandt et al. This study excluded patients who had comorbid illness, for instance Tourette syndrome/Tic disorder, intellectual disability and anxiety disorder. They observed 54 subjects in 3 groups which were autistic spectrum disorder (n=19), OCD

(n=17) and normal developing control group (n=18). Repetitive behaviour measures were assessed by The Repetitive Behaviour Questionnaire (RBQ) and the Children's Yale Brown Obsessive-Compulsive Scale (CY-BOCS). The results found that compulsions and obsessions were more prevalence in autistic group and OCD group than control group, similar to stereotypic movements. Moreover, obsessions and compulsions in OCD were higher score than those with autism.

Stereotypies can present either as a primary psychiatric disorder or a part of complex syndrome for instance tics disorder, focal brain lesion and encephalitis lethargica.

OCD was thought to be related with various basal ganglia disorders, in particular Parkinson's disease and Sydenham's chorea, and Tourette's syndrome. Previous researches in OCD showed that neurobiological basis of OCD related to neurotransmitter (dopamine-serotonin), abnormal neuroanatomy, genetics and neuroimmunology.

Schizophrenia and Catatonia

In the beginning, stereotypies were observed as one of multiple symptoms in patients who had catatonia. Kahlbaum described catatonia as the "symptom complex characterised by psychotic negativism, catalepsy, mutism, stereotypies, verbigeration and muscular symptoms". Kraepelin included catatonic symptom within "dementia praecox" and suggested that catatonia could be presented in other diseases such as mood disorder, secondary from focal brain lesions. Bleuler proposed term "schizophrenia" using instead of dementia prarecox and he considered catatonia as subtype of schizophrenia. He observed that stereotypies of motor, speech (echolalira, palilalia and verbigeration) and thought were frequently seen in schizophrenia. Stereotypies ranging from simple (clapping, body rocking) to complex (walking, bowing) were also noted. Some complex stereotypies, for

example rewriting of a phrase were particularly in schizophrenia but not in other conditions.

Likewise, DSM-IV included catatonia within the group of catatonic schizophrenia which was characterized by one or more of the following essential features: "immobility, mutism, negativism, mannerisms, stereotypies, posturing, grimacing, excitement, echolalia, echopraxia, muscular rigidity, and stupor". It become clear that catatonia can also be seen in other psychiatric disorders (eg. mood disorders) and a vast number of medical conditions (Table 1)

Schizophrenic patients have been observed with variety of movement disorders before discovering antipsychotic agents. Oral and perioral dyskinesia, choreiform movements, tremor and catatonia were often noted in the unmedicated patients.

Caligiuri et al. conducted a study in 24 schizophrenic patients who had never received neuroleptic drugs [73]. The results showed that parkinsonian features including rigidity and bradykinesia were commoner among these patients (21% and 12%, respectively) than normal control group without psychiatric symptoms correlation.

Spontaneous dyskinesia in neuroleptic-naïve schizophrenia were reviewed in 14 studies [74], Fenton found that prevalence in first-episode schizophrenic patients is about 4% and seem higher up to 40% for those who aged over than 60 years.

Causes of Catatonia

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(Source: Galenberg AJ. The catatonic syndrome. Lancet 1976;1:1339-1341)

Psychiatic	- Schizophrenia - Mood disorders - Dissociative disorders
Neurologic	- Frontal lobe lesions - Temporal lobe lesions - Limbic system lesions - Basal ganglia lesions (eg. Globus pallidus) - Diencephalic lesions (eg. Thalamus) - Traumatic brain injury - Epilepsy - Infection (eg. Syphilis) - Wernicke's encephalopathy - Narcolepsy - Tuberous sclerosis
Medical	- Hypercalcemia - Diabetic ketoacidosis - Hepatic encephalopathy - Membranous glomerulonephritis - Pellagra - Acute intermittent prophyria - Homocystinuria

Causes of Catatonia (Continued)

Drugs and Toxins	- Aspirin - Neuroleptics - Adrenocorticotropin (ACTH) - Ethanol - Amphetamine - Mescaline - Phencyclidine (PCP)

5. Post infectious and autoimmune disorder

Encephalitis lethargica (EL)

Encephalitis lethargica or von Economo's disease has been a subject for the interest of neurologists from neurologist after worldwide epidemic during 1916-1927. Since then, the incidences has declined but there have been occasionally reported for sporadic cases. Classical EL features usually start with pharyngitis, lethargy and headache. EL patients subsequently developed various symptoms and signs including hypersomnolence or abnormal sleep-wake cycle, opthalmological abnormalities (opthalmoplegia, ptosis, papilledema/optic neuritis and pupil abnormalities), movement disorders (both hyper- and hypo-kinetic). Oculogyric crisis and central cardiorespiratory features are distinct symptoms. A range of neuropsychiatric disorders, for instance catatonia, obsessive-compulsive disorder, agitation, depression and mutism were also reported in survivors from case series.

