Motor Disturbance in ASD

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ORIGINAL PAPER

Motor Disturbance in ASD: A Pilot Study Showing Hypokinetic Behavior?

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Abstract

Data supporting theoretical models linking autism spectrum disorders (ASD) to motor disturbance are inconclusive. In the present study, children and adolescents with ASD (n = 44) were compared with a matched group of typically developing individuals (n = 49) on both instrumental and observational assessments of motor abnormalities. No group differences were found in the instrumental data. However, more bradykinetic motor behavior was found using an observational scale in the ASD groups. More rigid motor behavior was found in the adolescents with ASD but not in the children. Individuals with ASD show significantly more hypokinetic behavior, which may not be strictly dopaminergic in origin, but may reflect a weak central coherency in neuronal networks related to the motor system in which developmental changes are present.

Keywords Autism spectrum disorder · Motor disturbance · Parkinsonism · Dyskinesia

Introduction

Motor difficulties are highly prevalent in autism spectrum disorder (ASD) (Van Damme et al. 2015), yet they are not considered to be part of the core symptoms of ASD. These include persistent deficits in social communication and -interaction, and repetitive patterns of behavior (APA 2013). However, social and motor skills are strongly related. Social interactions change as young children learn to walk (Clearfield 2011), and through children's play in which motor behavior is essential, social connections are build. Poor motor skills limit these interactions.

The interactive relationship between motor skills, social impairment (MacDonald et al. 2013; Pusponegoro et al. 2016) receptive and expressive language skills (Mody et al. 2017) has been demonstrated in children with an ASD. Hilton et al. (2012) describe motor impairment in individuals with ASD. Motor skills in unaffected siblings were normal, indicating that motor impairment is a core characteristic of the disorder and not an ASD endophenotype. The question arises whether motor difficulties are indeed part of a symptom cluster in ASD. Dyspraxia is more prevalent in adults with ASD than in controls. Also, in the general population, dyspraxia is associated with higher autistic traits and lower empathy, which could suggest that motor coordination skills are important in empathy and effective social interaction

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(Cassidy et al. 2016). Several studies have reported benefits of physical exercise on motor skills and social interaction in children with ASD (Brand et al. 2015; Srinivasan et al. 2015). Sensory-motor therapy is a promising intervention, since improvement on perceptual and social functioning in children with ASD has been found (Woo and Leon 2013). Altogether, identifying motor problems in individuals with ASD is of great importance, since it enables clinicians to integrate interventions that facilitate motor behavior in care planning. It also contributes to the understanding of the complex nature of this developmental disorder.

Abnormal functioning of the basal ganglia might be a link between movement abnormalities and other symptom clusters in ASD. The basal ganglia are connected with the cortex through several segregated but parallel loops, the so-called cortico-basal-ganglia-thalamocortical circuits. However, besides motor loops, the basal ganglia also contain associative (cognitive), and limbic (emotional) loops. They deal, with the control of behaviour and cognition, together with reward and emotions (Obeso et al. 2014). Therefore, motor dysfunctions, which are often seen in autism, may directly be related to dysfunctions of behaviour and cognition. Indeed, striatal volume changes in ASD have been observed previously (Staal et al. 2015).

Motor difficulties in ASD encompass a large range of abnormalities, like problems in coordination and balance, fine and gross motor delays (van Damme et al. 2015). Because of the resemblance of some characteristics in both disorders, a potential link between ASD and Parkinson's disorder (PD) has been proposed before (Damasio and Maurer 1978; Vilensky et al. 1981; Hollander et al. 2009). Rigid behavior patterns and difficulties in starting and stopping movements are amongst them. However, age at onset is different in both disorders. PD is an age-related progressive neurodegenerative disorder with onset of illness generally between ages of 60 and 65 and young onset ages < 50 (Ball et al. 2019). ASD is a neurodevelopmental disorder in which, for most children, declines in social interaction are observed during the first years of life (Ozonoff and Iosif 2019). PD is characterized with selective loss of dopaminergic neurons in the substantia nigra (Cacabelos 2017). Dysregulation of the dopamine system is also associated with both ASD (Nguyen et al. 2014; Staal 2015) and motor function (DeLong and Wichmann 2007; Obeso et al. 2014). And interesting, the SNP rs167771 of the dopamine-3-receptor gene (DRD3) has recently been found to be associated with repetitive and stereotyped behavior in ASD (Staal 2015), while the same SNP was earlier reported to be linked to acute risperidone-induced extrapyramidal symptoms in patients with mainly psychotic disorders (Gassó et al. 2009).

Another neuropsychiatric disorder in which movement disorders are an integral part, is schizophrenia (Van Harten and Tenback 2009) and studies indicate that also autism and schizophrenia share genetic factors (Burbach and van der Zwaag 2009). These authors suggest that both neuropsychiatric disorders might share pathogenic mechanisms involving altered brain development. Stone and Iguchi (2011) state that ASD and schizophrenia share similarities in genetic components and phenotypes, however, they remain distinct entities with important differences in for example age of onset. Results presented by Koning et al. (2010) could imply that movement disorders are core symptoms of psychotic disorders, since they are strongly associated with dyskinesia and parkinsonism in antipsychotic medication naïve patients. In conclusion, it might then also be possible that movement abnormalities are symptoms of the autism spectrum.

Dyskinesia is a hyperkinetic movement disorder characterized by involuntary writhing and purposeless, irregular movements that may or may not be continuous (Koning 2011). Dyskinesia is suggested to arise from aberrant striatopallidal activity, which results in reduced output in the globus pallidus interna and disinhibition of the thalamocortical pathway (Obeso et al. 2014). Dyskinesia had also been associated with smaller volumes of the putamen (Mittal et al. 2010, 2013). Parkinsonism is an akinetic rigid syndrome with the following features: rigidity, bradykinesia, resting tremor and postural instability (Obeso et al. 2014). Parkinsonism is thought to arise from hypodopaminergia in the extrapyramidal motor system, which induces inhibition of thalamocortical projections (Obeso et al. 2014). Both dyskinesia and parkinsonism can be measured with observational rating scales as well as with mechanical instruments.

