Psychiatry Research 272 (2019) 135–140

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Instrument-based assessment of motor function yields no evidence of dyskinesia in adult first-degree biological relatives of individuals with schizophrenia and schizoaffective disorder

Jerillyn S. Kent[a,b], Michael P. Caligiuri[c], Mallory K. Skorheim[d], Timothy J. Lano[a,b], Vijay A. Mittal[e], Scott R. Sponheim[b,a,f,*]

[a] Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA
[b] Minneapolis VA Health Care System, Minneapolis, MN, USA
[c] Department of Psychiatry, University of California San Diego, San Diego, CA, USA
[d] Department of Psychiatry and Behavioral Science, University of North Dakota, Fargo, ND, USA
[e] Department of Psychology, Northwestern University, Evanston, IL, USA
[f] Department of Psychology, University of Minnesota, Minneapolis, MN, USA

ARTICLE INFO

Keywords:
Schizophrenia
Psychosis
Dyskinesia
Basal ganglia
First-degree biological relatives
Endophenotype
Genetic liability

ABSTRACT

There is accruing evidence of spontaneous dyskinesia in individuals with schizophrenia that is independent of medication exposure. Dyskinetic motor behavior is also present in individuals who are at high risk of schizophrenia and appears to have prognostic value for the development of psychosis. Nonetheless, it remains unclear whether dyskinesia is present in first-degree relatives of individuals with schizophrenia and thus associated with genetic liability for schizophrenia (i.e., an endophenotype), or whether the motor abnormality is a biomarker specific to the disease state spectrum. There is also limited information about links between dyskinesia and clinically relevant phenomena such as symptoms and cognition. Because dyskinesia marking genetic liability is likely to be subtle, we used sensitive instrument-based measurement of handwriting fluency to quantify dyskinesia in medicated individuals with schizophrenia or schizoaffective disorder, unaffected first-degree biological relatives of individuals with schizophrenia and schizoaffective disorder, and control participants. Results indicated that medicated individuals with schizophrenia or schizoaffective disorder exhibited more dyskinesia than both relatives and controls, with no difference between relatives and controls. Dyskinesia in individuals with schizophrenia or schizoaffective disorder was unrelated to current antipsychotic medication dosage, but associated with worse working memory function and greater positive formal thought disorder. These results provide evidence that dyskinesia is not associated with unexpressed genetic liability for schizophrenia.

1. Introduction

Among several types of aberrant movements (e.g., neurological soft signs, abnormal gestures, catatonia), spontaneous dyskinesias are of particular relevance to schizophrenia because of their potential as prognostic indicators for later development of psychosis (van Harten et al., 2017) and the shared potential mechanism of dopamine dysregulation common to both dyskinesia and psychosis (Alexander et al., 1990; Howes and Kapur, 2009). "Spontaneous" distinguishes these involuntary ballistic, jerking, or slow/writhing movements from motor behavior associated with antipsychotic medication side effects (e.g., tardive dyskinesia), and instead, speaks to the role these characteristic movements may play in reflecting underlying pathological processes affecting dopamine dysregulation (Caligiuri and Lohr, 1994; Pappa and Dazzan, 2009). Several studies have documented the presence of dyskinesia in individuals with schizophrenia who are antipsychotic-naïve (Caligiuri and Lohr, 1994; Pappa and Dazzan, 2009), and dyskinesia has been shown to be predictive of conversion to psychosis in individuals at ultrahigh risk of psychosis (Callaway et al., 2014; Mittal and Walker, 2007). However, it is unclear whether dyskinesia is specific to individuals expressing at least some degree of psychosis spectrum symptomatology or if it is also present in unaffected family members, in which case dyskinesia may represent unexpressed genetic liability (i.e., an endophenotype). A meta-analysis of six studies examining dyskinesia in first-degree relatives versus controls reported a small but significant effect (Koning et al., 2008), though many of the original studies

* Corresponding author at: Minneapolis VA Medical Center, 1 Veterans Drive (B68-2), Minneapolis, MN 55417, USA.
E-mail address: sponh001@umn.edu (S.R. Sponheim).

https://doi.org/10.1016/j.psychres.2018.12.007
Received 23 July 2018; Received in revised form 12 November 2018; Accepted 2 December 2018
Available online 06 December 2018
0165-1781/ Published by Elsevier B.V.

Table 1
Group demographics and cognitive and symptom indices. Unless otherwise noted, values are calculated for the entire sample for each group. Means of global SANS total and IQ estimate were derived from 47 individuals with schizophrenia or schizoaffective disorder. Mean chlorpromazine (CPZ) equivalent dosage (mg) was derived from the 40 individuals with schizophrenia or schizoaffective disorder with complete medication information. SPQ mean was derived from 39 relatives.

