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Primary Stereotypies: video analysis and clinical characterization in a group of children

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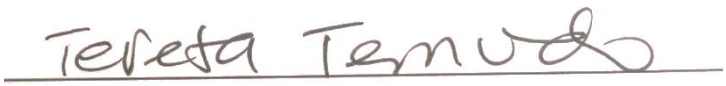
Assinatura Orientador: 

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DEDICATÓRIA

Aos meus pais, irmão e “irmã”, por todo o apoio e compreensão para com as minhas escolhas ao longo da vida. Aos meus amigos de dentro e fora da faculdade, pela amizade e por me inspirarem a ser o meu melhor para um mundo melhor.

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ABSTRACT:

BACKGROUND: Stereotypies are hyperkinetic movement disorders characterized by involuntary, repetitive, rhythmic, patterned and purposeless movements. They may be categorized in primary - if occurring in healthy typically developed patients - or secondary, - when associated with neurological or psychiatric diseases. Primary stereotypies are still an underexplored field in terms of clinical description and evolution.

AIMS: To describe the clinical features of primary stereotypies and characterize a group of individuals with primary stereotypies in terms of clinical background, cognitive and behavioural profile, family medical history and evolution after a five year-period.

METHODS: We carried out a descriptive cross-sectional study with two main timings of data collection: time I) participant's enrolment and clinical standardized evaluation with videotaped sessions; and time II) five-years later follow-up interview to explore the clinical evolution of each participant. We gathered a consecutive sample of twenty individuals with primary stereotypies (11 males, 9 females), with a mean age of 4 ± 1,34 years.

RESULTS: Age of onset for stereotypies ranged from 4 to 60 months (median of 24). During recording sessions sixteen out of twenty participants presented stereotypies, with a median frequency of stereotypies of twelve (range: 6-28). The most prevalent types of stereotypies were: "jumping", hand flapping" and "bending over". Fifty-one percent were complex stereotypies. Primary stereotypies were predominantly: bilateral (71,5%), out of midline of the body (84,3%), and had a small amplitude (51,6%). Excitement and imagination were the most frequent triggers for stereotypies (58,8 and 12,2%). Eighty-five percent of the participants showed at least one comorbidity and the most frequent were anxiety and symptoms of attention deficit or hyperactivity. After a five years-period, attention deficit hyperactivity disorder was identified on five out of the twelve participants screened for the disorder. Three individuals with primary stereotypies were later considered to fulfill criteria for Autism Spectrum Disorder.

CONCLUSIONS: The resulting data supports some aspects of the previous descriptions of primary stereotypies (age of onset, comorbidities, triggers) and add more precise information of others (frequency, types, topography, duration, family history). The noteworthy prevalence of anxiety and attention deficit hyperactivity disorder found in our study, point toward the importance of a systematic study of both, in children with primary stereotypies.

BIBLIOGRAPHY: PubMed database accessed between July 2017 and May 2018.

KEYWORDS: *Movement Disorders, Stereotypic Movement Disorder, Comorbidity, Paediatrics, Video Recording*.

ABBREVIATIONS:

ACC Anterior Cingulate Cortex
ADHD Attention Deficit Hyperactivity Disorder
ADI™-R Autism Diagnostic Interview™, Revised
ADOS 2 Autism Diagnostic Observation Schedule-Second edition
ASD Autism Spectrum Disorder
BANC Coimbra Neuropsychological Assessment Battery
CHP-EPE Centro Hospitalar do Porto, Entidades Públicas Empresariais
CMS Complex Motor Stereotypies
DEFI Departamento de Ensino, Formação e Investigação (teaching, development and investigation department of CHP).
DSM-5 - Diagnostic and Statistical Manual of Mental Disorders, 5th edition, text revision
I.C. Informed Consent
ID Intellectual Disability
IQ Intelligence Quotient
IMM Intense Imagery Movements
MRI Magnetic Resonance Imaging
OCD Obsessive Compulsive Disorder
RTT Ret Syndrome
SD Standard Deviation
SMD Stereotypic Movement Disorder
SPSS Statistical Package for the Social Sciences
WISC Wechsler Intelligence Scale for Children
WPPSI Wechsler Preschool and Primary Scale of Intelligence

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INTRODUCTION

Stereotypies are hyperkinetic movement disorders characterized by involuntary, purposeless, repetitive, rhythmic and coordinated movements with a predictable and fixed pattern[1,2]. Examples include arm/hand flapping, waving, hand rotation or finger wiggling [3,4]. This heterogeneous movement disorder is more frequent in children but can persist into adulthood [5,6]. Although being a common finding in clinical practice, either in children with neurodevelopment disorders or typically developing children, its formal prevalence is yet to be revealed [1,7]. This may be due to a lack of consensus regarding to the definitive description and terminology of stereotypies among authors, with consequent diagnostic difficulties [7]. Systematic classification and extensive clinical characterization are essential to better define and distinguish stereotypies from other movement disorders or repetitive behaviours [1].

Definition and Classification

The Diagnostic and Statistical Manual of Mental Disorders, 5TH edition (DSM-5), introduces the term "stereotypic movement disorder" (SMD) instead of stereotypies, defining SMD as "repetitive, seemingly driven, and non-functional motor behaviours that interfere with normal activities or result in injury" [1,8]. The majority of the authors agree that stereotypies are purposeless, non-goal directed movements [9]. They are repeated constantly in a period of time and on multiple occasions, and can be suppressed with distraction (e.g., calling one's name), as many authors state [5,9]. Although, suppressibility is not a consensual characteristic of stereotypies: while they can be easily suppressible in typically developed children, it can be almost impossible in the case of children with neurological disturbances (e.g., Rett Syndrome (RTT)) [1]. Perhaps, the polymorphic clinical variants can be explained by different pathophysiology and hence further categorization and definition is needed.

Stereotypies can be classified in "primary" or "secondary" [1,3]. Primary stereotypies occur without any neurodevelopmental disorder associated, typically in the first three years of children who are otherwise developing normally. Secondary stereotypies, on the other hand, arise associated with other neurological or psychiatric conditions [6,10], such as Autism Spectrum Disorder (ASD), intellectual disability (ID) or people with sensorial deficits (e.g. blindness, deafness) [4,6,11].

Stereotypies can further be classified in "simple", involving just one type of movement (e.g., pencil tapping, clapping, finger drumming) or "complex", involving sequences of different movements always performed equally [12]. Besides, although motor stereotypies are the commonest by far, there are also stereotypies purely vocal [13] or visual

[14]. Vocal stereotypies include bruxism, repetitive words, phrases or sounds and visual stereotypies include hand or object gazing [1]. Motor stereotypies should be furthermore classified accordingly to the predominant body part involvement - head, trunk, hands, arms or legs [1].