The purpose of the present study is to investigate whether movement disorders, as measured with both observational and instrumental assessments, are more prevalent in children and young adults with ASD than in typically developing individuals. We use both observational and instrumental assessments as both present certain advantages. The observational rating scales we choose are widely used in both clinical practice and research. Therefore results can be easily understood and compared with other research. With observational rating scales, dyskinesia or parkinsonism in all body parts are taken into account. Mechanical instruments on the other hand only focus on certain parts of the body and are less widely used, but they are more sensitive and reliable than observational rating scales (Caligiuri and Lohr 1990; Koning 2011; Lohr and Caligiuri 1992). Another reason why it is interesting especially for the study of individuals with ASD to use both methods, is that it has been observed before that they perform different on measurements assessing a particular construct, depending on the amount of social interaction needed during testing (Ozonoff 1995).

It is expected that individuals with ASD experience more movement difficulties than control individuals. We hypothesize to find these difficulties especially in both observational and instrumental assessment of parkinsonism, based on the

clinical features often described in ASD. We do not expect differences in instrumental measurements assessing dyskinesia between the ASD group and controls, since involuntary and purposeless, irregular movements are not typically described for this clinical group. However, since ASD and psychotic disorders share genetic factors, and dyskinesia is associated with psychotic disorders, we choose to investigate dyskinesia also.

Method

Participants

High functioning children and young adults (age 6–26) with ASD (n = 44) were recruited from the department of child and adolescent psychiatry at the University Medical Centre Utrecht, the Netherlands. Controls (n = 49) were recruited through local schools. Inclusion criteria for both groups were age (between 6 and 26 years). All participants had a full scale intelligence quotient (FSIQ) > 70, determined by the short form of the Wechsler scales (four subtests: vocabulary, similarities, block design, object assembly) (Wechsler 2005a, b). To prevent the inclusion of individuals with possible other causes of movement disorders, the exclusion criteria for both groups were a history of neurological disease, the use of antipsychotic medication, and substance abuse. Controls with a first- or second-degree relative with developmental disorder were also excluded. The groups were matched for sex, age and FSIQ.

Individuals in the ASD group were diagnosed by a child and adolescent psychiatrist. The ADI-R (Lord et al. 1994), or the ADOS (Lord et al. 2000) and in most cases both instruments were available. Ethical approval for the study was obtained and all participants or their parents, if appropriate, gave written informed consent.

Measures and Materials

Data Collection Procedure

Participants were invited to the UMC Utrecht for an appointment that took approximately 75–90 min of their time. The Wechsler scales were administered and the individuals were evaluated with the Abnormal Involuntary Movement Scale (AIMS) (Guy 1976) for clinical dyskinesia, and the Unified Parkinson Disease Rating Scale (UPDRS) (Martinez-Martin et al. 1994) for clinical parkinsonism. Manual dexterity was assessed by observing and questioning participants and/or parents. After that, the mechanical measurements were administered. A research assistant together with a neuropsychologist, both trained by an expert in the field of movement disorders (JK), assessed all scales and tasks. Only one tester was present in the room, the second tester was placed behind a one-way screen. Both testers scored the observational measurement independently. Afterwards, scores were evaluated. Inter rater agreement was 96%. In case both tests had different scores, the lower score was used in the analysis.

Clinical Assessment of Dyskinesia and Parkinsonism

Clinical Dyskinesia The AIMS divides the body into seven different areas (face, tongue, lips, jaw, upper limbs, lower limbs and neck, shoulders and hips). Each item is scored from 0 to 4 to indicate disorder severity (0 = absent, 1 = questionable, 2 = mild, 3 = moderate, and 4 = severe). Clinical dyskinesia was defined as a score of 2 or greater on any of the seven items of the AIMS, based on the research criteria for dyskinesia (Glazer 2000).

Clinical Parkinsonism The motor examination part of the UPDRS was used to assess speech, facial mobility, resting tremor (face and each limb), rigidity (neck and each limb), rapid hand and foot movements, rising from chair, posture, gait, postural stability and body bradykinesia. Each item is scored from 0 to 4 to indicate disorder severity (0 = absent, 1 = questionable, 2 = mild, 3 = moderate, and 4 = severe). Clinical parkinsonism was considered a case when any item was scored at least "mild" (a score of 2 or greater) on the UPDRS (Martinez-Martin et al. 1994).

Mechanical Assessment of Dyskinesia and Parkinsonism (Resting Tremor and Bradykinesia)

Dyskinesia Using Mechanical Measurement Dyskinesia is a hyperkinetic movement disorder characterized by involuntary writhing and purposeless, irregular movements that may or may not be continuous (Koning 2011). When present in the hands, this leads to instability in tasks requiring the exertion of a constant pressure. Variability in exerted force [force variability (FV)] in the lower (< 3 Hz) frequency range can therefore be used as a quantification of dyskinesia (Caligiuri and Lohr 1990). An instrument based on this principle was used to assess dyskinesia mechanically by measuring the FV, as indicated by the individual's attempt to exert constant pressure on a load cell and measuring the variations in the force applied over time. Participants were asked to exert constant target pressure, first by pushing a button with the index finger of their dominant hand, then of their non-dominant hand (Koning et al. 2010). The button was connected to a cell attached to a monitor showing a real-time graph indicating target and actual force applied. The strength required to achieve the target height on the graph was set to an equivalent of 3 N for the index finger (Dean et al. 2004). All participants performed each exercise three times for duration of 20 s each, separated by 5-s rest peri-

ods. The first trial was used to accustom the test taker to the procedure. Mean data of the two subsequent measurement trials were used for analysis. The force generated was measured continuously and presented graphically to the subject with virtually no delay. The average force was calculated for each 20-s test period. After subtracting this mean from the signal, it was Fourier transformed. Total power in the 0 to 3 Hz range was calculated and converted to find the standard deviation for the 0 to 3 Hz signal components. This standard deviation is technically equivalent to the one found after a very sharp 3 Hz low-pass filtering of the force signal. The standard deviation was presented as the percentage of error, or coefficient of variation (CV, standard deviation divided by mean force). For dyskinesia, only force measured in the 0 to 3 Hz frequency range was used as this reflects dyskinesia best (Lohr and Caligiuri 1992) and is unaffected by resting tremor (which measured at the 4 to 6 Hz frequency band) (Stein and Oguztoreli 1976). This technique has been extensively validated for finger dyskinesia (Lohr and Caligiuri 1992). For a more detailed explanation of the procedure/apparatus, we refer to "Appendix". Examples of force variability/force variation are presented in Illustrations 1, 2 and 3.