	Schizophrenia/Schizoaffective Disorder (n = 48)	Relative (n = 43)	Control (n = 45)
Mean age (SD)	41.02 (11.49)	45.86 (10.96)	44.93 (11.53)
Number male (%)	33 (68.80)	18 (41.86)	24 (53.33)
Mean IQ (SD)	96.00 (13.33)	110.51 (13.99)	108.67 (14.82)
Mean global SANS total (SD)	8.49 (4.38)		
Mean global SAPS total (SD)	6.63 (3.91)		
Mean SPQ total (SD)		9.69 (8.76)	10.16 (9.55)
Mean CPZ equivalent (SD)	510.00 (360.06)		

reported no group difference (e.g., Tarbox and Pogue-Geile, 2006). In the present study we used an instrumental assessment to yield sensitive characterization of dyskinesia in first-degree biological relatives of individuals with schizophrenia or schizoaffective disorder in an attempt to better determine whether this motor sign is present in individuals who carry genetic liability for psychotic disorders and are generally beyond the typical age of onset for schizophrenia.

Traditionally, studies of dyskinesia have employed examiner- or observer-based rating or coding methods of assessing this motor behavior. However, these methods are subjective, and the ordinal ratings often used in these rating systems fail to capture the temporal dynamics and variability of motor behavior that can only be characterized through instrumentation. The emergence of instrument-based assessments of motor dysfunction has yielded techniques that are efficient, more reliable, and capture the dynamics of motor behavior through a time series of data points (see van Harten et al., 2017 for review). Importantly, instrument-based measurement has been shown to have greater sensitivity than traditional methods for detecting dyskinesia (Dean et al., 2004; Cortese et al., 2005; Koning et al., 2011). Therefore, we employed an instrumental measurement of dyskinesia in the present study in order to sensitively probe for dyskinesia in unaffected relatives. The one published study that used instrumental assessment to examine dyskinesia in first-degree relatives of individuals with psychosis reported a significantly higher incidence of dyskinesia in relatives than controls (Koning et al., 2011). The current study is unique in that (1) we examined dyskinesia across the full spectrum of liability to psychosis (individuals with psychotic disorders, first-degree relatives, and controls) using sensitive instrumental measurement and (2) we used a different instrumental measurement of dyskinesia than Koning et al. (2011), which is commercially available and highly sensitive, thus setting the stage for easier replication and comparison of results of the current study with future related studies.

Broadly speaking, dyskinesia is believed to be instantiated by basal ganglia dysfunction (Alexander et al., 1990; Obeso et al., 2014), with striatal hyperdopaminergia as a possible contributing mechanism (Alexander et al., 1990). This is of particular interest in light of long-standing theories of schizophrenia involving dopamine dysregulation, including striatal hyperdopaminergia (see Howes and Kapur, 2009 for review).

In addition to investigating dyskinesia in first-degree relatives, this study also aimed to capitalize on the quantitative and continuous measurement of dyskinesia afforded by instrumental measurement to examine the relationship between dyskinesia and working memory. Shared neural circuitry and neurotransmitters between the cognitive and motor systems provides a broad rationale for examining the link between these variables. Specifically, in addition to their role in motor control, the basal ganglia are also connected to higher-order cortical areas and are believed to contribute to cognitive functioning (Obeso et al., 2014), likely mediated by striatal dopamine (Nieoullon, 2002). Indeed, significant relationships have been reported between different domains of motor behavior and cognitive function in the schizophrenia spectrum (D'Reaux et al., 2000; Mittal et al., 2010; Silver and Shlomo, 2001; Snitz et al., 1999). Working memory dysfunction has been reported in first-degree relatives and is a candidate endophenotype (Conklin et al., 2000; Gottesman and Gould, 2003; Park and Gooding, 2014), and recent models of working memory implicate both striatal and prefrontal dopamine (Cools and D'Esposito, 2011) consistent with a possible common neural substrate contributing to both working memory dysfunction and dyskinesia in schizophrenia. Thus, we sought to examine the relationship between dyskinesia and working memory in individuals with schizophrenia and schizoaffective disorder and first-degree relatives.

This experiment addressed the question of whether dyskinesia is an endophenotype or a biomarker that is specific to the disease state not expressed in first-degree relatives. The presence of dyskinesia in unaffected first-degree relatives would provide converging evidence of dyskinesia as a candidate endophenotype, which in turn could highlight genes of interest for further investigation (Gottesman and Gould, 2003). Indeed, given that dyskinesia stems from dysregulation within circumscribed basal ganglia circuits (Alexander et al., 1990; Obeso et al., 2014) it may be less polygenic in origin and therefore provide somewhat direct implications for select genetic loci (see Gottesman and Gould, 2003 for discussion). Alternatively, evidence of dyskinesia as a disease state-specific biomarker would inform our understanding of the pathophysiology for the development of psychosis as compared to genetic liability for the condition, and dovetail with the hypothesis that the origin of psychosis centers on motor-relevant circuitry (Howes and Kapur, 2009).