Stereotypies have occasionally been observed in EL patients but other movement disorders were more common. Stereotypy types were different in each case and non specific. Parkinsonian symptoms were found in 60% of EL patients. Oculogyric crises help

to differentiate EL from idiopathic Parkinson's disease. Several movement disorders have been noted in case reports. Myoclonus, facial tics, chorea and pyramidal signs can be present in EL. Dystonia, jaw/tongue tremors, open-mouth postures were found in historical review. In some case, they had also abnormal body posture (retrocolis) and gait abnormality (festination and hemiparetic gait). Recently, there were 2 cases report suspected EL who presented with catatonia, stereotypy and dystonia-parkinsonism[75]. CSF lymphocytoses was documented in both cases with the presence of oligoclonal bands. They had parkinsonism which was responsive to levodopa treatment. During admission, they developed side effects from dopamine antagonists with oculogyric crises and neuroleptic malignant syndrome. Both of them had complete recovery after 12 months of onset without neurological deficit.

Movement disorders associated with Antibasal ganglion antibody

Antibasal ganglia antibodies (ABGAs) were originally recognised in Sydenhem's chorea in 1976. Subsequently, a great deal of conditions have been discovered and thought to be related to ABGAs for example, Post-streptococcal acute disseminated encephalomyelitis, Encephalitis lethargica, Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), Tourette's syndrome and obsessive-compulsive disorder etc. Patients are usually presented with various kinds of movement disorders (tics, chorea, dystonia) and psychiatric symptoms.

Complex syndrome including tic disorder, stereotypies and abnormal behaviour were proposed to be another condition that associated with ABGA[76]. In this study, Edwards et al. reported four patients who presenting with adult onset tics and positively antibasal ganglia antibodies. The age of onset was ranging from 27-42 years. Three of four patients had also psychiatric symptoms which were cognitive impairment, fearful of social

situations, paranoid, compulsive symptoms and anxiety. Motor stereotypies were reported in one case which involved her right hand and foot. She had also multiple motor tics which were able to temporary suppressible while stereotypies were persistent and unable to be restrained by distraction.

6. Secondary to basal ganglia and structural lesions

Focal basal ganglia lesions can cause a range of movement disorders. Dystonia was the most common movement which cause by lesions of the basal ganglia [77].

Sterotypies from stroke were also often reported. Sterotypies from ischemic stroke was firstly reported by Maraganore et al. They described 17-year-old boy who developed complex hand stereotypies 5 months following aortic coarctation surgery. He had throwing movements of the hand and continuous chewing. He had obsessive thoughts and was emotionally labile. Subsequently, he developed a variety of stereotypies including clasping hands behind his back and head, flailing his arms, protruding tongue, sniffing, rubbing his eyes and hopping with two steps at a time. A small infarct of right putamen was documented by MRI brain. Post-stroke unilateral parkinsonism and complex stereotypic movements including repetitive opening mouth, body-rocking and pacing legs after 4 weeks of stroke onset was also reported[78].

Fung et al. described four patients who developed stereotyped movement disorders hours to days after of stroke. Stroke lesions were located at basal ganglia in three patients and thalamus in one patient [79]. Scratching or rubbing of the hands in upper limbs and movements of the heel up and down in the lower limbs were commonly observed in these patients.

Although basal ganglia lesions were commonly observed in stereotypies, there were some cases which involved other areas. Sato et al. described stereotyped stepping

movement in one patient who presented with generalized tonic-clonic seizure in the aged of 50. His stepping movement intermittently occurred for 15 days for several minutes to more than an hour in each episode. MRI showed hyperintensity lesions in bilateral medial frontoparietal areas. The authors suggested that this area may affect locomotion as a higher control level of brainstem or spinal cord. More recently, Nguyen et al reported a case of 54-year-old man who had a basilar artery stroke and subsequently developed punding-like behaviour including watching television, shopping from internet and compulsive eating [80]. He exhibited hypergraphia with writing recipes and spend most of the time on cooking recipes. He was not feeling relieved but became frustrated when stopped from doing these activities.

There was one report of stereotypies developing after evacuation of subdural hematoma in a 21-year-old man. He had previous history of ischemic stroke at right anterior cerebral artery. He exhibited stereotypies including body rocking and teeth clicking accompany with impulsivity and occasionally agitation 10 week after operation. CT brain revealed 1.5 cm left frontal lobe subdural hematoma with mass effect when he had stereotypies. His symptoms were gradually improved by sertraline.

All of previous case reports were summarized in Appendix

7. Drug induced stereotypies

Psychostimulants

Amphetamine and Cocaine are well known to be the cause of stereotypy. These were firstly described in amphetamine addicted patient by Rylander [1]. He used the term "punding" to describe stereotyped behaviour in these patients.

In order to evaluate occurrence of repetitive reward-seeking behaviours (RRSB) syndrome and punding which were classified as the most severe form of RRSB in cocaine

addiction, fifty cocaine addicts were studied by psychiatric interview[81]. From this study, 8% of cocaine addicts had punding and majority of repetitive seeking behaviour developing soon after first drug intake.

Furthermore, other movement disorders related to cocaine were also reported in previous case reports [82, 83]. Tourette's syndrome were commonly seen while OCD, dystonia, tremor, opsoclonus-myoclonus and chorea were also observed after using cocaine [83, 84].

Dopamine replacement therapy

Friedman first reported punding in a parkinson's disease (PD) patient who developed these symptoms 6 year after receiving levodopa treatment[85]. He also characterised punding as "a complex stereotyped behaviour which is composed of intense fascination with repetitive purposeless movements, in particular taking apart mechanical objects, handling, examining and sorting common objects, or picking at oneself without stopping". Since then, punding has been interested from clinician and recognised as behavioral disorder that associated with dopamine replacement therapy in parkinson's disease.