Parkinsonism (Resting Tremor and Bradykinesia) Using Mechanical Measurement The data generated in the preceding procedure were also used to mechanically evaluate resting tremor, by calculating the amount of variability in the force applied, with the difference that now only total force in the 4 to 6 Hz frequency range was used, as this frequency reflects resting tremor best (Stein and Oguztoreli 1976) and movements in this range are unaffected by dyskinesia.

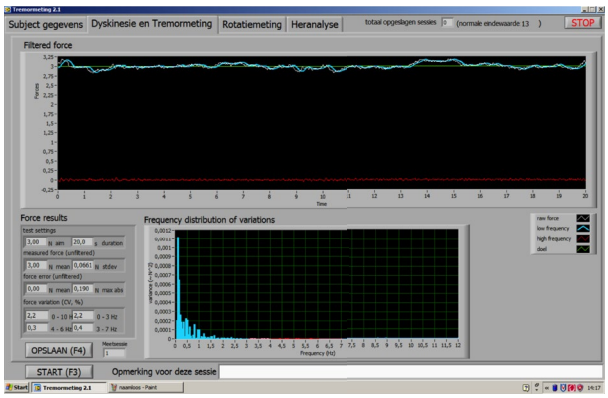

Illustration 1 Subject: no dyskinesia, no tremor. This is an example of force variability. The bluish/green line indicates the actual force applied over time in the 03 Hz frequency range. In the box you can see the frequency distributions of the variations. There have been norm scores for normal healthy subjects, and they resemble this line, so here there is "no dyskinesia" and "no tremor"

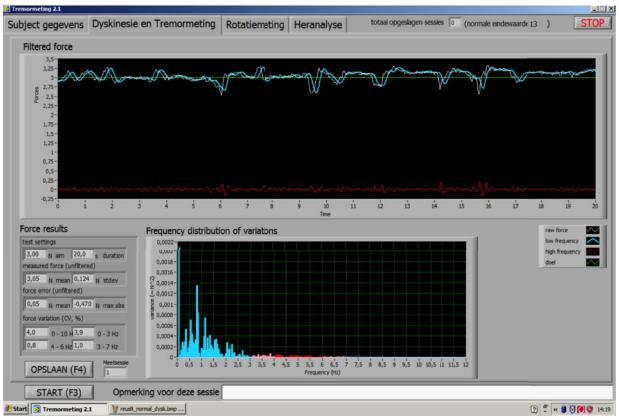

Illustration 2 Subject: with dyskinesia, but no tremor. As depicted in the bleu line (low frequency) and bars, a person with dyskinesia shows more variation around the green target line. If we look at the frequency distributions of the force variation, you will see a little (blue) peak emerging in the 0–3 Hz frequency range

Bradykinesia can be mechanically quantified by measuring the ability to adjust movement velocity to changing distances (Caligiuri et al. 1998, 2006). Participants with bradykinesia (parkinson's disease or drug induced parkinsonism) are less able to scale their movement velocity and require more time as distances increase. Velocity scaling (VS) scores are expressed as degrees per second per degree (°/s/°). Participants were instructed to flex a handle with their wrist as fast but as accurately as possible in order to move a flexible cursor presented on the computer screen

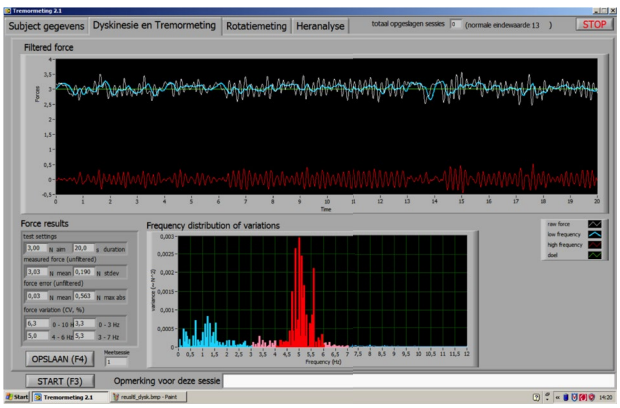

Illustration 3 Subject: with resting tremor, but no dyskinesia. If we look at the same graph of a person with resting tremor, but no dyskinesia, it looks like this. As you can see, red line shows oscillations in the 4–6 Hz frequency range. The blue line shows some variation around the target line, but less extensive compared to the former person with dyskinesia. So you can see that this method can differentiate between resting tremor and dyskinesia. If we look at the frequency distributions of the force variation, you will see a little peak emerging in the 4–6 Hz frequency range, and a very little one in the 0–3 Hz frequency range

to a target cursor located at 25° and 45° from the midline of the wrist flexion (Caligiuri et al. 1998). The handle was connected to a potentiometer attached to a monitor showing in real-time the target and flexible cursor. Participants started with the dominant hand and then switched to the non-dominant hand and performed 32 movement measurements, consisting of 16 measurements for each of the two randomly presented target locations, for each hand, for a total of 64 movements (Caligiuri et al. 1998).