2. Methods

2.1. Participants

There were 136 total participants. Forty-eight were individuals meeting DSM-IV criteria for schizophrenia or schizoaffective disorder, 43 were first-degree biological relatives (8 parents, 33 siblings, and 2 offspring), and 45 were control participants (see Table 1 for demographic characteristics of the sample). Diagnoses were determined through review of clinical research assessments that incorporated structured interviews (described below) and were carried out by advanced clinical psychology graduate students or postdoctoral researchers in consultation with doctoral level clinical psychologists, and required consensus agreement on all diagnoses by two reviewers. Control participants denied family history of psychotic disorders and had no current or past Axis I mood or psychotic disorders, and all participants were free of current alcohol or drug dependence. Relatives were excluded for any suspected Axis I psychotic disorder. Individuals with schizophrenia or schizoaffective disorder who were taking anti-Parkinsonian medications were excluded. Forty-two individuals with schizophrenia or schizoaffective disorder were taking atypical antipsychotics, three were taking conventional antipsychotics, two were taking both, and one participant was unmedicated. Chlorpromazine equivalent dosages were computed for participants with complete medication information (Andreasen et al., 2010), and duration of illness was computed using participants' ages and ages of onset.

2.2. Procedures

2.2.1. Clinical and cognitive assessment

All procedures were approved by the Minneapolis VA Health Care System and University of Minnesota IRBs which monitored the ethical conduct of the study, and were in accordance with the Declaration of Helsinki. Participant recruitment strategies are described in detail elsewhere (Docherty and Sponheim, 2008); data were collected as part of a larger study of individuals with psychotic disorders and their first-degree biological relatives. Twenty-six of the first-degree relatives were related to 14 patients in the sample. After obtaining full written consent, all participants were administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1994), as well as the Schizotypal Personality Questionnaire (SPQ; Raine, 1991), and the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS-III) to yield an estimate of IQ (Wechsler, 1997). A subset of participants ($n = 32$ individuals with schizophrenia or schizoaffective disorder, $n = 33$ controls, and all relatives) were administered the Digit Span subtest of the WAIS-III to assess working memory. Individuals with schizophrenia or schizoaffective disorder were additionally assessed with the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1981) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1983).

2.2.2. Handwriting assessment

Handwriting movements were recorded on a Wacom Intuos 3 9″ × 12″ (active area of 22.9 cm × 30.5 cm) digitizing tablet (Wacom, Saitama, Japan) connected to a desktop computer. Pen movements were sampled using MovAlyzeR software (Neuroscript, LLC http://www.neuroscriptsoftware.com/ Tempe, AZ, USA) with settings of 100 samples/second resulting in spatial sensitivity of 0.01 cm. Using a non-inking pen, participants completed a cursive handwriting task in three different size conditions (1 cm, 2 cm, and 4 cm). Specifically, participants wrote "lleellee" in cursive (see Fig. 1), and each participant completed five trials in each size condition. For some participants, trials were discarded due to having too few strokes or inadvertent interruptions affecting the trials; however, every participant produced a minimum of three acceptable trials. The first eight strokes of each trial (i.e., "llee") were subjected to subsequent analyses. Blocks of five trials per condition were performed in random order. Participants began the trial when audibly prompted by the experimenter. For each trial, recordings began at the moment the pen came in contact with the tablet and ended after 15 s. Trials having false starts and stops were re-administered. The total duration of the handwriting assessment was less than 10 min.

Fig. 1. Examples of "lleellee" written by two individuals with schizophrenia, one with low average normalized jerk (ANJ; top sample) and another with higher ANJ (bottom sample).

2.2.3. Data analysis

Data processing and analysis were performed with MovAlyzeR software using previously reported procedures (Caligiuri et al., 2015). In general, pen movement data in both X and Y coordinates were low pass filtered at 8 Hz using a sinusoidal transition band of from 3.5 to 12.5 Hz following procedures by Teulings and Maarse (1984). Subsequently, the first, second, and third time derivatives (i.e., velocity, acceleration, and jerk, respectively) were calculated. Movements were then segmented into successive up and down strokes. As in Dean et al. (2013), fluidity of movement was quantified via average normalized jerk (ANJ), an established index of movement smoothness (Hogan and Flash, 1987). ANJ was calculated from the following formula: $\sqrt{(0.5 \times \Sigma(\text{jerk}(t)^2) \times \text{duration}^5 / \text{length}^2)}$ after Teulings et al. (1997). This method normalizes jerk amplitudes for changes in stroke size and duration (Kitazawa et al., 1993) and results in a unit-free value. ANJ is then averaged across strokes and trials. Increased acceleration peaks during movement (i.e., changes in acceleration; jerk) result from irregular activation and timing of the agonist and antagonist muscles involved in a movement (Teulings et al., 1997), and therefore higher ANJ values reflect dysfluent movement, or dyskinesia (Caligiuri et al., 2015; 2010; Dean et al., 2013; Teulings et al., 1997).