Clinical Features and differential diagnosis

The diagnosis of primary stereotypies is clinical, and it can be challenging. Children are sometimes incorrectly diagnosed with ASD due to motor stereotypies alone [7]. Besides, there are other hyperkinetic movement disorders that must be distinguished such as tics, chorea, myoclonus, tremor, drug induced movements and psychogenic movement disorders [1,11]. While some of these differential diagnoses are readily made, based on other clinical features, tics can be particularly challenging to differentiate from stereotypies and they can even co-exist in the same patient [1]. They both are among the most common movement disorders in children, are equally involuntary, repetitive and have a stereotyped appearance (*id est* identically performed each time). The main differences lay on the absence of "premonitory urge" or compulsion in stereotypies (that is typical in tics) and the rhythmicity (that is common in stereotypies but not in tics) [11,15] . The age of onset, also, tends to be different: tics usually appear by five to seven years whereas stereotypies usually begin before three years of age [1,11]. Additionally, in contrast with tics, stereotypies do not change much over time neither in anatomic location nor complexity [11].

Stereotypies are mainly triggered by periods of excitement, captivating activities, stress, tiredness, and/or dullness [4,6]. They can happen in *clusters*, lasting seconds to minutes, several times per day and being absent during sleep [1,6].

Despite the fact stereotypies are usually of little concern to the children performing them, parents are frequently worried about disruptions, social stigmatization, self-injury or socially offense [5] and may be pervasive to psychomotor development.

Epidemiology

The epidemiological studies on stereotypies are scarce and numbers vary greatly between studies, probably because of incorrect use of terminology and definitions. Some studies claim that about 20% of normally developing children may present primary stereotypies, with the complex type affecting up to 7% [2,6].

There is also a lack of published data in what is concerned to associated comorbidities and long-term clinical course[4]. Some cohort studies showed a resolution of primary stereotypies in 3-20% of the cases [16,17] while other longitudinal study with a ten-year follow-up found that 94% of the subjects persisted with stereotypies [6].

Although primary stereotypies occur, by definition, in typically developing children, almost half of the children were reported to have comorbidities; these include learning disabilities, attention-deficit–hyperactivity disorder (ADHD; co-occurring in 25-50%), tics (18-43%), obsessive compulsive behaviours (in 10-12%) and Tourette's disorder (7%) [3,4,6,11]. Mahone et al. also showed that children with primary stereotypies performed significantly worse than children without it, in motor skills and IQ tests, although IQ was constantly in the normal range and they have normal neuropsychological profiles [3]. It is worth noting, though, that the severity of stereotypies seems to be proportional to the severity of the cognitive delay in secondary stereotypies while in primary stereotypies this is not clear [5,18].

Pathophysiology

The pathophysiology of both primary and secondary stereotypies is still unknown. Probably aetiologies are numerous and complex [7]. Both biological and psychological factors are being investigated [6]. In terms of psychological factors, the suggested explanations for the arising of stereotypies, are: the need to compensate external sensory deficits; a substitute for imaginary activities; a way to moderate levels of arousal or as part of anxiety or obsessive-compulsive-related behaviours [6,19]. Although most patients are unaware of the stereotypic behaviours, some may report feeling happy and satisfied when displaying them; this may corroborate the explanation of arousal moderation [5,6,19]. Environmental factors, such as isolation and lack of attention, are also claimed to contribute for the arising and severity of stereotypies, as studies in orphanages have shown [2,6]. In terms of biological factors, reports based on animal models, human observational studies and functional MRI have shown neurochemical and brain structural abnormalities. Although it is not known the neuroanatomical circuits for stereotypies, the cortical-striatal-thalamo-cortical (CSTC) brain circuit seems to be implicated [1,6]. MRI studies reported decreased striatal volume [20] and reductions in total putamen volume [6]. This may have a pathophysiological meaning, since premotor putamen seems to be associated with patterned behaviours [21]. Studies on neurochemical abnormalities, showed decreased levels of g-Aminobutyric acid (GABA) in the anterior cingulate cortex (ACC) and striatum, also, suggested that dopamine has a contributory role in the onset of stereotypies [22,23]. Genetics seem to play a role in the pathophysiology since family history of stereotypies was found in a quarter of the children with primary stereotypies in one study [3]. Still, despite the investigatory effort to find genes or mutations (sporadic or inherited), no gene variants have been reported yet [6].

Primary Stereotypies*: state of the art*

Description and standardization of stereotypies is essential for a better diagnose, approach and research. Temudo et al. had already carried out a study, based on videotape analysis, to define the spectrum of secondary stereotypies in children with RTT[12] and Goldman et al. in children with ASD [24] (with 83 and 500 videos analysed, respectively). Similarly, Goldman and Temudo (2012) conducted a comparative study based on videotaped standardized observations of hand stereotypies in RTT and ASD, where striking differentiating findings, that allow differential diagnosis between the two [14], were exposed. These were the first studies where standardize direct observation (from video) was used to characterize and classify stereotypies in depth and it showed to be a valuable method for that purpose. It even allowed the recognition of variances in similar clinical presentations of different disorders. Video analysis was used before to characterize primary and secondary stereotypies, but only if available [25], not as the main resource of data nor in a standardize manner.

Regarding to primary stereotypies, there is still a need for further clinical description [3]. The aim of this study is to comprehensively characterize the clinical features of primary stereotypies of a sample of typically developed children and to describe the group in terms of their neuropsychological profile, past medical history, comorbidities and family medical history. Furthermore, we intended to follow-up the sample, in a five-year period of time, in order to assess the clinical course of primary stereotypies, to screen ADHD and other comorbidities. Likewise, this follow-up intends to check if the first diagnose of primary stereotypies was maintained over time or if stereotypies end up being part of other nosological entity.

METHODS and MATERIALS

Ethics

This study was included on a research project approved by the Administration Council, Ethics Committee and DEFI of CHP [166/12 (130-DEFI/122-CES)]. This study is part of a PhD research project of Dr. Cláudia Melo, under the orientation of Prof. Doutora Teresa Temudo. Parents gave their informed consent, at the time of enrolment, for participation in the study including for the videotaping.

Study design

We carried out a prospective study with two main timings for data collection: 1) time I – participants' enrolment, standardized clinical evaluation, videotaping and video analysis; and 2) time II - a five-year-later follow-up interview to explore the clinical evolution of each participant.

Participants

Participants were recruited from the outpatient clinic of the Paediatrics Department and Child Psychiatry Department of CHP, E.P.E. Twenty children (n=20, 11 males, 9 females), with a median age of four years old (range 2.0-7.0 years; mean 4 ± 1,34) at the time of first evaluation (time I), were consecutively enrolled in the study, between January and December of 2013.