Data Analysis

Statistical analyses were performed using SPSS-24®. A p value < .05 was deemed significant. A Chi square analysis was conducted to test whether the two groups differed relative to gender and manual dexterity. Age and FSIQ were analyzed using a T-test for independent groups. A series of analyses of variance were performed to test for differences between the ASD and the control group in the mechanical assessments of parkinsonism (tremor, bradykinesia) and dyskinesia separately. Although this resulted in smaller groups, we choose two different age groups; children (age 6–12 years, n = 44) and adolescents/young adults (age 13–26 years, n = 49) since developmental effects on motor behavior are expected to be high. Outliers were identified by using bivariate scatterplots for each group and was scored an outlier with Z-score > 3.29 (P < .001, two tailed). Evaluation of the data led to the conclusion that present extreme scores were proper part of our sample, and were therefore not removed. Data were transformed using log transformation in order to pull outliers closer to the center of the distribution.

Differences between groups on the clinical assessments are calculated with Mann–Whitney U tests.

For the mechanical measurements, power was adequate (0.80) for the detection of medium effect sizes f = .029. For the rating scales we were able to detect large effect sizes. In the children group, a power of 0.8 was reached at effect size d = 0.87 and for the adolescents at effect size d = 0.84.

Results

Descriptive Statistics

Demographic characteristics of the participants are presented in Table 1. In both the child and adolescent/young adult group, the individuals with ASD and controls did not differ relative to age, gender, FSIQ and handedness.

Clinical Assessment of Dyskinesia and Parkinsonism

Results are presented in Table 2. Non-parametric analysis showed no significant differences in dyskinesia between the ASD and control group. However, significantly more bradykinetic motor behavior using the observation scales (UPDRS) for parkinsonism (p < 0.0001) was present in children and adolescents with ASD. More rigid motor

Table 1 Demographic characteristics

	6–121			3–26		
	ASD (n = 22)	Controls (n = 22)	p	ASD (n = 23)	Controls (n = 26)	P
Age in years (M/sd)	10.4 (1.7)	10.3 (1.8)	.84	18.7 (4.6)	20.2 (4.1)	.25
Sex (n male)	17	17	.99	17	20	.81
FSIQ (M/sd)	113.7 (17.0)	114.6 (15.0)	.87	107.7 (19.8)	113.5 (14.6)	.26
Handedness (n right)	21	21	.99	19	25	.23

Table 2 Cases of dyskinesia and parkinsonism based on clinical assessment

	6–12			13–26		
	ASD (n = 22) Cases n (%)	Controls (n = 22) Cases n (%)	*p	ASD (n = 23) Cases n (%)	Controls (n = 26) Cases n (%)	*p
Dyskinesia	4 (18.2)	1 (4.5)	.546	4 (17.4)	0	.093
Parkinsonism	12 (54.5)	1 (4.5)	.000	17 (73.9)	3 (11.5)	.000
Bradykinesia	11 (50.0)	1 (4.5)	.000	15 (65.2)	2 (7.7)	.000
Rigidity	1 (4.5)	0	.325	7 (30.4)	0	.000
Tremor	2 (9.1)	0	.144	4 (17.4)	1 (3.8)	.439

Cases are defined as a score of 2 or higher on any item on the AIMS for dyskinesia and the UPDRS for parkinsonism. For bradykinesia, rigidity and tremor, a score of 2 or higher on one or more items pertaining to the relevant domain was used for case definition. *p values from Mann–Whitney U tests

behavior was found in the adolescent group, as compared to controls. This was not present in the younger age group.

Mechanical Assessment of Dyskinesia and Parkinsonism (Resting Tremor and Bradykinesia)

The results are presented in Table 3. A series of analyses of variance revealed no significant main effects of group membership (ASD versus controls), on mechanical tests for parkinsonism and dyskinesia. There were main effects for age for dyskinesia and resting tremor in both hands, the adolescent/young adults showed less dyskinesia and tremor than the children. Bradykinesia did not show a main effect for age. There were no significant effects for group × age. These results indicate there was no difference between the ASD group and controls on mechanical measurements for dyskinesia, resting tremor and bradykinesia.

Correlations Between Observational and Mechanical Measurements

Considering the discrepant findings of the observational rating scales versus the mechanical measurements, we calculated Pearson's correlations between their corresponding items/results. For dyskinesia, the correlation between item 5 of the AIMS (dyskinesia of the upper extremities: arms, wrists, hands, fingers) and FV was .17 ($p = 0.132$) for the ASD group and .42 ($p = 0.002$) for the control group. For bradykinesia of the arms/hands UPDRS item 24 (hand movements: patient opens and closes hands in rapid succession) and 25 (Rapid alternating movements of the hands: Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible) were combined and correlated with VS. R was .06 ($p = 0.362$) for the ASD group and − .07 ($p = 0.331$) for the control group.

Discussion

We found differences between the ASD group and controls with a rating scale assessing parkinsonism, but not with a mechanical instrument measuring force variability and movement velocity. With the rating scale, we observed more bradykinesia in both age groups with ASD compared to the typically developing control groups. In the adolescents/young adults with ASD, but not in the children, more rigidity was found than in the control group. Resting and action tremors were not observed using the mechanical instrument and the rating scales. For dyskinetic movements, the difference between the ASD group and the control group did not reach significance in the children but was significant at trend level in the adolescent/young adult group.

Surprisingly, our groups performed similar on the mechanical measurements assessing movement velocity, a quantification of bradykinesia. Effect sizes for the effect of group and the group × age interaction were very small (partial η squared ≤ 0.008 for all measurements) indicating that results could not be explained by a lack of power in our analyses. These findings are unexpected, since we found higher rates of bradykinesia in children and young adults with an ASD, compared to controls, using the observational instrument. Individuals in the ASD group showed rapid fatiguing, slowness in performed movements, speaking in soft monotone voices and little facial expression. These symptoms were scored in the mild range. Notably, slowness and rapid fatiguing were also seen in hand movement, whereas ASD groups performed normally on the instrumental task requiring rapid hand movements. We also found higher rates of rigidity in the ASD group compared to the control group in the adolescents/young adults. In the children, there was somewhat more rigidity as well in the ASD group than in the control group, with the difference between the groups showing a small to intermediate effect size, which probably may have reached significance if we had had larger groups.