3. Results

3.1. Sample characteristics

One-way ANOVAs revealed no significant group effects for age or number of trials in each size condition (all p values > 0.05). A Pearson chi-square test revealed that gender differed significantly between groups ($\chi^2(2) = 6.72$, $p = 0.04$). As a result, gender was included as a between subjects factor in the statistical analysis of ANJ. See Table 1 for demographic variables and cognitive and symptom indices for the sample.

3.2. Dyskinetic movement (ANJ) in schizophrenia and schizoaffective disorder

Visual inspection of the data for all 3 size conditions revealed a logarithmic distribution, both for the entire sample ($n = 136$) and for each group separately. A log base 10 transformation of the data was therefore conducted, and statistical analyses were performed using these transformed ANJ values (subsequently referred to as "ANJ" and "ANJ values"). ANJ values were analyzed using a repeated measures ANOVA with size condition as the within subjects factor (3 levels: 1 cm, 2 cm, and 4 cm) and group (3 levels: individuals with schizophrenia or schizoaffective disorder, relatives, and controls) and gender (2 levels: male and female) as the between subjects factors. There were significant main effects of group ($F(2,130) = 5.50$, $p = 0.005$, partial eta squared = 0.08) and gender ($F(1,130) = 5.96$, $p = 0.02$, partial eta squared = 0.04) (ANJ was larger in males compared to females). The group × gender interaction was not significant ($F(2,130) = 0.81$, $p = 0.45$). There were no significant within subjects effects or interactions (main effect of size: $F(2,260) = 1.97$, $p = 0.14$; size × group interaction: $F(4,260) = 0.68$, $p = 0.61$; size × gender interaction: $F(2,260) = 0.39$, $p = 0.68$; size × group × gender interaction: $F(4,260) = 0.13$, $p = 0.97$). Three post-hoc pairwise comparisons of the estimated marginal means for ANJ values for each group controlling for gender and collapsed across size condition revealed significantly greater ANJ for individuals with schizophrenia or schizoaffective disorder (mean = 1.38, $SE = 0.04$) compared to both controls (mean = 1.23, $SE = 0.03$) (mean difference = 0.15, $SE = 0.05$, $p = 0.003$) and relatives (mean = 1.25, $SE = 0.04$) (mean difference = 0.13, $SE = 0.05$, $p = 0.01$) (see Fig. 2). Both of these statistical tests survive Bonferroni correction for multiple comparisons ($p < 0.017$). The difference between relatives and controls was not significant ($p > 0.05$). Supplementary Table 1 shows observed mean

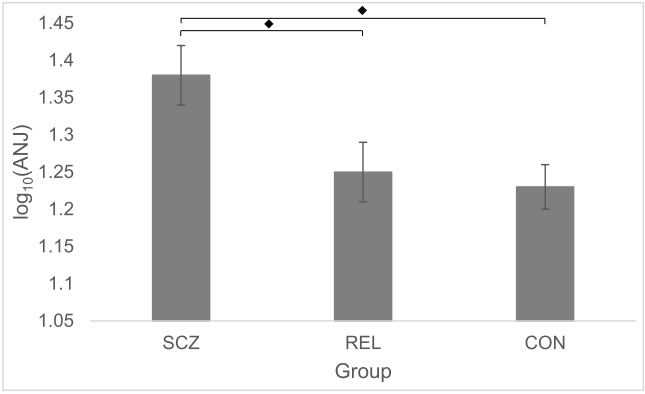

Fig. 2. Estimated marginal means of log transformed ANJ values for each group (error bars represent standard error) are depicted, with significant post-hoc differences between groups indicated. (SCZ: individuals with schizophrenia or schizoaffective disorder; REL: first-degree biological relatives; CON: non-psychiatric controls) (◆ indicates $p < 0.017$).

ANJ values for each group for each condition.