Participants were included if they had been diagnosed with stereotypies (observed during the consultation by the paediatric neurologist or through home videos brought by parents). The diagnosis of a primary stereotypy implied: 1) repetitive, purposeless, rhythmic movements with a fixed pattern; 2) movements not better characterized as tics; 3) presence for a minimum of 4 months. Exclusion criteria were: 1) diagnosis of ASD at the enrolment or previously; 2) diagnosis of developmental delay or intellectual disability; 3) diagnosis of a moderate or severe sensorial deficit; 4) history of head trauma or other relevant neurological insult. For ruling out ASD, every potential participant was evaluated with Autism Diagnostic Observation Schedule, second edition (ADOS-2™) and Autism Diagnostic Interview™, Revised (ADI™-R). ADI™-R is a standardized interview and scoring system which provides categorical results in social interactions, communication and repetitive comportments or interests, aiding in the diagnose of ASD and its distinction from other developmental disorders.

Evaluation protocol and videotaping (time I)

Developmental and cognitive profile of participants was assessed using standardized tests, including: Griffith's Mental Development Scale, for children younger than six years old and Wechsler Intelligence Scale for Children III (WISC-III) or Wechsler Preschool and Primary Scale of Intelligence (WPPSI) for children with six years-old or older. The Vineland Adaptive Behaviour Scale, Third Edition (Vineland™-3) was also applied to assess adaptive function.

Griffiths Mental Development Scale is a commonly used neurodevelopmental assessment instrument, which includes six subscales [26,27]: A) Locomotor: evaluates gross motor skills, counting the ability to balance and to coordinate and control movements; B)

Personal-social: evaluates proficiency in daily live activities, independence level and peer-interaction; C) Language: evaluates receptive and expressive language; D) Eye and hand coordination: manual dexterity, fine motor and visual monitoring skills; E) Performance: visuospatial skills including speed of working and precision; F) Practical reasoning: evaluates the understanding of basic mathematics and moral issues and the ability to resolve practical problems[28]. For each sub-scale, raw scores are computed and converted to Global Quotient or mental age[28]. WISC-III is an intelligence test with six verbal and seven performance subtests, for children between six and sixteen years old [29,30]. The verbal (VIQ), performance (PIQ), and full-scale IQ (FSIQ) scores are normative IQs, with a mean of 100 and a standard deviation of fifteen. WPPSI is a similar test applicable to children from two to eight years-old. Vineland™-3 is a psychometric test to measure a person's adaptive level of functioning [31].

Besides developmental and cognitive evaluation, a clinical questionnaire was completed in order to collect clinical data: children's past medical history; age of onset of stereotypies; comorbidities (sleep disorders, febrile seizures, epilepsy, bruxism, behaviour problems, feeding behaviour problems, ADHD, language delay, motor delay, anxiety disorder, learning disorder); drug history; family history of neurological or psychiatric disorders; family history of stereotypies or tics.

All the participants were observed by the same team which included a: paediatric neurologist (TT), paediatrician (CM), child psychiatrist (VM) and a child psychologist (TPR).

Evaluation sessions were scheduled according with parent's availability to maximize their participation. In each session, ADOS-2™ was administered to the participants, by a trained psychologist. ADOS-2™ is a standardized evaluation of social interaction through a sequence of structured tasks between participant and assessor, in which the assessor identifies key aspects of the individual's behaviour [32]. ADOS-2™ includes four modules accordingly to age and language skills of the individual. Modules one through three also give a comparative score that indicates the level of autism spectrum-related symptoms comparing to children with ASD with comparable language skills and with the same age. Administration of ADOS usually lasts from 40 to 60 minutes. Analysis of stereotypies was performed using the first twenty minutes of the sessions.

The research room was designed to be neutral and homogeneous, covered with one colour floor and walls and it was equipped with four synchronized video-cameras. The equipment in the room consisted in two chairs, a table, and the ADOS-2™ material. Figure 1 summarizes the study design in a timeline with the essential tasks of each phase of the study.

The resulting videos were assessed by two independent researchers (IM and CM) and reassessed by an experienced child neurologist (TT) with the intention of identifying

motor, vocal and visual stereotypies. To be classified as a stereotypy, the movement had to be seen at least twice in each session, in order to meet the distinctive feature of repetitiveness implied in the definition of stereotypy [5].

The stereotypies were characterized according to ten categories: 1) type of stereotypy (motor, vocal, visual); 2) morphology (e.g.: hand flapping, clapping); 3) topography (a) midline or away from the body; b) body segments involved - head, arms, hands/fingers, legs); 4) laterality (bilateral or unilateral), 5) amplitude (e.g. large or small); 6) presence of dystonic features; 7) frequency (number of stereotypies per twenty minute-session); 8) duration in seconds; 9) use of an object; 10) complexity (simple or complex). Simple stereotypies were defined as single movements (e.g., tapping, clapping, body rocking, head nodding) [1,25]. Complex stereotypies as clusters of different single coordinated movements performed always in the same sequence [1], including any simple hand/arm movement occurring with other movements that use another group of muscles (facial, mouth, legs, body contortions) [25]. Moreover, researchers analysed the context and triggers for the stereotypy. We also tried to identify the occurrence of tics (motor or vocal).

Follow-up evaluation (time II)

A follow-up evaluation, five years after the videotaping, was conducted in order to: a) assess the current state of the stereotypies; b) screen for ADHD and c) evaluate for new comorbidities or new diagnosis such as ASD. The participants were called for a medical appointment where a paediatrician and a researcher (IM) performed a new clinical interview and exam and delivered Conners' questionnaires. Conners' questionnaire is a Parent–Teacher Rating Scale widely used for ADHD assessment, with a strong sensitivity [33]. The scoring is based on the results of the two ten-item questionnaires (for parents and teachers) and is adjusted for gender and age. ADHD is considered when the subject's score is two-SD apart from the mean value for age and gender.

Statistical analysis

Quantitative data were summarized by means ± SD when there was a normal distribution or median and range values. Categorical data were summarized by absolute and percent frequencies. Group differences for demographic, clinical and neuropsychological measures were explored using unequal variance t-tests for continuous variables and $\chi 2$ analyses for categorical variables. For group comparisons and correlations, assumptions for parametric analyses were assessed using Kolmogorov–Smirnov tests for normality of distributions, with non-parametric analyses used as indicated. Significance was set at $p<0.05$. Statistical analyses were performed using SPSS 24.0.