Table 3 Mechanical assessment of dyskinesia and parkinsonism; ANOVA results

	Group			Age			Group × age		
	F	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
Dyskinesia									
Right hand	0.668	.416	.008	30.181	.000	.276	0.133	.717	.002
Left hand	0.321	.573	.004	34.816	.000	.306	0.044	.834	.001
Parkinsonism									
Tremor right hand	0.227	.635	.003	21.530	.000	.214	0.103	.749	.001
Tremor left hand	0.292	.591	.004	15.715	.000	.166	0.121	.729	.002
Bradykinesia right hand	0.033	.857	.000	1.229	.271	.015	0.327	.569	.004
Bradykinesia left hand	0.357	.552	.005	0.960	.330	.012	0.035	.852	.000
Bradykinesia towards	0.025	.876	.000	0.003	.953	.000	0.051	.822	.001
Bradykinesia reverse	0.079	.78	.001	0.188	.666	.002	0.582	.448	.007

Higher rates of parkinsonism in individuals with an ASD, and thus partly in line with our results, were found by Starkstein et al. (2015). Also using the UPDRS, higher rates of tremor, rigidity, bradykinesia and postural instability were found in older adults (age > 39 years) with an ASD. The participants in that study were older, had lower IQ's and several were on neuroleptic medication. These factors, especially the use of neuroleptics (Shin and Chung 2012), influence motor performance. Human perception of movement is highly complex and mechanical measurements as used might not (yet) be able to identify certain attributes of movement. Still, these results are important in the understanding of the clinical presentation of motor disturbance and underlying pathology in ASD and offer material for future research.

Our results are in contrast with a study in siblings of patients with non-affective psychosis, in which parkinsonism and dyskinesia were observed with instrumental measurements, but were not observed with rating scales. The authors concluded that the mechanical instrument provided more sensitive measures of dyskinesia and parkinsonism (Koning et al. 2011). It is therefore remarkable that in a disorder in which dopaminergic involvement is assumed (Nguyen et al. 2014; Staal 2015), no differences in task performance could be detected on instrumental measurements. An explanation for these contrasting findings might be that the movement disorders seen in ASD are different in nature than those seen in the psychosis spectrum. Where movement disorders in the latter are thought to stem from abnormalities in dopaminergic transmission in the striatum, in ASD they may be caused by other neurobiological mechanisms.

We did not find an increase in instrumentally measured dyskinetic movements in individuals with ASD compared to healthy control participants. With the AIMS we observed slightly more dyskinesia in the ASD groups. In the children group, the difference had a small effect size and was not significant. However, in the adolescent/young adult group, the difference had a medium effect size and was significant at trend level. To the best of our knowledge, there a no other publications on spontaneous dyskinesia in patients with ASD.

The fact that significant differences in bradykinesia, and on a trend level dyskinesia, were found with the UPDRS and AIMS respectively, but not with the mechanical instrument, was unexpected. To gain more insight into this finding, correlations between the instrumental measurements and items from the observational ratings scales measuring thought to measure bradykinesia and dyskinesia were determined. We were surprised by the absence of a correlation between the items of the UPDRS determining bradykinesia of the hands, and VS in the ASD and control group. An explanation might be that different constructs are being measured. Caligiuri et al. (1998) argue that FV measures predominantly neuromotor retardation, while with observational ratings, both psychomotor and neuromotor slowing are being taken into account (Caligiuri et al. 1998). For dyskinesia, a significant intermediate to strong correlation between dyskinesia of the upper extremities on the AIMS and FV was found for the control group while the correlation in the ASD group was weak to intermediate and not significant. This might be understood by looking at research suggesting that individuals with an ASD perform better under conditions in which social interaction is minimized. Computerized versions of cognitive tasks will be discussed in more depth later in our discussion.

Taken together, our findings may reflect movement abnormalities caused by other neurobiological processes than those seen in psychotic disorders. Rather than disturbed dopaminergic transmission, an alternative, more appealing explanation for the movement abnormalities observed in ASD may be provided when linking the results to the vast literature on impaired functional and structural connectivity. Due to under (Müller et al. 2011) or overconnectivity of brain regions, among which are fronto-striatal connections and the basal ganglia (Fournier et al. 2010), problems in coordination of motor, cognitive and social activities occur in ASD. In a computational approach, abnormalities were found in two areas in motor behavior; poor integration of information for efficient motor planning and increased variability in basis sensory input and motor outputs. Motor learning was relatively intact (Gowen and Hamilton 2013). Mounting evidence suggests that brain connectivity might be altered in ASD. Most findings show a decrease in long-range connectivity whereas findings on proposed local over-connectivity have been inconsistent (O'Reilly et al. 2017; Rane et al. 2015). Evidence also suggests that connectivity is related to symptom severity in ASD (Hahamy et al. 2015). Recent work shows an anti-correlation, or underconnectivity between anterior and posterior brain regions in individuals with ASD (Heinsfeld et al. 2017). Functional connectivity has also been linked to behavior in ASD; higher scores on the ADI-R were correlated with weaker functional connectivity (Monk et al. 2009; Weng et al. 2010).

Regarding networks related to motor behavior, hyperconnectivity between striatal and cortical regions (Di Martino et al. 2011) and in thalamocortical networks (Woodward et al. 2017) have been reported in studies using resting state fMRI paradigms. In school aged children with ASD, Di Martino et al. (2011) found excessive connectivity between striatal subregions and associative and limbic cortex. Woodward et al. (2017) using data from the Autism Brain Imaging Data Exchange (ABIDE) database found hyperconnectivity between the thalamus and cortical regions including motor, somatosensory and prefrontal cortex in ASD. In males with autism a different functional organization of the primary motor cortex, characterized by a lack of differentiation

between lower limb/trunk and upper limb/hand parcels has been found (Nebel et al. 2014).