3.3. Exploratory analyses: cognitive and clinical correlates of dyskinetic movement

For individuals with schizophrenia or schizoaffective disorder, there was a significant negative correlation between Digit Span scaled score and ANJ in the 2 cm condition ($r(30) = -0.35$, $p < 0.05$) (see Fig. 3), indicating that patients with higher ANJ in the 2 cm condition tended to have worse working memory function as measured by the Digit Span subtest of the WAIS-III. There were no significant correlations between Digit Span and ANJ in any size condition in relatives (all p values > 0.05; see Supplementary Table 2 for r and p values for all working memory correlations).

Exploratory analyses were carried out to test for associations of ANJ in all 3 size conditions for individuals with schizophrenia or schizoaffective disorder with the reality distortion and positive formal thought disorder dimensions of the SAPS and the negative symptoms dimension of the SANS (based on the factor analysis conducted by

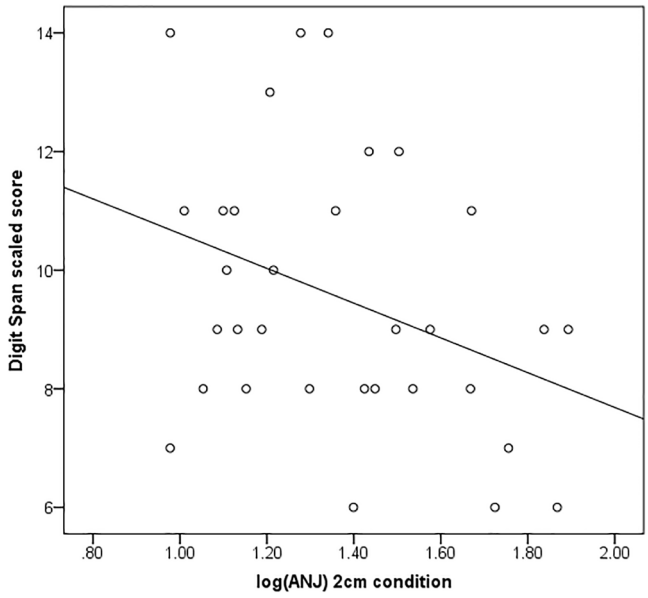

Fig. 3. Scatterplot of ANJ and working memory values in individuals with schizophrenia or schizoaffective disorder is depicted with fitted regression line ($r(30) = -0.35$, $p < 0.05$).

Table 2
The statistics investigating possible relationships between ANJ and antipsychotic medication dosage.

	Correlation with Chlorpromazine Equivalents		
	r	*df*	*p* value
$\log_{10}$(ANJ) 1 cm	−0.06	38	0.73
$\log_{10}$(ANJ) 2 cm	0.21	38	0.20
$\log_{10}$(ANJ) 4 cm	0.07	38	0.65

Andreasen et al., 1995). There was a correlation between ANJ in the 4 cm condition and the positive formal thought disorder dimension of the SAPS ($r(46) = 0.33$, $p = 0.02$), indicating that individuals with schizophrenia or schizoaffective disorder with more dysfluent handwriting in the 4 cm condition were more symptomatic in the domain of positive formal thought disorder. No other symptom correlations were statistically significant.

Additional exploratory analyses were conducted examining the relationship between SPQ factor scores (cognitive-perceptual, social-interpersonal, and disorganization; Calkins et al., 2004) and ANJ in all size conditions in relatives and controls. In relatives, ANJ in the 2 cm condition was significantly correlated with the social-interpersonal factor of the SPQ ($r(37) = -0.34$, $p = 0.04$). In controls, ANJ in the 2 cm condition was significantly correlated with the cognitive-perceptual factor of the SPQ ($r(43) = -0.30$, $p = 0.045$). For both correlations, increased schizotypal symptoms were associated with decreased ANJ.

3.4. Testing the relationship between ANJ and chlorpromazine equivalent dosages and duration of illness

There were no significant correlations between chlorpromazine equivalent dosages and ANJ in any size condition (all p values > 0.05) (see Table 2). Duration of illness, which we used as a proxy estimation of the length of antipsychotic treatment, was significantly correlated with ANJ in the 4 cm size condition ($r(46) = 0.35$, $p = 0.01$) (p values > 0.05 for the 1 cm and 2 cm size conditions).

4. Discussion

The main finding of this paper is the normal handwriting fluency in first-degree relatives of individuals with schizophrenia and schizoaffective disorder measured using instrumental methods. An absence of handwriting movement dysfluency in unaffected relatives suggests that dyskinesia is not an endophenotype. These results are consistent with previous research showing specificity of childhood motor abnormalities to individuals who later convert to psychosis compared to siblings (Walker et al., 1994). These results are also consistent with a prospective study that revealed that childhood clinical assessments of unusual movements, which map roughly onto dyskinesia, were predictive of diagnostic status as an adult affected by schizophrenia, while childhood clinical assessment of dysfunctional motor coordination, which maps more onto other domains of motor behavior such as neurological soft signs or cerebellar-mediated motor processes, predicted status as both an adult affected by schizophrenia and being a biological relative of an affected individual (Rosso et al., 2000).