From Diagnostic and Statistical Manual of Mental Disorders version IV (DSM IV), punding was classified in dopaminergic medication-related impulse control behaviours in Parkinson's disease. Impulsive control behaviours encompass gambling, hypersexuality, compulsive shopping, eating and compulsive medication use.

Pathophysiology of dopamine replacement induced punding is thought to be similar as stereotypy in amphetamine and cocaine addicts which are related to excessive dopamine stimulation, striatal plasticity change and dopamine receptor sensitivity.

There have been studies of various aspects of punding including epidemiology, risk factors and treatment. In terms of prevalence, there were only a few previous punding prevalence studies in Parkinson's disease. Evans and colleagues conducted an interview study in 50 PD patients who were currently on high dopamine replacement therapy (more than 800 levodopa equivalent units per day). They found punding in 14% of these patients [86]. Conversely, prevalence of punding in another study by Miyasaki et al. was very low. There were only 1.4% of patient who had punding from 373 PD patients [87]. They argued that this disparity could be related to difference in methods, population in studies and treatments.

Tardive dyskinesia

Stereotypies are a part of tardive dyskinesia. Orofacial-lingual-masticatory movement was traditional term of tardive dyskinesia. It considers one of the features of stereotypic movement disorder. Legs, arms, trunk and pelvis can also be involved. Since there were phenomenologies overlapping between stereotypyies and tardive dyskinesia, these would be difficult to distinguish. In addition, their similar phenomenon and terminology led to confounding prevalence studies of both diseases.

Hand stereotypies from tardive syndrome were also reported by Keneko et al. They reported 83-year-old lady who developed stereotyped hand clasping after initiating neuroleptic treatment one and a half year. She originally presented with resting tremors both hands and head with predominatedly left arm rigidity and parkinsonian gait. She was subsequently diagnosed vascular parkinsonism from clinical and globus pallidus ischemic lesions from CT brain. These stereotypies were suppressible for up to half a minute without generating inner tension and disappeared during sleep. Her hand clasping sterotypies continued even after stop haloperidol over a year.

8. Paraneoplastic syndrome (Anti-NMDA Ab encephalitis)

Paraneoplastic limbic encephalitis (PLE) is a paraneoplastic syndromes which patients usually present with cognitive dysfunction, seizures and prominent psychiatric features[88]. Small cell lung carcinoma has been proved to be associated with PLE and is the most common underlying tumour. Although Anti-Hu antibodies (Anti-Hu Ab) were frequently found in these patients[89, 90], up to 40% of patients do not have Anti-Hu Ab and these group seem to have better prognosis. They were less likely to develop extensive disease (eg. paraneoplastic encephalomyelitis- PEM) and more often respond to treatment compared to those who have Anti-Hu antibodies [89]. Apart from Anti-Hu Ab, other antineuronal antibodies has been found including Anti-Ta(Anti-Ma2) and Anti-Ma but they were less common than Anti-Hu Ab and had more resistant to treatment[90].

Paraneoplastic Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis associated with Ovarian Teratoma has been described recently[91]. Indeed, there were several case reports from previous articles before identifying the target autoantigens. These syndrome causes by NMDAR antibodies which target NR1/NR2 heteromers of NMDA receptor. Since NR1/NR2B are particularly expressed in the hippocampal region and forebrain, patients typically present acute psychiatric symptoms, behavioural change, decreased level of consciousness, seizures, autonomic dysfunctions, multiple types of hyperkinetic movement disorders[91].

Considering the involuntary movements, choreiform movements including orofacial dyskinesia, dystonic posturing of the extremities, myoclonus and stereotypies were observed in previous case reports. Most of the patients had favourable outcome after teratoma resection.

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9. Associated with sensory deprivation (Blindness, Deafness and Confinement)

Sensory deprivation has been linked with stereotypies. The evidence firstly came from evidence from rhesus monkeys which were confined (cage-stereotypy). Human and animals in solitary incarceration in adulthood are vulnerable for developing stereotypies with abnormal limb movements and body-rocking [5].

Prevalence and causes of stereotyped behaviour in blind infants were observed by Troster et al[92]. They asked parents of 85 blind children between the ages of 10 months to 6 years. The result showed that stereotypy was found in every child and eye poking and body rocking were the most common stereotypies in this cohort.

Recently, stereotypies in congenitally blind children with neurodevelopment disabilities were compared to those who did not have disabilities using video recording for assessing[93]. Of 26 blind children, stereotypies were noted in 19 patients (73%). Body rocking was the most common stereotypy (30.7%), lying face downwards (22.8%) and jumping (11.4%) respectively.

5.3 Treatment

Since pathogenesis of stereotypy remains uncertain and aetiologies of stereotypy are diverse, treatments of stereotypies depend upon individual pathogenesis and aetiology. Severities of stereotpies and psychosocial impact are also taken into account.

The articles from database and cross-reference about treatment in stereotypic movement disorder can be summarized in **Appendix A3**

A range of behavioural treatments have been used for stereotypies treatment. Positive reinforcement, including differential reinforcement of other behaviours (DRO) and differential reinforcement of behaviour incompatible with the targeted maladaptive behaviour (DRI) were frequently used. Aversive procedures such as time-out and overcorrection etc. were also reported to help stereotypies in mentally retarded and autistic patients. Unfortunately, the efficacy of results could not be concluded and unclear because of the limited number of subjects in each study [94].