Few studies relating aberrant connectivity directly to motor tasks in ASD have been published and studies focused on various different aspects of the motor network and used different tasks. Mostofsky et al. (2007) observed that in children with ASD, increased white matter volume in the primary motor and premotor cortex in the left hemisphere was associated with poorer motor skills, whereas in the control group, increased white matter volume in the primary motor cortex in both hemispheres was associated with better motor performance. In another study, children with ASD showed a slightly different activation pattern and a general decrease in connectivity across the motor network during a finger tapping task compared to typically developing control children (Mostofsky et al. 2009). Furthermore, atypical lateralization of motor network connectivity has been reported in children with ASD, which correlated with motor skill impairment measured with a finger-tapping test (Floris et al. 2016).

Connectivity and developmental trajectory hypotheses could shed light on our findings. Due to under and or over-connectivity, the coordination of motor, cognitive and social activity is hypothesized to be problematic. The developmental trajectory hypothesis states that hyperconnectivity is more characteristic in young children with ASD, while hypoconnectivity is more prominent in adolescence and adulthood (Uddin et al. 2013; Nomi and Uddin 2015). In line with this is the suggestion that ASD could be a disorder of aberrant white matter growth patterns at young age and reduced white matter integrity at older age (Maximo et al. 2014). However, Woodward et al. (2017) found that hyperconnectivity between thalamus and motor and temporal cortex was more pronounced in older adolescents than in children/young adolescents and adults. Rigidity, or the resistance to passive movement, has been related to dysfunctional brain connectivity and motor performance in individuals with PD (Baradaran et al. 2013). Hypothetically, it could be possible that the higher degree in rigidity in the adolescent/young adult group in the present study and in the Starkstein et al. (2015) work, might stem from underconnectivity in the brain, which is not yet present in younger children. An important finding in relation to motor impairment is an age-dependent relationship between social adaptability and motor coordination in high functioning children with an ASD (Kostrubiec et al. 2017). Thus, developmental changes are important to account for.

In their study, Marko et al. (2015) found that children with an ASD outperformed controls when learning from errors trough proprioception, but underperformed controls when learning form errors through vision. Altered connectivity might play a role in this difference. In our study, motor performance during rating scale observation might be more demanding to individuals with an ASD, because there is a high amount of social interaction during assessment. Individuals have to observe the test taker, process this visual, social and motor information and react with motor performance in relation to the test taker. High demands are placed on motor and social networks, and they might interact differently in ASD as they do in healthy controls. Individuals with ASD suffer under more complex circumstances (Koolen et al. 2014). We argue that the demands on these networks are lower during the mechanical assessment. All individuals receive a training session in which the test instructor shows the computer task. Individuals are asked to follow instruction on the computer screen, lowering the amount of social interaction. After the instruction is given, all individuals perform a solo flight were social information processing is low. This difference has been demonstrated before on set-shifting tasks. Individuals with an ASD performed better on computerized versions of cognitive tasks in which social interaction is minimized (Ozonoff 1995).

Of course the new hypothesis that altered connectivity is responsible for our findings is preliminary and must be examined in (RS)-fMRI or EEG studies. However, the use of observational rating scales might mimic expectations of daily live more than a mechanical measurement would in this population. Understanding the role of movement abnormalities in ASD, especially in developing children, is important as it can help to gain insight into the underlying neurobiological processes and the interrelationship of symptom clusters including movement abnormalities. As stated before, a relationship between motor skills and social interaction problems has been demonstrated in ASD, and benefits of physical exercise on motor skills and social interaction in children with ASD have been shown. Another clue that motor problems might be part of a symptom cluster is that dyspraxia is more prevalent in adults with ASD than in controls. In the general population, dyspraxia is associated with higher autistic traits and lower empathy, which could suggest that motor coordination skills are important in empathy and effective social interaction (Cassidy et al. 2016). Identifying motor problems in individuals with ASD might be of great importance in care planning and the effect of interventions.

The current study has several limitations. Test takers were not blinded to group membership. We think it is difficult to prevent raters from knowing whether a participant is in the ASD or control group. In future study, one could keep the raters blind to study hypothesis. In this study however, inter rater agreement was high (96%) and raters were trained by a professional (JK) in the field of motor disorder in psychiatric populations. Second, we used rating scales, which are not typically developed for the use in pediatric populations. However, we used an age and IQ matched control group, and understanding of the instructions and collaboration were excellent with all participants. Third, we had a relatively small sample size and therefore a reduced chance of

detecting true effects. It is also possible that false positive results occur. Looking at other studies in this field, number of participants range, with exception by the study of Green et al. (2009) from 11 to 51. Still, future research should focus on larger groups. Fourth, data distribution forced us to use Mann–Whitney tests in the rating scale analysis, with all of its shortcomings. We could not control for age and IQ, factors that are known to influence motor performance. Nevertheless, we used an age and IQ matched control groups. Another important shortcoming could be that the method and analysis used in the instrumental measurement are not specific enough to capture impairments in movement in ASD. Using time series analysis in future research could give us more information.

Despite the shortcomings, this study has important methodological advantages. Participants with ASD were carefully diagnosed; ADI and ADOS, the 'gold standard' for diagnosing ASD, were used in the procedure. None of the participants were on antipsychotic or antiepileptic drugs, thus our results cannot be explained by medication effects. As mentioned before, ASD, PD and psychotic disorders share similarities in phenotypes, but also seem distinct entities with important differences in for example age of onset. Although our pilot study creates valuable insights, it also raises many new questions. Future research should therefore focus on the differences between (older) individuals with ASD, Parkinson's disease and psychotic disorders on instrumental and observational measurements of movement disorder. Additional indexes may then be used in the analysis such as approximate entropy, sample entropy and signal-to-noise ratio (Chow and Stokic 2016; Deutsch and Newell 2004; Slifkin and Newell 1999).