The finding that first-degree biological relatives are statistically indistinguishable from controls on an instrumental measurement of dyskinesia supports the interpretation of dyskinesia as a biomarker of schizophrenia rather than an indicator of genetic liability. Interestingly, increased dyskinesia has also been reported in individuals at ultrahigh risk of developing psychosis using a very similar task and the same commercially available handwriting data collection and analysis program (Dean et al., 2013), indicating that dyskinesia quantified in this way is also evident in individuals with attenuated psychotic

symptomatology (i.e., the ultrahigh risk sample in Dean et al., 2013 displayed prodromal symptoms). This is relevant to the current findings since the relatives in the present study were essentially unaffected by even mild levels of symptomatology. Questionnaire-based assessment of schizotypal traits indicated that the first-degree relatives were no more likely to have schizophrenia spectrum symptoms than control participants (see Table 1). Given the hypothesis linking striatal hyperdopaminergia and the symptoms of psychosis (see Howes and Kapur, 2009) and the possible role of striatal hyperdopaminergia in dyskinesia (Alexander et al., 1990), it is possible that intermediate levels of dyskinesia might only be present in first-degree relatives with some expression of schizotypal traits. Thus, future studies might examine dyskinesia in first-degree relative samples displaying a broad range of schizotypal symptom severity to further explore the relationship of dyskinesia to genetic liability and intermediate symptom expression. The significant correlations between SPQ factors and ANJ in relatives and controls indicating greater ANJ was associated with fewer endorsements of schizotypal characteristics suggests that while elevated ANJ is evident in individuals at clinical high risk for psychosis, larger ANJ within unaffected populations (i.e., no elevation in schizotypal characteristics in the present sample of relatives) does not relate to subtle manifestations of symptoms. Another possibility is that the nature of the relationship between ANJ and schizotypal characteristics is not well represented when schizotypy is largely absent from samples of biological relatives and healthy comparison subjects.

The lack of increased ANJ in relatives is inconsistent with a previous report of dyskinesia in first-degree relatives as indexed by force variability (measured via instrumental assessment) (Koning et al., 2011). ANJ during handwriting and force variability during constant application of pressure are both measures of subtle dyskinesia wherein the fluidity of these motor behaviors is disrupted by discoordinated and irregular muscle activity. However, ANJ during handwriting is believed to result from failure to control the timing and contraction of multiple muscle groups within the hand and wrist during movement (Teulings et al., 1997), while maintenance of muscle force steadiness demands controlled contraction of a single agonist-antagonist pair in the absence of proprioceptive feedback (see Caligiuri and Lohr, 1994; Mittal et al., 2011 for discussion). One alternative interpretation of the current findings, then, is that the current study's lack of increased ANJ during handwriting in relatives and the higher incidence of increased force variability during constant pressure exertion in relatives versus controls reported by Koning et al. (2011) could point to the presence of dyskinesia in relatives when subjected to more demanding neuromuscular control tasks. Future work should therefore aim to use instrumental assessments to characterize the fluency of motor functioning along a spectrum of motor behavior complexity in first-degree relatives of individuals with schizophrenia.

A major limitation of the current study concerns the interpretability of the increased ANJ in individuals with schizophrenia or schizoaffective disorder; we are unable to address the question of the origin of the dyskinesia demonstrated by these individuals via increased ANJ in this study given the medication status of the current sample. Our attempts to examine the relationship between antipsychotic medication and ANJ, via correlations with chlorpromazine equivalent dosages and duration of illness, are relevant to report though inadequate for drawing complete conclusions regarding the impact of antipsychotic medication on ANJ. Given the established link between antipsychotic medication and motor side effects including dyskinesia the potential confound remains of concern.

Although exploratory and in need of replication, the associations of greater dyskinesia with worse symptomatology and working memory in patients are consistent with some published scientific literature. For example, the correlation indicating that dyskinesia in individuals with schizophrenia or schizoaffective disorder predicted worse working memory function is consistent with the dual cognitive-motor role of basal ganglia and more specifically the hypothesis that striatal dopamine is involved in working memory (see Cools and D'Esposito, 2011 for review). Interestingly, research has shown poor working memory function to predict formal thought disorder (Becker et al., 2012) which is broadly consistent with our finding of increased positive formal thought disorder in individuals with schizophrenia or schizoaffective disorder who tended to display greater dyskinesia. Thus, striatal hyperdopaminergia could be a common element to dyskinesia, working memory deficits, and formal thought disorder. Given the limitations of the current study with respect to antipsychotic medication, replication and additional examination of this possibility are necessary.