RESULTS

1. Clinical characterization of stereotypies

From the initial twenty participants, four of them did not show stereotypies during the videotaped session. Clinical data of the stereotypies from the other sixteen participants (80%) is displayed below.

The median age of onset of primary stereotypies was reported to be 24 months of age (range: 4 to 60 months).

The median frequency (number of stereotypies per twenty minute-session) per participant was twelve (range 6-28). The median duration of the stereotypies in each participant was three seconds. The maximum duration of a single stereotypy was 39 seconds and the minimum one second. The mean time spent on stereotypies was one minute and five seconds (range: 23 seconds – 2 minutes, 32 seconds; 3% of the time of the session).

During the recorded sessions, a total of 221 stereotypies were marked and analysed; since 51,58% of these stereotypies were complex (combining different movements in one stereotypy), the number of single stereotypies is higher (366). We identified and described 34 classes of different motor stereotypies and also visual and vocal stereotypies (Table I and II). The three more frequent types of motor stereotypies were “jumping”, “hand flapping” and “bending over”. Each participant performed a mean of six different stereotypies in terms of morphology (different single movements; range:1 to 16). Vocal stereotypies were identified in two participants and visual stereotypies - “hand inspection” and “object gazing” - in four patients. Four participants used objects while performing stereotypies; two of them had also visual stereotypies.

The majority of the primary stereotypies were bilateral, not in the midline and without dystonic features. The table III summarizes the dichotomous characteristics of the stereotypies (e.g. bilateral/unilateral; large/small amplitude; presence/absence of dystonic features). The most frequent body segment used were hands and arms (table IV).

Stereotypies were more frequently triggered by periods of excitement and imagination (table V).

Tics were identified on seven of the participants, all of them were head motor tics.

2. Neuropsychological profile

Griffiths Mental Development Scale was applied in thirteen out of twenty participants showing a median Global Development Quotient (GDQ) of 90.0 (range: 80.0 – 108.0). The

highest score was identified on sub-scales B (personal-social interaction) and C (language), and the lowest on sub-scales E (eye-hand coordination) and F (practical reasoning). The complete values are presented on Table VI. Seven of the participants were evaluated using WISC-III and displayed a median global IQ of 100.0 (range: 78.0-139.0) (Table VII). Regarding to adaptive function, Vineland scale was applied in 16 of the participants showing a range of Adaptive Behavior Composite percentile of 0.5 to 93.0 with a median value of 20.5.

3. Comorbidities

Seventeen of the twenty participants had at least one comorbidity, and 50% (10/20) displayed more than three comorbidities (time I). The most prevalent comorbidity was symptoms of anxiety (70.0%), (based on parental reported symptoms; one participant had two panic attacks reported, with medical intervention needed). Parents described symptoms of attention deficit or hyperactivity on 35.0% of the participants. Other frequent comorbidities were: sleeping problems (difficulties in sleeping initiation or maintenance, somnambulism, screaming or agitation), motor and language delay history and learning difficulties (Table VIII).

4. Family history

A family history of psychiatric or neurological disorders was positive on 50% (10/20) of participants. Three of these ten cases were diagnosis of ASD on first or second-degree relatives. Other conditions were: schizophrenia (3/10), bipolar disorder (1/10), depression (2/10), substances abuse (2/10) and epilepsy (3/10).

Regarding family history of stereotypies and/or tics, seven participants (35%) revealed a positive history. Two of those cases reported to have the same type of motor stereotypies of the participants they were related with.

5. Follow-up

Most of the participants (90%) agreed to be included on the follow-up evaluation, however only twelve out of eighteen delivered the filled Conners' questionnaire. The score of five of these twelve participants was two or more SD away from the mean score for age and gender, on parents or teacher's questionnaire, meeting criteria for ADHD. In four of the five participants diagnosed with ADHD, parents had already reported symptoms in the first evaluation (time I).

Regarding the evolution of stereotypies, all the participants conserved the same stereotypies after the five year-period; four developed additional stereotypies. Parents

reported a perception of improvement of stereotypies (either in frequency or exuberance) on five of the participants, while four apparently got worse during this period.

After five years since first evaluation, we found that three of the twenty participants fulfilled criteria for ASD meanwhile. Considering this new finding, we performed a secondary analysis to compare the stereotypies in this group with the remaining sample. The mean duration of stereotypies was similar (between two and five seconds) and they showed frequencies of 12, 24 and 28 stereotypies per session (the mean frequency of the rest of the sample was 13). The percentage of complex stereotypies performed by these individuals was 30%, 50% and 75%; the mean percentage in the remaining sample was 43%. The majority of the stereotypies of this particular group were bilateral, of large amplitude and without dystonic features; two of the three used object in some stereotypies. There was no predominance in terms of midline topography; the major body segments used were hands, arms and trunk. The most frequent stereotypies in these were: “bending over”, “grabbing”, “jumping” and “flapping”. In the two participants expressing vocal stereotypies, one was later diagnosed with ASD; also one in the four participants with visual stereotypies, had later the diagnose of ASD. In the follow-up, one of these three particular participants reported worsening of stereotypies (in frequency, exuberance and number), with maintenance in the others two.

In the follow-up we found that three of the participants of all sample are currently under psychotropic drugs [risperidone (one), methylphenidate and risperidone (one), atomoxetine (one)]; and two participants are medicated with melatonin.

DISCUSSION and CONCLUSIONS

In this study we evaluated a group of typically developed children to characterize the semiology of primary stereotypies and clinical features associated to these individuals. Clinical analysis of primary stereotypies has been underexplored by previous studies, and the majority of them are based on reports and not on direct observation. As far as we know, this is the first study describing clinical characteristics of primary stereotypies based on videotaped standardized sessions.

The median age of onset for primary stereotypies of our sample (24 months) is in line with the previously reported typical age of onset - before 36 months [4,11]. However the maximum age of onset was higher in our study (61 months) when compared to the reported maximum of 51 months [18] or 48 months [4]. Gosh et al, reported an even broader range of onset – 6 weeks to 11 years – with an average age of onset of 20 months [25].

Our study showed that each participant had high frequency of stereotypies during a twenty minute-session (median of twelve). We weren’t able to find data in the literature to

compare this result. There is, though, studies (based on questionnaires and medical records), that report frequency per day. One study revealed that 90% of children had episodes of stereotypies more than once a day [34] and other exposed that the majority was "less than ten per day" (72,7%), with only 4,5% doing it "more than twenty times a day". Nevertheless, the high frequency reported by our results, may not reflect entirely the real frequency in daily live, since in the sessions children got all the attention and were very stimulated with games or exciting activities. Moreover, we didn't consider the four children that didn't show any stereotypy during the session.