Conclusion

The results of this pilot study should only be interpreted within the context of its limitations. In this study, individuals with ASD show significantly more hypokinetic behavior compared to healthy controls, which may not be strictly dopaminergic in origin, but may rather reflect a weak central coherence of neuronal networks related to the motor system in which developmental changes are present. However, many questions remain. Our data encourage explanation of motor disturbance in ASD by future research.

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Author contributions MALMK conceived of the study, participated in its design and coordination, performed the measurement, performed the statistical analysis and drafted the manuscript; AW participated in the interpretation of the data, performed statistical analysis and drafted the manuscript; JPK participated in the design and coordination of the study and helped to draft the manuscript; DET participated in the interpretation of the data and helped to draft the manuscript; PVH participated in the interpretation of the data and helped to draft the manuscript; WGS conceived of the study, participated in its design and coordination, participated in the interpretation of the data and helped to draft the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

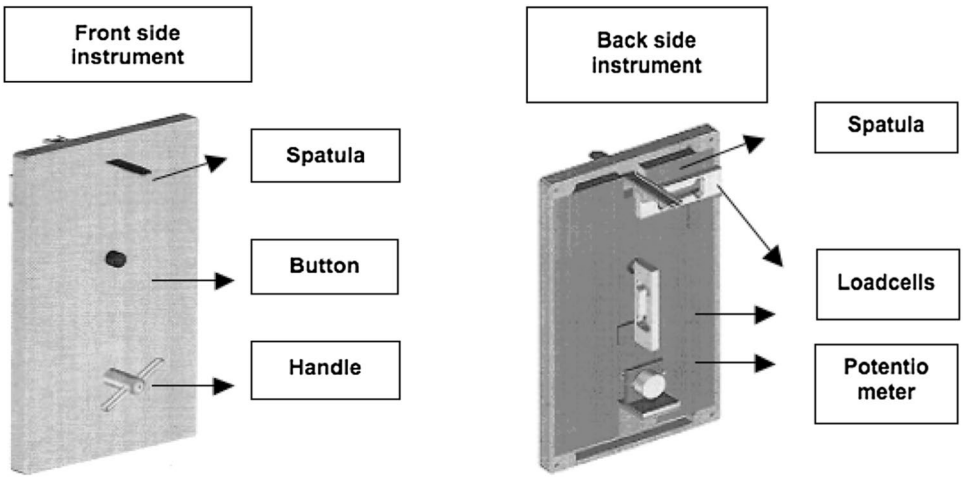

Fig. 1 Mechanical instrument for measuring force variability and velocity scaling

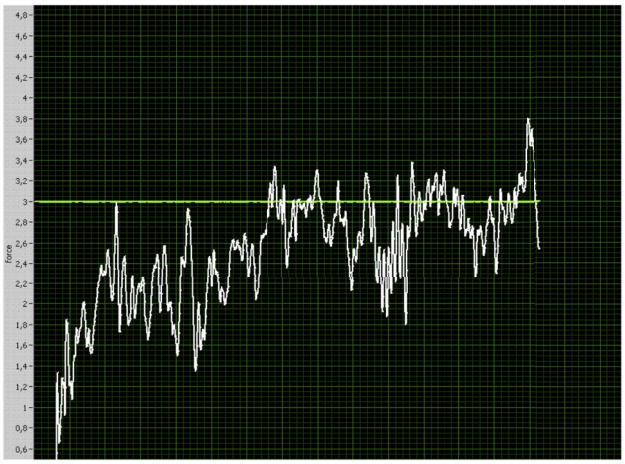

Fig. 2 Test for force variability, as seen on the computer screen. Example subject's force variability when trying to match the target height of 3 N. *N* Newton

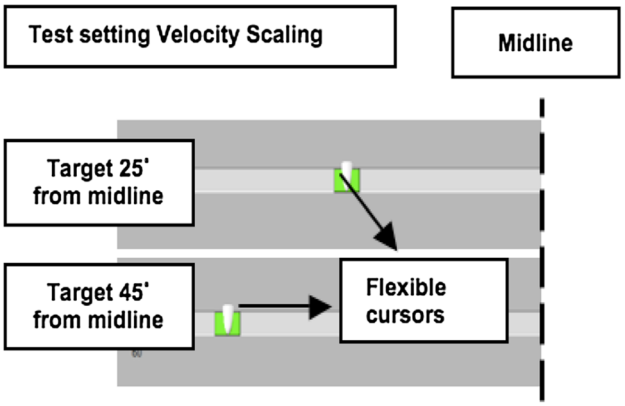

Fig. 3 Test for velocity scaling

Appendix: Details of the Procedure and Apparatus

Mechanical Instruments for Measuring Force Variability and Velocity Scaling

Measurement of Dyskinesia and Resting Tremor Using Force Variability (FV)

Dyskinesia can be assessed mechanically by measuring FV, as indicated by the subject's attempt to exert constant pressure on a load cell (see Fig. 1) and measuring the variations in the force applied over time (Caligiuri and Lohr 1990, 1994; Cortese et al. 2005; Dean et al. 2004) (see Fig. 4).

Procedure Participants are instructed to exert constant target pressure, first by pushing a button with the index finger of their hand to measure hand dyskinesia (Koning et al. 2011). The button and spatula are connected to a load cell attached to a monitor showing a real-time graph indicating target and actual force applied (Figs. 1, 2). The strength required to achieve the target height on the graph is set to an equivalent of 3 Newton for the index finger (Dean et al. 2004; Koning et al. 2011). Participants perform each exercise 3 times for a duration of 20 s each, separated by 5-s rest periods. The first trial is used to accustom the patient to the test. Mean data of the two subsequent measurements are used for analysis. For dyskinesia, only force variation measured in the 0 to 3 Hz frequency range is used as this reflects dyskinesia best (Lohr and Caligiuri 1992) and is unaffected by resting tremor (which is measured at the 4 to 6 Hz frequency band) (Stein and Oguztoreli 1976). This technique has been validated for finger dyskinesia (Caligiuri and Lohr 1990, 1994; Caligiuri et al. 1995, 1997; Cortese et al. 2005; Dean et al. 2004).