Self-injurious behaviour (SIB) has been considered to be the most severe form of stereotypies so there has therefore been a particular target of treatment.

A number of pharmacological treatments have been suggested for treating stereotypies. Dopamine, opioid and serotonin systems were the main targets for treating SIB because of evidences in animal model.

Singh and Millichamp reviewed pharmacological treatment of SIB in mental retardation. They found that about 50% of institutionalized retarded patients were prescribed an antipsychotic. They divided antipsychotics into Phenothiazine group (Chlorpromazine, Thioridazine and Mesoridazine), Butyrophenones group (Haloperidol) and Rauwolfia Alkaloids (Reserpine). Most of the studies on antipsychotic treatment show some benefit in decreasing SIB but all studies have design problems, for example, number

of participants, lack of control group, results confounded by other treatment (behavioural therapy).

Haloperidol was proved to have benefit in decreasing stereotypic behaviour in autism by Campbell and colleagues. This double-blind, placebo-controlled study showed that Haloperidol (dosage range from 0.5 to 4 mg per day) has significant effects on reducing stereotypies and social withdrawal in hospitalized autistic patients. Furthermore, subsequent study from the same group also showed benefit when compared to placebo without cognitive side effect. Nevertheless, neuroleptic treatment for stereotypies and SIB should be used only for the last option because it can cause tardive syndrome.

Atypical antipsychotics were also reported a benefit in SIB because the wider receptor blockage activities compared to typical antipsychotic agents. Olanzapine was studied in 7 patients who had learning disability and SIB [95]. In terms of SIB, olanzapine showed benefit in 4 patients, 1 deteriorated and 2 remaining the same. Further larger trials are needed to confirm this efficacy. Risperidone was one of atypical antipsychotics that proving benefit in 100 autistic child with severe behavioural problems. In this study, they conducted a multicenter, randomized, double-blind using risperidone compared to placebo. Population included children 5-7 years old and primary outcomes were the score on the Irribility sub-scale of the ABC and Clinical Global Impressions-Improvement (CGI-I) scale. The results showed that after receiving resperidone 8 weeks, 56.9% reduction in the irritability score. There was a 69% improvement on the CGI-I scale while 12% in placebo group. This study confirmed the benefit of risperidone on autistic SIB.

Opioid overactivity is proposed to be an underlying mechanism of stereotypies[96, 97]. Therefore, opiate antagonists (naloxone and naltrexone) have been studied in SIB patients. Naloxone and Naltrexone were used in clinical practice with uncertain results. Some cases had positive results while others reported negative effects. Recently,

Naltrexone double-blind placebo-controlled trial was conducted. 32 mental retarded autistic patients with or without SIB were treated with naltrexone for 4 weeks and the outcome was evaluated by direct observations and the set of checklists including the Aberrant Behavior Checklist (ABC), list of target behaviour and the Clinical Global Impression Scale. Naltrexone failed to show improvement on SIB and autism. Moreover, the incidence of stereotypies seemed higher from ABC score and Clinical Global Impression Scale.

Selective serotonin reuptake inhibitors (SSRI) are another group of drugs that could be useful to treat stereotypies and SIB. This comes from evidence of serotonin deficiency in autism and OCD which are commonly associated with SIB. Benefits from fluoxetine, paroxetine were also reported in SIB with mental retardation [98, 99]. However, fluoxetine has been reported to cause complex abnormal movements were also reported [100].

Benzodiazepines, methylphenidate, reserpine and clonidine may also be useful in some patients who had SIB and stereotypies. However, the results are still uncertain.

Stereotypies in some conditions, in particular punding in Parkinson's disease, can be sometimes improved by gradual reduction of dosage of dopaminergic drugs. Rescued therapy for example apomorphine injection should be avoided. Benefits from Quetiapine and Amantadine have been observed only in case reports of punders [101].

Bilateral simultaneous deep brain stimulation targeted in both antero-ventral and posterior part of globus pallidus interna was reported in a Leshch-Nyhan patient. Self-injurious behaviour disappeared after surgery with gradual improvement of dystonia and dyskinesia [102].

6.0 Discussion

Despite developing knowledge in stereotypies, the exact pathogenesis is still unclear. Several theories have been proposed resulting from research in animal models, mentally retarded and autistic patients.

From literature searching about pathogenesis, research in stereotypies divided into psychology models and neurochemical models. In view of psychology models, stereotypies were thought to be related to neuromuscular development, practice functions, self-stimulation and relieving anxiety.

Neurochemical models started from manipulating amphetamine induced stereotypy in animals and dopaminergic system were proved to be the major neurotransmitter causing stereotypies. NMDA-type Glutaminergic neuron, GABAergic neuron and neuropeptides were subsequently proved to contribute stereotypies. Discovering subcomponents of striatum, striosomes and matrix, led to a new hypothesis for dopamine-dependent stereotypies which were created by neuroplasticity in cortico-basal ganglia circuits.

Physiological stereotypies, in particular body rocking, head rolling and head nodding, are commonly seen in normal infants but usually disappear when they are grown up. There are many associated diseases which can be present with stereotypies, therefore, other conditions are worth considering before diagnosing physiological stereotypies.

Other neuropsychiatic conditions, especially Tic disorders and Tourette's syndrome, schizophrenia, OCD, ABGA associated diseases were also considered particularly those who come with multiple abnormal movements and prominent psychiatric symptoms. Post-stroke stereotypies have been often reported but the exact prevalence is not known.