The median duration of each individual episode of primary stereotypies was three seconds (range: 3-12 seconds). Previous studies referred roughly that stereotypies could last "seconds to minutes"; a study, based on parents reports, referred that in 30% of their sample, primary stereotypies were less than ten seconds and in other 30% more than 60 seconds [34]. Video analysis of primary stereotypies is a more precise way of evaluating this topic, comparing to parental report.

In our study, hands, arms and trunk were the body segment predominately used; with a clear predominance of the hand stereotypies. Previous studies also reported a great involvement of the arms in 70% and hand and finger in 48%[34] but less of the trunk/waist like bending or body rocking (8%)[34]. The reason for these variations is still unknown.

We found that half of the stereotypies were complex (51%); regarding this, literature is not consensual, with studies finding higher (65%)[34] or lower (43%) [25] percentages. This may be due to the use of different definitions of complexity.

A previous study that compared primary and secondary stereotypies [25], stated that primary stereotypies were more commonly simple, less frequent and shorter than secondary. Plus, vocalizations were infrequent in primary stereotypies comparing to secondary. In our study, we found two cases of vocal stereotypies in one child with normal cognitive profile and other that later was diagnosed with ASD. Nevertheless, there is not sufficient data to take conclusions from this fact. In what complexity is concerned, when we segregate the sample in two groups - later diagnosed with ASD and the rest - we found that indeed the first group had slightly more percentage of complex stereotypies comparing to the latter. A larger comparative study is needed to validate the conclusions that stereotypies are more often complex in children with ASD. Atypical object/hand gazing was previously described as more associated with ASD [2]; in our study we found in three participants (one later diagnosed with ASD). We don't have the sample power to do a comparative study between primary and secondary stereotypies.

Excitement was the most frequent trigger for primary stereotypies in our study. Accordingly, this seems to be a consensual characteristic among authors [34]. The other frequent trigger was imagination; Robinson et al, already reported a distinct subgroup of

children performing primary stereotypies while in intense imagery or imagination context (termed Intense Imagery Movements – IMM)[35]. It was proposed that stereotypies have a functional drive and support the imaginative process[35].

Tics were identified in seven participants. Other studies had already reported similar percentages of co-occurrence of tics and primary stereotypies (18% [16,34]). However, the distinction between tics and primary stereotypies by video analysis maybe particularly challenging since we can only rely on the differential aspect of rhythmicity (compulsion, wax and wane over time and time of onset cannot, obviously, be seen).

Suppressibility was not assessed; in the sessions, children were allowed to perform stereotypies freely in order to better picture them. A study had found suppressibility in 98% of the subjects with primary stereotypies [34], but this topic it is still under debate, hence its evaluation in future studies may be important.

In terms of neuropsychological profile, our study revealed that children were typically developed or with a normal range of IQ, which is consistent with previous studies [3]. On the contrary, we did not found developmental motor coordination disorder as much as expected by previous descriptions (approximately one-third[3]) although on Griffiths the lowest subgroup score was eye-hand coordination.

To classify stereotypies as primary the child should have a normal development. Some stricter definitions imply the absence of other neurological or psychiatric conditions. In the extreme field it would be necessary to exclude any other disorder such as ADHD or language disorder. Our study showed that children with primary stereotypies, although considered to be "typically developed", have, in most cases, other behavioural or psychiatric conditions (85%). This seems to be the scenario in every other study [4,16]. Anxiety was the most reported comorbidity (70%), which is concordant to a previous longitudinal follow-up study (73%[4]). This may mean that primary stereotypies and anxiety share some pathophysiology and give clues for treatment.

Sleep disorders and feeding disorders were extremely common. This high frequency should be interpreted with caution due to the non-randomized sample and high proportion of sleep and feeding problems in the general paediatric population.

ADHD was other commonly reported (and posteriorly confirmed) comorbidity found in our study (35%). Other studies had already showed this association (25%[34] up to 63%[4]). We can speculate that primary stereotypies can either be a source of attention deficit or a consequence of it: they can represent imaginary activities (e.g. IMM) and thus segregate the attention of the subject from the reality or, on the contrary, be a useful tool for them to channel thoughts of an overstimulated mind.

As expected according to previous data [4,34], all participants maintained the stereotypies after a five-year period of time. A study had shown that unexpectedly,

worsening of stereotypies was higher in primary stereotypies comparing to stereotypies associated with autism [25]. In fact, in the four participants that got worse only one was diagnosed with ASD. Nevertheless, this fact cannot corroborate the previous statement, due to the limited data.

Given the possibility of a genetic link for stereotypies, family history was explored in order to identify family members with history of stereotypies, neurological or psychiatric disorders or tics. A large percentage (50%) had at least one of these criteria. Stereotypies/tics were found in 35% of first-degree relatives; other studies had found similar percentages (25%[10]). This enforce the genetic link hypothesis. Interestingly, we also found two cases of equal stereotypies between relatives; this may also mean that stereotypies features can also have genetic linkage.

Limitations and strengths

The main limitation of this study is the limited number of participants included. Also, it would be preferable to enrol community identified individuals with primary stereotypies than clinical based patients. Referral bias must be accounted when interpreting these results. Also, the neuropsychological evaluation of the sample should include a broader battery of tests, standardized for the Portuguese population. Maybe in the future it will be possible to apply a neuropsychological evaluation battery such as BANC.

Frequency of stereotypies may be underestimated if we believe that many of these individuals may suppress their stereotypies. On the contrary, the “evaluation” environment may trigger stereotypies and thus, overestimated it.

Clinical interview, according to DSM-5 criteria[8], is the valid evaluative method for ADHD diagnose. In our follow-up interview we opted to use the Conner’s questionnaire for ADHD assessment since it showed, in other studies, to have high sensibility and validity comparing to formal criteria[33]. Plus, using only the questionnaire, we could abbreviate follow-up sessions. However, this strategy increased the missing numbers in the ADHD evaluation, since some parents did not send questionnaires back for evaluation.

Strengths of the present study include, first, the assessment of the stereotypies based not only on parent’s clinical description but also on video recording; and second, the subsequent evaluation allowing for a longitudinal characterization. Also, a detailed and independent analysis of clinical features of stereotypies were performed, enabling for future comparisons with secondary stereotypies groups.

Conclusion

This study enriched the clinical data available for primary stereotypies characterization, which contributes for a better diagnose and research. This ultimately may lead to better pathophysiology understanding and treatment/management options.

We found a noteworthy prevalence of anxiety and ADHD among our sample; hence we believe that both should be systematically studied in this group of children and guided accordingly.