In addition to the limitations already described related to antipsychotic medication, there are other limitations to the current study. One concerns the composition of the relative sample, which comprises mostly siblings, but also some parents and a few offspring. Prevalence of dyskinesia has been observed to be positively associated with age in antipsychotic-naïve schizophrenia (Whitty et al., 2009), and there are data to suggest that incidence of spontaneous dyskinesia in the general population, though rare, increases with age (Merrill et al., 2013). Therefore, it is possible that additional variance in ANJ was introduced by including relatives spanning 3 generations. Indeed, it is possible that a homogenous sibling relative group would have demonstrated even lower ANJ. Relatedly, another limitation of the current study is the age of the participants more broadly. Given that prevalence and incidence of dyskinesia appear to increase with age, research examining dyskinesia across groups may benefit from using younger samples than those reported on in the current study.

There are several productive avenues for further investigation. First, future work investigating dyskinesia quantified via instrumental assessment across the spectrum of liability to psychosis and the relationship of dyskinesia to clinical and cognitive variables should include medication-naïve individuals with schizophrenia and schizoaffective disorder. Second, the present study investigated dyskinesia using instrumental assessment of handwriting kinematics. As discussed above, force steadiness is another instrumental method for assessing dyskinesia, and could be combined with handwriting kinematics in future investigations to characterize dyskinesia at multiple levels within the motor system in first-degree relatives. Finally, future studies should include first-degree biological relatives with a range of schizotypal symptom expression, which will provide a clearer picture of how dyskinesia relates to genetic liability for psychosis and the expression of intermediate symptomatology.

In conclusion, the main finding of the current study is that first-degree relatives of individuals with schizophrenia and schizoaffective disorder did not demonstrate dyskinesia via assessment of movement fluidity during an instrumental handwriting task, which is consistent with the conceptualization of dyskinesia as a biomarker of the clinical disorder and not an unexpressed genetic liability for the condition (i.e., not an endophenotype). Possible alternative explanations for an absence of dyskinesia in relatives include the lack of schizotypal symptomology in our relative sample, or the nature of the motor task we used to probe for dyskinesia. Dyskinesia appears to be partially associated with working memory impairment and greater psychotic symptomatology (i.e., positive formal thought disorder) in individuals with schizophrenia and schizoaffective disorder. Overall, results are consistent with dyskinesia representing a biomarker of the development and expression of schizophrenia rather than genetic liability for the disorder.

Funding

This work was supported by funding to SRS provided in part by a Merit Review Award #I01CX000227 from the U.S. Department of Veterans Affairs, Clinical Sciences Research and Development Research Program and award U01MH108150 from the National Institute of Mental Health. JSK was supported by a postdoctoral Ruth L. Kirschstein

National Research Service Award (Award number F32MH112334) from the National Institute of Mental Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Department of Veterans Affairs or the National Institutes of Health. These funding sources played no role in study design, data collection, analysis, and interpretation, writing this report, or the decision to submit this article for publication.

Contributors

SRS, MPC, and JSK conceived of the study. MKS and SRS oversaw data collection. JSK, MKS, MPC, SRS, and TLJ analyzed the data. JSK, SRS, VAM, and MPC interpreted the results. JSK drafted the manuscript. SRS, VAM, and MPC provided critical feedback and substantially edited the manuscript.

Conflict of interests

The authors have no conflicts of interests to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.007.

References

Alexander, G.E., Crutcher, M.D., DeLong, M.R., 1990. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, “prefrontal” and ‘limbic’ functions. Prog. Brain Res. 85, 119–146.

Andreasen, N.C., 1983. Scale for the Assessment of Positive Symptoms (SAPS). University of Iowa, Iowa City.

Andreasen, N.C., 1981. Scale for the Assessment of Negative Symptoms (SANS). University of Iowa, Iowa City.

Andreasen, N.C., Arndt, S., Alliger, R., Miller, D., Flaum, M., 1995. Symptoms of schizophrenia: methods, meanings, and mechanisms. Arch. Gen. Psychiatry 52, 341–351. https://doi.org/10.1001/archpsyc.1995.03950170015003.

Andreasen, N.C., Pressler, M., Nopoulos, P., Miller, D., Ho, B.C., 2010. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol. Psychiatry 67, 255–262.

Becker, T.M., Cicero, D.C., Cowan, N., Kerns, J.G., 2012. Cognitive control components and speech symptoms in people with schizophrenia. Psychiatry Res. 196, 20–26.