NMDA antibody encephalitis is the latest condition that can be presented with stereotypies. Peculiar clinical features are thought to be remote effect of teratoma. This

condition is important and prompt searching for teratoma should be considered because it has favourable outcome after tumor resection.

Treatment for stereotypies is mainly symptomatic. Treatments are focus on self-injurious behaviours which could be dangerous for the patient. A range of drugs has been used for treat stereotypies and SIB. SSRI and Atypical antipsychotic drugs are the most promising drugs apart from traditional antipsychotics which can cause tardive dyskinesia/dystonia. Methylphenidate and benzodiazepine were reported some benefit in case reports and case series but lack a controlled trial.

In conclusion, stereotypies are not pathognomonic for any conditions. There are many causes of stereotypies and the clinician should thoroughly evaluate patient to make a diagnosis and consider appropriate treatment. Further studies of the pathogenesis of stereotypies are essential to verify new modality of treatments which have more efficiency without side effects.

7.0 Summary and Conclusions

7.1 Pathophysiology of stereotypy

- Most of previous researches about pathophysiology of stereotypy used animal model for studying.

- From psychological point of view, confinement and deprivation were proposed to be the cause of stereotypy.

- On contrary to psychological aspect, neurochemical substances were mainstay research of stereotypy.

- Nigrostriatal dopaminergic system is essential network that thought to be the origin of stereotypy and D2 receptors were proved to have crucial role.

- Other neurotransmitter systems, in particular Glutaminergic system and GABAergic system contribute to dopaminergic system generating stereotypy

- Neuropeptides is another neurchemical agent that related to stereotypy

- Discovering Patch-matrix organization of striatum led to more understanding in stereotypy.

- Measuring of striatal function can predict motor stereotypy which resemble to mechanism of excessive dopaminergic action in levodopa-indcued dyskinesias.

7.2 Causes of stereotypies

Physiological stereotypy and Primary stereotypy

- Physiological stereotypy (ie.finger/hand sucking) is common condition that can be found in normal infants.

- The delayed of physiological stereotypy can be the indicator for abnormal development.

- Primary stereotypies were often studied in the past. Non-autistic children, Non-disabled children and Normal developing children can have stereotypic movement disorders but affective disorder (ie.anxiey disorder), ADHD should be excluded because there were regularly seen in prior studies.

Secondary stereotypy

1. Associated with development delay

Mental retardation and Intellectual disabilities

- The prevalence of stereotypies is higher in mentally retarded group than normal developing children.

- The frequency of stereotypies is even higher in those with lower IQ.

- Institutionalized retarded persons have higher prevalence of stereotypies than those who are non-institutionalized mental retardation.

- Self-Injurious behaviour (SIB) is more common in retarded person but there were substantial conditions, particularly tourette's syndrome, neuroacanthocytosis and Lesch-Nyhan syndrome should also be considered.

Autistic spectrum disorders

- Stereotypies are well-known features among autistic patients, apart from language developmental abnormalities.

- Body-rocking, foot-tapping, flapping upper extremities are common stereotypies in autism but none of stereotypy is specific for autism

- Stereotypies are more common in mentally retarded person with autism than those without autism.

- SIB can be seen in up to a half of autistic children. Moreover, history of perinatal diseases higher degree of autism were risk factors of SIB in autism.

- Hand stereotypies are classical feature in Rett syndrome but other types of steretypies can also be seen.

2. Neurodegenerative disorders

- Neuroacanthocytosis, in particular Chorea-acanthocytosis and McLeod syndrome can present with self-Injurious behaviours. Lip-Tongue biting and head banging were more common in Chorea-acanthocytosis.

- Stereotypies can be one of complex symptoms of Pantothenate kinase-associated neurodegeneration (PKAN). It usually presents with other features for instance complex tics, dystonia and psychiatric symptoms.

- Self-Injurious behaviour, especially biting lip and fingers are salient features of Lesch-Nyhan syndrome.

- Wilson's disease is a rare cause of stereotypic movement disorder.

- Stereotypic behaviours are another features for differentiate frontotemporal dementia from Alzheimer's disease.

3. Tics disorder and Tourette's syndrome

- Stereotypies can occur with Tics and Tourette's syndrome and sometimes both features are another presenting features of specific syndromes (ie Autistic spectrum disorder, Rett's syndrome, Lesch-Nyhan syndrome)

- There are some overlap phenomenon between autistic spectrum disorder and Tics.

4. Psychiatric disorders

- There are overlapping features in Obsessive-compulsive disorder (OCD) and stereotypies.

- Stereotypic movement disorder are more prevalence in OCD group than control group.

- Stereotypies are also found in schizophrenic and catatonic patients but the exact prevalence is unknown because cooccurence of dyskinesia.

5. Post infectious and autoimmune disorder

- There were a few reports of stereotypies in Encephalitis lethargica patients but other movement disorders (ie parkinsonism, dystonia) are more common.

- There was one report of Antibasal ganglia antibodies associated with movement disorders who present with stereotpies, tic disorder and behavioural changes.

6. Secondary to basal ganglia and structural lesions

- Not only focal brain lesions in basal ganglia but also medial frontoparietal and frontal lesions can generate stereotypic movements.

7. Drug induced stereotypies

- Psychostimulants and antipsychotic drugs (in tardive dyskinesia) can be causes of stereopy (Also known as "Punding").