Although children performed normally in the neurocognitive tests, the results were never very high. Additionally, three participants in a sample of twenty end up being diagnosed with ASD after it had been excluded before. This shows that: first, the available diagnostic tools for ASD are not completely sensible, and second, that the spectrum of ASD may be wider than we think, and perhaps it includes children with primary stereotypies and milder cognitive disparities. For all of these reasons, it is of uttermost importance to follow primary stereotypies in long-term medical appointments and not just classify it as "physiological" or a "variant of the normal".

Nevertheless, although we didn't find any striking difference in stereotypies between typically developed children and those who developed ASD, efforts to clinically differentiate primary and secondary stereotypies should be made, with larger comparative studies.

Our study also found a strong family history of neuro-psychiatric disorders and stereotypies/tics. In the era of whole genome studies, exploring the copy number variants and polymorphisms of these patients and crossing these variants with genetic studies of ASD patients with stereotypies may allow the identification of genetic variants associated with stereotypies.

A population based longitudinal study, studying prevalence of stereotypies in both individuals with and without developmental disorders would help to overcome the limitations of our and other published studies, and enlighten the main question: why do some individuals develop stereotypies and how can we treat them? Could primary stereotypies have a sentinel role for the diagnose of neurodevelopmental problems?

APPENDIX

TABLES

Table I - **Type of Stereotypy and Frequency**

All the simple stereotypies were counted up; the total number of stereotypies performed is inferior (n= 221) since some are performed jointly (complex stereotypies).

Types of Stereotypy:	N
Motor	352
Visual	10
Vocal	4
TOTAL	366

Table II – **Morphology of motor Stereotypies and Frequency**

All the simple stereotypies were counted up; the total number of stereotypies performed is inferior (n= 221) since some are performed jointly (complex stereotypies). See the stereotypies vocabulary supplement.

Morphology of Motor Stereotypy:	N	Morphology of Motor Stereotypy:	N
Jumping	44	**Clapping**	4
Flapping	33	**Dystonic smile**	4
Bending over	32	**Rubbing**	4
Fingers wiggling	28	**Shoulder elevation**	4
Tapping	27	**Hands Rotation**	3
Shaking	23	**Lap touching**	3
Arms flexion	22	**Lips protrusion**	3
Head touching	19	***Phalen's* manoeuver**	3
Fist clenching	15	**Pill rolling**	3
Grabbing	13	**Fingers picking**	2
Arms extension	11	**Fumbling**	2
"Opisthotonos"-like posture	8	**Hands clawing**	2
Hands dystonic posture	7	**Hands washing**	2
Hands up	7	**Legs crossing**	2
Arms waving	6	**Neck extension**	2
Legs waving	6	**Weight alternation**	2
Fingers mouthing	5	**Stepping**	1
		TOTAL:	352

Table III - **Characteristics of the Different Stereotypies found**

Number and percentage of each dichotomous feature of the total stereotypies performed by the participants.

Characteristics	% / N
Complex	51,58% (114)
Topography: Midline	39,82% (88)
Laterality: Bilateral	71,49%(158)
Use of object	5,43% (12)
Amplitude: Large	48,42% (107)
Presence of dystonic features	20,81% (46)

Table IV - **Body Segments used in Stereotypies**

Percentage of each body segment used on the different types of motor stereotypies (in some stereotypies are used more than one body segment).

Body Segment	%
Hands/Fingers	87,40
Arms	32,17
Legs	21,30
Trunk	10,87
Head	6,96
Face	1,74
Shoulders	1,30

Table V **- Triggers for Stereotypies**

Triggers expressed in percentage from the total stereotypies presented (n=221).

Triggers	% (N)
Excitement	58,82 (130)
Imagination	12,23 (27)
Fear	2,71 (6)
Anxiety	1,81 (4)
Expectation	1,81 (4)
Post imitation	0,45 (1)
Undetermined	22,17 (49)

Table VI - **Griffiths Mental Development Scale**

Scale applied in participants <6 years old. Q – Quotient of: subscale A (QA) - locomotor, subscale B (QB) - personal-social, subscale C (QC) - language, subscale D (QD) - performance, subscale E (QE) - eye-hand coordination, subscale F (QF) - practical reasoning. GDQ - Global development quotient. Interpretation: values >114 – higher than average; 88-113 average; <88 inferior to average.

	QA	QB	QC	QD	QE	QF	GDQ
Median	92,0	95,0	95,0	94,50	88,0	88,0	90,0
Minimum	76,0	70,0	71,0	62,0	76,0	70,0	80,0
Maximum	108,0	113,0	113,0	118,0	124,0	103,0	108,0

Table VII **- WISC-III Scale**

Scale applied in participants ≥6 years old. Interpretation: >130 very superior; 120-129 superior; 110-119 medium-high, 90-109 medium; 80-89 medium low; 0-79 inferior, 69 very inferior.

	Verbal IQ	Non verbal IQ	Global IQ
Mean	105,86	102,86	105,14
Median	109,00	102,00	100,00
Std. Deviation	28,78	12,12	22,49
Minimum	68,00	85,00	78,00
Maximum	147,00	121,00	139,00

Table VIII **- Comorbidities**

	% (N)		% (N)
Sleeping Problems	25,0% (5)	**Febrile Seizure**	10,0% (2)
Night Bruxism	15,0% (3)	**Epileptic Seizure**	00,0% (0)
Day Bruxism	15,0% (3)	**ADHD**	35,0% (7)
Behaviour Problems	20,0% (4)	**Language Delay**	20,0% (4)
Feeding Problems	20,0% (4)	**Motor Delay**	5,0% (1)
Anxiety	70,0% (14)	**Learning Difficulties**	20,0% (4)

STEREOTYPIES VOCABULARY SUPPLEMENT

Below we present the explanation of the terms used to describe the stereotypies found. Some of the terms less understandable are depicted in figures.