Technical Specifications Force Variability Measurement

Force Measurement

Force measurement finger	
Button	Plastic, directly connected to the loadcell
Load cell	Load sensor for 3 kg nominal
Intended power	3.0 N (approx. 300 grams)
Pressure point height	Approx. 25 cm above table top
Force measurement direction	vertical, downward
Force measurement general	
Measuring range	> 2 times intended force
Overload capability	Safe up to 1.5 × nominal power of the sensor
Deviation	< 0.4 mm at nominal force of the sensor
Inaccuracy	According to specs sensor: < 0.3% at the intended force
Analog filtering	1st order Low Pass, − 3 dB at 200 Hz
Sampling	12 bit, 2.5 kHz
Digital filtering	Low Pass, − 10% at 10 Hz, − 3 dB at 18 Hz
Software	MS Windows, MatLAb
Hardware Laptop	Dell Inspiron 1525,
Processor	Intel Pentium duo core T2370
LCD display	15.4″ widescreen with a 1280 × 800 resolution

Measurement of Bradykinesia Using Velocity Scaling (VS)

Bradykinesia can be mechanically quantified by measuring the ability to adjust movement velocity to changing distances (Caligiuri et al. 1998, 2006). For example, normal individuals, when moving from one fixed target

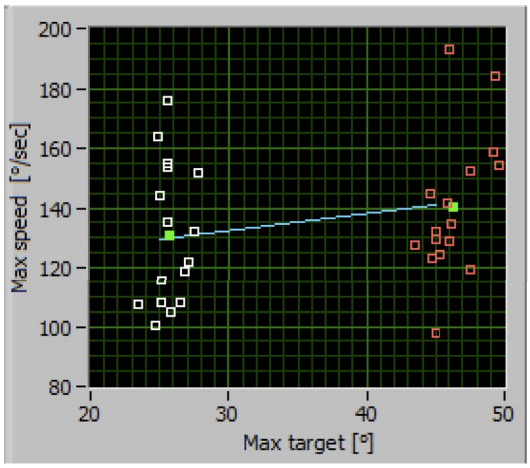

Fig. 4 Example of subject with bradykinesia (unable to increase peak velocity when distance increases). Y-axis: maximum speed (peak velocity) of flexing wrist. X-axis: targeted distance located at 25° and 45° from the midline of the wrist flexion

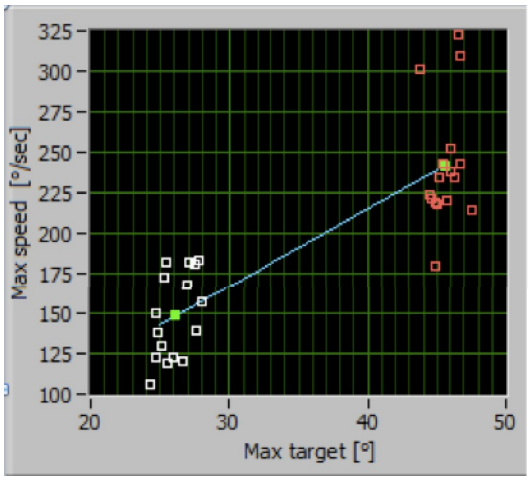

Fig. 5 Example of subject without bradykinesia (able to increase peak velocity when distance increases). Y-axis: maximum speed (peak velocity) of flexing wrist. X-axis: targeted distance located at 25° and 45° from the midline of the wrist flexion

to another, perform different movements in roughly equal time. Thus, moving from one object to another 20 cm away takes approximately the same time as moving to an object 40 cm away when instructed to move as quickly as possible. To do this, the average velocity of the arm movement must increase to compensate for the longer target distance. Participants with bradykinesia (e.g. with Parkinson's' disease or drug-induced parkinsonism) are less able to scale their movement velocity and require more time as distances increase (Figs. 3, 4) (Benecke 2002; Berardelli et al. 1986; Caligiuri et al. 1998).

Procedure Participants are instructed to flex a handle (Fig. 1) with their wrist as fast but as accurately as possible in order to move a flexible cursor presented on the computer screen to a target cursor located at 25° and 45° from the midline of the wrist flexion (Fig. 3) (Caligiuri et al. 1998). The handle is connected to a potentiometer (Fig. 1) attached to monitor showing in real-time the target and flexible cursor (Fig. 3). Participants perform 32 movement measurements consisting of 16 measurements for each of the two randomly presented target locations, for each hand, for a total of 64 movements (Caligiuri et al. 1998). VS scores are expressed as degrees per second per degree (°/s/°). The VS measure is a valid and reliable measure of antipsychotic-induced bradykinesia (Caligiuri et al. 1998, 2006) (Fig. 5).

Technical specifications velocity scaling	
Measuring range	Measured with a potentiometer with a range of ≥ 18°. The range is limited by working end stops.
Inaccuracy	Angle between end stops (120°) within ± 1% degree Position measurement potentiometer within ± 2 degrees (according to specs potentiometer).
Handle plate	With rubber handle, dimensions approx. 90 × 45 mm^2.
Rest position handle	Vertical (rest = middle between end stops). This position is not visible or tangibly indicated on the mechanical arrangement
Direction axis of rotation	Horizontal, approximately straight away from the person. Turns to the left (viewed counter-clockwise from the test subject) are measured as positive.
Handle rotary	Friction smooth running, mounted
Potentiometer	Rotary
Data acquisition instrument	Hardware: National Instruments (NI) USB-6008
Sampling frequency	12-Bit, 10 kS/s
Movements	Self-paced

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