- Dopamine replacement therapies, levodopa and dopamine agonist, are associated with punding with the incidence between 1.4-14%.

8. Anti-NMDA Ab encephalitis

- Stereotypy and several movement disorders have been reported in NMDAR encephalitis associated with ovarian teratoma.

- This condition has favourable outcome after teratoma resection.

9. Sensory deprivation (Blindness, Deafness and Confinement)

- Sensory deprivation can generate stereotypies from captive monkeys model.

- Researches in blind children showed high prevalence of stereotypies.

7.3 Treatment of stereotypy

- Treatment of stereotypic movement disorder based on aetiology, severity and psychosocial impact.

- Behavioural treatments including positive reinforcement, aversive procedures were reported benefit for stereotypies in mental retardation and autistic patients.

- Pharmacological treatments were also used for self-injurious behaviours which are considered to be the most severe form of stereotypies.

- Traditional antipsychotic drugs (ie. Haloperidol) can use for treating stereotypies but should be used only for the last resource because these drugs associated with tardive syndrome.

- Atypical antipsychotic drugs (ie. Olanzapine and Risperidone) are other optional drugs for treating stereotypic movement disorder and had benefit for treating SIB

- Naloxone and Naltrexone had benefit in some SIB patients but these fail to prove a benefit in randomized-controlled trial.

- Selective serotonin reuptake inhibitors (SSRI) (ie. Paroxetine) can be use in stereotypies or SIB in OCD.

- Stereotypies in some condition for instance punding from dopamine replacement therapy can sometimes be treated by decreasing dose of dopaminergic drugs and avoiding apomorphine injection.

- Deep brain stimulation was reported benefit in one Leshch-Nyhan patient but it is only case study.

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Appendix A1 Studies related to pathophysiology of stereotypies

Table 1 : Studies related to pathophysiology of stereotypies

Study	Author, Year, Journal
Studies from database search (n=6)	Karler et al., 1998, Pharmacology Biochemistry & Behaviour Barwick et al.,2000, Neuroreport Canales and Graybiel, 2000, Nature neuroscience Glickstein and Schmasuss, 2004, Journal of Comparative Neurology Mcnamara et al.,2006, Synapse Ishiguro et al.,2007, International Journal of Neuroscience
Studies from cross-reference (n=10)	Costall et al., 1977, Brain research Chipkin et al.,1987, Pharmacology Biochemistry& Behaviour Crawley et al.,1987, Brain research Tschanz and Rebec, 1989, Pharmacology Biochemistry &Behaviour Kuczenski and Segal, 1989, Journal of Neuroscience Hiroi et al.,1989, Pharmacology Biochemistry & Behaviour Karler et al.,1995, Brain research Zanella et al,1996, Physiology and Behaviour Presti et al., 2003, Pharmacology Biochemistry & Behaviour

Appendix A2 : Studies related to causes of stereotypies

Table 1 Physiology and Primary sterotypy

Study	Author, Year, Journal
Studies from database search (n=4)	**Castellanos et al., 1996, Journal of Clinical Psychiatry** **Rafaeli-Mor et al., 1999, American Journal on Mental Retardation** **Mahone et al., 2004, Journal of Pediatric** **Harris et al.,2007, Pediatric Neurology**
Studies from cross-reference (n=9)	Kravitz and Boehm, 1971, Child Development Sallustro and Atwell, 1978, The journal of Pediatrics Field et al.,1977, Developmental Psychobiology Thelen, 1979, Ethology and Sociobiology Schwartz et al, 1986, American Journal of Mental Deficiency MacLean et al., 1991, Journal of Abnormal Child Psychology Troster, 1994, Journal of Abnormal Child Psychology Tan et al, 1997, Movement Disorders Kates et al., 2005, Pediatric Neurology

Table 2 Stereotypy Associated with developmental delay : Mental retardation

Study	Author, Year, Journal
Studies from database search (n=4)	**Castellanos et al., 1996, Journal of Clinical Psychiatry** **Newell et al., 1999, American Journal on Mental Retardation** **Berkson and Andriacchi, 2000, Research in Developmental Disabilities** **Hottingger-Blanc et al., 2002, European Journal of Paediatric Neurology**
Studies from cross-reference (n=12)	Baumeister et al., 1980, Journal of Abnormal Child Psychology Schwartz et al., 1986, American Journal of Mental Deficiency Rojahn, 1986, American Journal of Mental Deficiency Dura et al., 1987, American Journal of Mental Deficiency Watkins and Konarski, 1987, American Journal of Mental Deficiency Rogers et al., 1991,British Journal of Psychiatry MacLean et al.,1991, Journal of Abnormal Child Psychology Rojahn et al., 1993, Annals of Clinical Psychiatry Bodfish et al., 1995, American Journal on Mental Retardation Haw et al.,1996, Movement Disorders Thompsom and Reid, 2002, British Journal of Psychiatry Symons et al., 2005, Journal of Intellectual Disability Research

Table 3 Stereotypy associated with developmental delay : Autistic spectrum disorder