Arms extension – it can be anatomical-position-like posture, with arms extended parallel with the body or extended posteriorly (Figure 2). Normally presented in the context of a complex stereotypy, accompanying other movements.
Arms flexion – flexion of the arms over the shoulders (Hercules-like posture; Figure 3).
Arms waving - swaying arms to the front and back, together or alternately**.**
Bending over – anterior flexion of the trunk (figure 2).
Clapping – clapping in an unsuitable context; it can be performed oddly (figure 4).
Dystonic smile – tense smile, performed out of context.
Fingers mouthing – touching rhythmically the mouth with fingers of one or both hands.
Fingers picking – grabbing one finger at a time of one hand with the other hand, repeatedly, with hands in the midline.
Fingers wiggling – jiggle the fingers, like grasping something, repeatedly.
Fist-clenching –clenching/tightening fingers in the palm of the hand, strongly, in a tense pose (figure 5).
Flapping - moving arms or hands up and down.
Fumbling - touching or handling nervously or futilely.
Grabbing – clenching the other hand or an object, tensely.
Hands clawing – putting the fingers of the hand as for scratching.
Hands dystonic posture – leaving one the hand flexed in a hypertonic position while performing other stereotypy with the other hand.
Hands Rotation – revolving hands in the midline, with arms flexed.
Hands up – elevation of the hands above the head.
Hands washing – vigorous hands and fingers washing (figure 6).
Head touching – gentle touch of the head (face, forehead, nose, jaw).
Jumping – hopping with two feet at the same time, rapidly.
Lap touching – pressing the lap with hands in the midline, normally with bending over.
Legs crossing – twisting legs repeatedly.
Legs waving - swaying legs to the front and back, together or alternately.
Lips protrusion – projection of the lips as for a kiss, repetitively.
Neck extension – leaning back the neck, tensely.
Opisthotonos-like posture - "bridging" or "arching" of neck and vertebral column; hyperextension (figure 7).
***Phalen's* manoeuver –** the same movement used in the diagnostic test for carpal tunnel syndrome: holding wrist in complete and forced flexion (pushing the dorsal surfaces of the hands against each other) (figure 8).
Pill rolling – rubbing the two first fingers in each other, continually, like rolling some pill.
Rubbing – scrubbing hands or an object.
Shaking – shaking-off hands as for taking something out of it (different from wiggling, that is a more restrained movement).
Shoulder elevation – shoulder uplift (like saying: "whatever").
Stepping – skipping with one foot at the time in the same place.
Tapping – beating rhythmically on hand with fingers, on table or with an object.
Weight alternation – altering feet that supports the body, like a pendulum.

FIGURES

Figure 1 - Methods' illustrative timeline

Examples of Motor Stereotypies:

Figure 2 – Arms posterior extension and bending over.

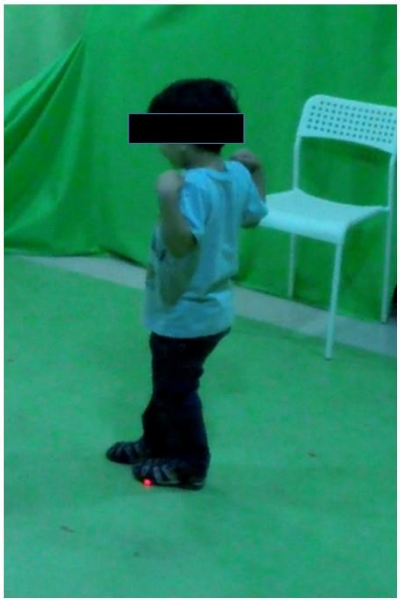

Figure 3 – Arms Flexion (Hercules' pose).

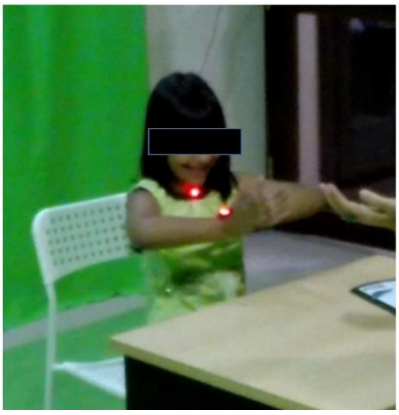

Figure 4 – Clapping.

Figure 5 – Fist Clenching.

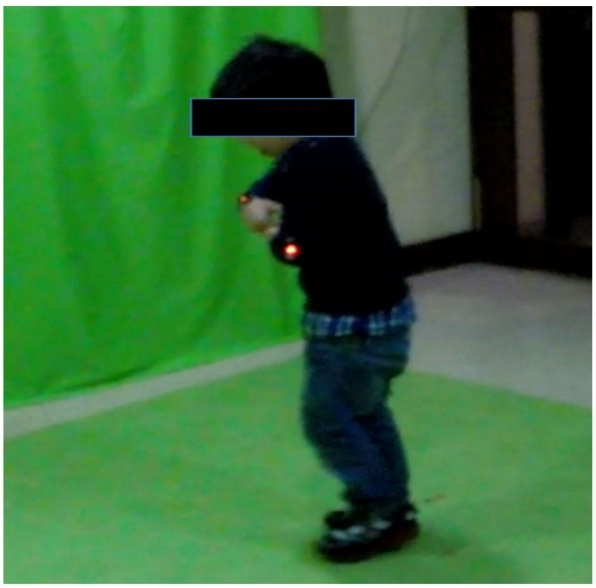

Figure 6 – Hands washing

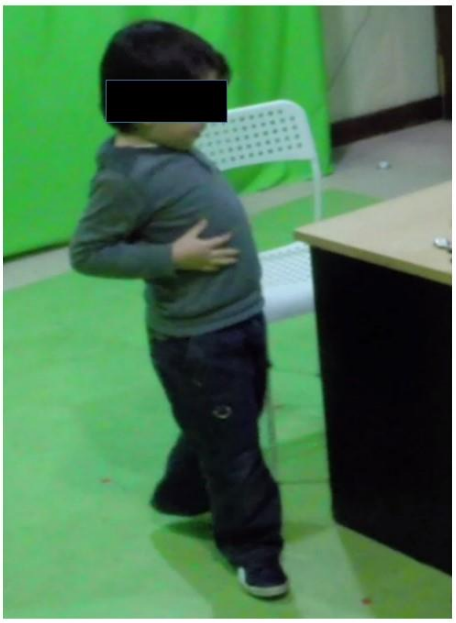

Figure 7 - Opisthotous posture.

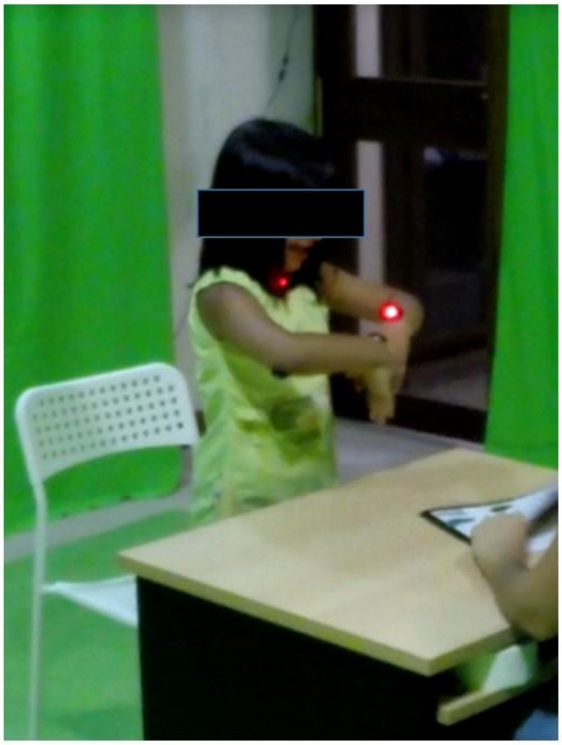

Figure 8 - Phalen's Manouver.

BIBLIOGRAPHY

1. Temudo T, Melo C. Stereotypies: From Normal to Pathological. Journal of Pediatric Neurology 2015;13:208-12.
2. Barry S, Baird G, Lascelles K, Bunton P, Hedderly T. Neurodevelopmental movement disorders - an update on childhood motor stereotypies. Dev Med Child Neurol 2011;53:979-85.
3. Mahone EM, Ryan M, Ferenc L, Morris-Berry C, Singer HS. Neuropsychological function in children with primary complex motor stereotypies. Dev Med Child Neurol 2014;56:1001-8.
4. Oakley C, Mahone EM, Morris-Berry C, Kline T, Singer HS. Primary complex motor stereotypies in older children and adolescents: clinical features and longitudinal follow-up. Pediatr Neurol 2015;52:398-403 e1.
5. Singer HS. Motor stereotypies. Semin Pediatr Neurol 2009;16:77-81.
6. Peter Z, Oliphant ME, Fernandez TV. Motor Stereotypies: A Pathophysiological Review. Front Neurosci 2017;11:171.
7. Hedderly T. Childhood motor stereotypies: questions of definition and management. Dev Med Child Neurol 2017;59:117-8.
8. Association AP. Diagnostic and Statistical Manual of mental disorders: DSM-5: Washington, D.C: American Psychiatric Association; 2013.
9. Edwards MJ, Lang AE, Bhatia KP. Stereotypies: a critical appraisal and suggestion of a clinically useful definition. Mov Disord 2012;27:179-85.
10. Muthugovindan D, Singer H. Motor stereotypy disorders. Current Opinion in Neurology 2009;22:131-6.
11. Zinner SH, Mink JW. Movement disorders I: tics and stereotypies. Pediatr Rev 2010;31:223-33.
12. Temudo T, Oliveira P, Santos M, et al. Stereotypies in Rett syndrome: analysis of 83 patients with and without detected MECP2 mutations. Neurology 2007;68:1183-7.
13. Fernández-Álvarez E. Estereotipias. RevNeurol;36:0054-.
14. Goldman S, Temudo T. Hand stereotypies distinguish Rett syndrome from autism disorder. Mov Disord 2012;27:1060-2.
15. Sanger TD, Chen D, Fehlings DL, et al. DEFINITION AND CLASSIFICATION OF HYPERKINETIC MOVEMENTS IN CHILDHOOD. Movement disorders : official journal of the Movement Disorder Society 2010;25:1538-49.
16. Harris KM, Mahone EM, Singer HS. Nonautistic motor stereotypies: clinical features and longitudinal follow-up. Pediatr Neurol 2008;38:267-72.
17. FREEMAN RD, SOLTANIFAR A, BAER S. Stereotypic movement disorder: easily missed. Developmental Medicine & Child Neurology 2010;52:733-8.
18. Cardona F, Valente F, Miraglia D, D'Ardia C, Baglioni V, Chiarotti F. Developmental Profile and Diagnoses in Children Presenting with Motor Stereotypies. Front Pediatr 2016;4:126.
19. Bos KJ, Zeanah CH, Jr., Smyke AT, Fox NA, Nelson CA, 3rd. Stereotypies in children with a history of early institutional care. Arch Pediatr Adolesc Med 2010;164:406-11.
20. Goldman S, O'Brien LM, Filipek PA, Rapin I, Herbert MR. Motor stereotypies and volumetric brain alterations in children with Autistic Disorder. Research in Autism Spectrum Disorders 2013;7:82-92.
21. Singer HS. Motor control, habits, complex motor stereotypies, and Tourette syndrome. Ann N Y Acad Sci 2013;1304:22-31.
22. Harris AD, Singer HS, Horska A, et al. GABA and Glutamate in Children with Primary Complex Motor Stereotypies: An ¹H-MRS Study at 7T. American Journal of Neuroradiology 2016;37:552-7.
23. Aliane V, Perez S, Bohren Y, Deniau JM, Kemel ML. Key role of striatal cholinergic interneurons in processes leading to arrest of motor stereotypies. Brain 2011;134:110-8.

24. Goldman S, Greene PE. Stereotypies in autism: a video demonstration of their clinical variability. Front Integr Neurosci 2012;6:121.
25. Ghosh D, Rajan PV, Erenberg G. A comparative study of primary and secondary stereotypies. J Child Neurol 2013;28:1562-8.
26. Griffiths R. The abilities of young children: A comprehensive system of mental measurement for the first eight years of life. London Child Development Research Centre; 1970.
27. Luiz DM, Foxcroft CD, Stewart R. The construct validity of the Griffiths Scales of Mental Development. Child: care, health and development 2001;27:73-83.
28. https://www.hogrefe.co.uk/shop/griffiths-mental-development-scales-extended-revised-2-to-8-years.html. Hogrefe House, Oxford, United Kigdom. (Accessed 04 April 2018).
29. Wechsler D. The Wechsler intelligence scale for children—third edition. San Antonio: The Psychological Corporation; 1991.
30. W. WM, C. KJ, J. GJ. Discriminant and predictive validity of the WISC-III ACID profile among children with learning disabilities. Psychology in the Schools 1997;34:309-19.
31. Pepperdine CR, McCrimmon AW. Test Review: Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) by Sparrow, S. S., Cicchetti, D. V., & Saulnier, C. A. Canadian Journal of School Psychology 2017;33:157-63.
32. Lord C, Rutter M, Goode S, et al. Austism diagnostic observation schedule: A standardized observation of communicative and social behavior. Journal of Autism and Developmental Disorders 1989;19:185-212.
33. Abdekhodaie Z, Tabatabaei SM, Gholizadeh M. The investigation of ADHD prevalence in kindergarten children in northeast Iran and a determination of the criterion validity of Conners' questionnaire via clinical interview. Research in Developmental Disabilities 2012;33:357-61.
34. Mahone EM, Bridges D, Prahme C, Singer HS. Repetitive arm and hand movements (complex motor stereotypies) in children. J Pediatr 2004;145:391-5.
35. Robinson S, Woods M, Cardona F, Hedderly T. Intense Imagery Movements (IIM): More to motor stereotypies than meets the eye. Eur J Paediatr Neurol 2016;20:61-8.