Study	Author, Year, Journal
Studies from database search (n=13)	Choi et al., 1991, Yonsei Medical Journal
	Yodnopaklow, 1996, Journal Medical Association of Thailand
	Granana and Tuchman, 1999, Seminar in Pediatric Neurology
	Bodfish et al.,2000, Journal of Autism and Develpmental Disorders
	Gritti et al., 2003, Functional Neurology
	Mahone et al., 2004, Journal of Pediatrics
	South et al., 2005, Journal of Autism and Developmental Disorders
	Carcarni-Rathwell et al.,2006, Journal of Child Psychology and Psychiatry
	Temudo et al., 2007, Neurology
	Iverson and Wozniak, 2007, Journal of Autism and Developmental Disorders
	Cuccaro et al., 2007, Child Psychiatry and Human Development
	Leekam et al., 2007, Journal of Child Psychology and Psychiatry
	Temudo et al., 2008, Movement disorders

Table 3 Stereotypy associated with developmental delay : Autistic spectrum disorder (Continued)

Study	Author, Year, Journal
Studies from cross-reference (n=8)	FitzGerald et al., 1990, Movement disorders
	Lewis and Bodfish, 1998, Mental Retardation and Developmental Disabilities
	Baghdadli et al.,2003, Journal of Intellectual Disability Research
	MacDonald et al., 2006, Research in Developmental Disabilities
	Roze et al., 2007, Movement disorders
	Temudo et al., 2007, Movement disorders
	Matson and Dempsey, 2008, Journal of Development and Physical Disabilities

Table 4 Stereotypy associated with neurodegenerative disorders

Study	Author, Year, Journal
Studies from database search (n=1)	**Mendez and Shapira, 2008, Movement Disorders**

Table 5 Stereotypy associated with Tics disorder and Tourette'syndrome

Study	Author, Year, Journal
Studies from database search (n=2)	**Kompoliti and Goetz, 1998, Movement Disorders** **Ringman and Jankovic, 2000, Journal of Child Neurology**
Studies from cross-reference (n=0)	-

Table 6 Stereotypy associated with Psychiatric disorder

Study	Author, Year, Journal
Studies from database search (n=1)	**Morrens et al., 2006, Schizophrenia Research**
Studies from cross-reference (n=0)	-

Table 7 Stereotypy associated with post infectious and autoimmune disorders

Study	Author, Year, Journal
Studies from database search (n=3)	**Lance et al., 1998, Movement Disorders** **Dale et al., 2007, Movement Disorders** **Edwards et al., 2004, Movement Disorders**
Studies from cross-reference (n=0)	-

Table 8 Stereotypy associated with Paraneoplastic syndrome (Anti-NMDA Ab encephalitis)

Study	Author, Year, Journal
Studies from database search (n=0)	-
Studies from cross-reference (n=3)	Sansing et al., 2007, Nature Clinical Practice Neurology Lizuka et al., 2008, Neurology Seki et al., 2008, Journal Neurology Neurosurgery Psychiatry

Table 9 Stereotypy associated with Secondary to basal ganglia and structural lesions.

Study	Author, Year, Journal
Studies from database search (n=3)	**Sato et al., 2001, Neurology** **McGrath et al., 2002, Brain Injury** **Nguyen et al., 2007, Stroke**
Studies from cross-reference (n=3)	Maraganore et al., 1991, Movement disorders Kulisevsky et al.,1996, Movement disorders Fung et al.,1997, Movement disorders

Table 10 Stereotypy associated with Drug-induced

Study	Author, Year, Journal
Studies from database search (n=1)	**Fernandez and Friedman, 1999, Movement Disorders**
Studies from cross-reference (n=1)	Kaneko et al., 1993, Movement Disorders

Table 13 Stereotypy associated with sensory deprivation (Blindness, Deafness and Confinement)

Study	Author, Year, Journal
Studies from database search (n=1)	**Fazzi et al., 1999, Brain and Development**
Studies from cross-reference (n=1)	Troster et al., 1991, Journal of Abnormal Child Psychology

Appendix A3: Studies related to treatment of stereotypies

Study	Author, Year, Journal
Studies from database search (n=10)	Bharucha and Sethi, 1996, Movement Disorders Davanzo et al., 1998, American Journal on Mental Retardation Fernandez and Friedman, 1999, Movement Disorders McDonough et al., 2000, Journal of Intellectual Disability Research Furusho et al., 2001, Brain and Development Hollway et al., 2005, American Journal of Psychiatry Helvink et al., 2006, The Journal of Neuropsychiatry and Clinical Neurosciences Keuthen et al., 2007, International Clinical Psychopharmalogy Kashihara and Imamura, 2007, Movement Disorders Jankovic et al., 2008, Movement Disorders
Studies from cross-reference (n=5)	Jankovic and Orman, 1988, Neurology Markowitz, 1990, Journal Clinical Psychopharmacology Willemsen-Swinkels, et al. 1995, Archive General Psychiatry Research Units on Pediatric Psychopharmacology Autism Network, 2002, The New England Journal of Medicine

Appendix B

Diagnostic criteria for 307.3 Stereotypic Movement Disorder

A. Repetitive, seemingly driven, and nonfunctional motor behavior (e.g., hand shaking or waving, body rocking, head banging, mouthing of objects, self-biting, picking at skin or bodily orifices, hitting own body).

B. The behavior markedly interferes with normal activities or results in self-inflicted bodily injury that requires medical treatment (or would result in an injury if preventive measures were not used).

C. If Mental retardation is present, the stereotypic or self-injurious behavior is of sufficient severity to become a focus of treatment.

D. The behavior is not better accounted for by a compulsion (as in Obsessive-Compulsive Disorder), a tic (as in Tic Disorder), a stereotypy that is part of a Pervasive Developmental Disorder, or hair pulling (as in Trichotillomania).

E. The behavior is not due to the direct physiological effects of a substance or a general medical condition.

F. The behavior persists for 4 weeks or longer. Specify if: With Self-Injurious Behavior: if the behavior results in bodily damage that requires specific treatment (or that would result in bodily damage if protective measures were not used)

Appendix C

Table 1: Stereotypy in physiological and primary stereotypy

Study: Number; Author; Year	Number of subjects	Age of patients	Study Method	Prevalence	Age of onset	Associated conditions
1.Kravitz and Boehm, 1971	140	0-12 m	Prospective	Yes	Yes	Marked Delay onset of stereotypies in infants with Down's syndrome and CP
2. Sallustro and Atwell, 1978	525	3 m- 6 years	Retrospective	Yes	Yes	-
3. Field et al., 1977	20	0-12 m	Group comparison	No	Yes	-
4. Thelen, 1979	79	0-12 m	Prospective	No	Yes	-
5. Schwartz, et al., 1986	12	4 m- 22 m	Group comparison	No	No	-
6. MacLean et al., 1991	10	NA (Mean age 5.8 m)	Prospective & Group Comparison	No	Yes	-

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Study: Number; Author; Year	Number of subjects	Age of patients	Study Method	Prevalence	Age of onset	Associated conditions
7. Troster, 1994	57	10 months-11 years	Cross-sectional study	Yes	No	-
8. Castellanos et al., 1996	20	9-48 years	Cross-sectional study	Yes	Yes	Affective and Anxiety disorders
9.Tan et al., 1997	10	2-7.5 year	Cross-sectional study	No	Yes	ADHD
10. Mahone, 2004	40	9 months-17 years	Retrospective	Yes	Yes	ADHD
11. Kates et al., 2005	6	9 -11 years	Cross-sectional study	Yes	Yes	ADHD
12. Harris, 2008	100	8 months-27 years	Prospective	Yes	Yes	ADHD, tics and OCD

Table 2 Previous case reports : stereotypies secondary to basal ganglia and structural lesions

Case Number [Ref.]	Gender	Age (Years)	Etiology	Onset of stereotypies	Imaging method and reported finding	Characteristic of stereotypies
1 [103]	Male	17	Stroke (Ischemic)	5 months after aortic surgery	MRI:right putaminal infarction	had throwing, continuous chewing, clasping hands, protruding tongue, sniffing, rubbing his eyes
2 [78]	Male	69	Stroke (Ischemic)	4 weeks after stroke onset	CT: right lentiform nucleus infaction	Opening and closing mouth, body-rocking while sitting and floor pacing and marching while standing
3 [79]	Male	62	Stroke (Ischemic)	1 week after stroke onset	CT: Dorsomedial and ventral posterolateral nucleus of right thalamus and occipital lobe	Stereotypic limbs movement; rubbing with right heel and flexion-extension of right elbow
4 [79]	Female	48	Stroke (SAH)	10 days after intracranial aneurysm clipping	Subarachnoid hemorrhage from bifurcation of basilar artery (Imaging method: NA)	Rubbing with right heel againt bed sheet and rubbing dorsum of the right food with the sole of left foot.

NA : Not available information , SAH : Subarachnoid hemorrhage

Case Number [Ref.]	Gender	Age (Years)	Etiology	Onset of stereotypies	Imaging method and reported finding	Characteristic of stereotypies
5 [79]	Female	54	Stroke (Ischemic)	1 week after stroke onset	CT: right corona radiate, putament and globus pollidus infarction	Stereotypic movements of right upper and lower limbs for 1 week then followed by rubbing of right hand over the chest and rubbing heel against bed sheet/dorsum of left foot, flexion-extension of right foot
6 [79]	Female	65	Stroke (Ischemic)	3 days after stroke onset	CT: bilateral thalamic infarction	Rubbing both heels against bed sheets and rubbing left hand against chest and epigastrium
7 [104]	Male	50	Chronic meningoencephalitis	4 weeks after encephalopathy	MRI: bilateral medial frontoparietal areas.	Intermittent stereotypic stepping movements
8 [105]	Male	21	Subdural hematoma	10 weeks after head injury and operation	CT: 1.5 cm left frontal lobe subdural hematoma with mass effect	body rocking and teeth clicking
9 [80]	Male	54	Stroke		MRI: Right ventral pons infarction	Hoarding and hypergraphia

Table 3 Stereotypies related to Anti-NMDA Ab encephalitis

Case Number [Ref.]	Gender	Age (Years)	Tumors	Symptoms and clinical features	Clinical feature of movement disorder	Characteristic of stereotypies
1 [91]	Female	26	Teratoma	Obsession, Fear, Delusion	Akinetic and nonresponsive to verbal commands, Orofacial dyskinesia and athetoid dystonic movements	Sustained jaw movements and forceful clenching of the teeth
2 [106]	Female	17	Not detected	Confusion, Obsession, Fear, Delusion and agitation, opening eyes, non-responsive to verbal command and noxious stimuli	Orofacial dyskinesia, athetoid dystonic	Sustained jaw movements and forceful clenching of the teeth
3 [107]	Female	18	Teratoma	Psychosis, Behavioural changes, non-responsive to verbal command	Orofacial dyskinesia	Widely opening and tightly closing eyes and mouth, sticking tongue and grimace