Caligiuri, M.P., Lohr, J.B., 1994. A disturbance in the control of muscle force in neuroleptic-naive schizophrenic patients. Biol. Psychiatry 35, 104–111.

Caligiuri, M.P., Teulings, H.L., Dean, C.E., Lohr, J.B., 2015. A quantitative measure of handwriting dysfluency for assessing tardive dyskinesia. J. Clin. Psychopharmacol. 35, 168–174.

Caligiuri, M.P., Teulings, H.L., Dean, C.E., Niculescu 3, A.B, Lohr, J.B., 2010. Handwriting movement kinematics for quantifying extrapyramidal side effects in patients treated with atypical antipsychotics. Psychiatry Res. 177, 77–83. https://doi.org/10.1016/j.psychres.2009.07.005.

Calkins, M.E., Curtis, C.E., Grove, W.M., Iacono, W.G., 2004. Multiple dimensions of schizotypy in first degree biological relatives of schizophrenia patients. Schizophr. Bull. 30, 317–325.

Callaway, D.A., Perkins, D.O., Woods, S.W., Liu, L., Addington, J., 2014. Movement abnormalities predict transitioning to psychosis in individuals at clinical high risk for psychosis. Schizophr. Res. 159, 263–266. https://doi.org/10.1016/j.schres.2014.09.031.

Conklin, H.M., Curtis, C.E., Katsanis, J., Iacono, W.G., 2000. Verbal working memory impairment in schizophrenia patients and their first-degree relatives: evidence from the digit span task. Am. J. Psychiatry 157, 275–277. https://doi.org/10.1176/appi.ajp.157.2.275.

Cools, R., D'Esposito, M., 2011. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol. Psychiatry 69, e113–e125. https://doi.org/10.1016/j.biopsych.2011.03.028.

Cortese, L., Caligiuri, M.P., Malla, A.K., Manchanda, R., Takhar, J., Haricharan, R., 2005. Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naive schizophrenia patients. Schizophr. Res. 75, 65–75. https://doi.org/10.1016/j.schres.2004.08.003.

D'Reaux, R.A., Neumann, C.S., Rhymer, K.N., 2000. Time of day of testing and neuropsychological performance of schizophrenic patients and healthy controls. Schizophr. Res. 45, 157–167. https://doi.org/10.1016/s0920-9964(99)00196-6.

Dean, C.E., Russell, J.M., Kuskowski, M.A., Caligiuri, M.P., Nugent, S.M., 2004. Clinical ratings scales and instruments: how do they compare in assessing abnormal involuntary movements? J. Clin. Psychopharmacol. 24, 298–304. https://doi.org/10.1097/01.jcp.0000125681.97466.e7.

Dean, D.J., Teulings, H.L., Caligiuri, M., Mittal, V.A., 2013. Handwriting analysis indicates spontaneous dyskinesias in neuroleptic naïve adolescents at high risk for psychosis. J. Vis. Exp. 81, e50852. https://doi.org/10.3791/50852.

Docherty, A.R., Sponheim, S.R., 2008. Anhedonia as a phenotype for the Val158Met COMT polymorphism in relatives of patients with schizophrenia. J. Abnorm. Psychol. 117, 788–798. https://doi.org/10.1037/a0013745.

First, M., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1994. Structured Clinical Interview for Axis I DSM-IV Disorders (SCID). Psychiatry Press, Washington, DC.

Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatry 160, 636–645. https://doi.org/10.1176/appi.ajp.160.4.636.

Hogan, N., Flash, T., 1987. Moving gracefully: quantitative theroies of motor coordination. Trends Neurosci. 10, 170–174.

Howes, O.D., Kapur, S., 2009. The dopamine hypothesis of schizophrenia: version III—the final common pathway. Schizophr. Bull. 35, 549–562. https://doi.org/10.1093/schbul/sbp006.

Kitazawa, S., Goto, T., Urushihara, Y., 1993. Quantitative evaluation of reaching movements in cats with and withoutvcerebellar lesions using normalized integral of jerk. In: Mano, N., Hamada, I., DeLong, M.R. (Eds.), Role of the Cerebellum and Basal Ganglia in Voluntary Movement. Elsevier, Amsterdam, pp. 11–19.

Koning, J.P., Kahn, R.S., Tenback, D.E., van Schelven, L.J., van Harten, P.N., 2011. Movement disorders in nonpsychotic siblings of patients with nonaffective psychosis. Psychiatry Res. 188, 133–137. https://doi.org/10.1016/j.psychres.2011.01.005.

Koning, J.P.F., Tenback, D.E., van Os, J., Aleman, A., Kahn, R.S., van Harten, P.N., 2008. Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis. Schizophr. Bull. 36, 723–731. https://doi.org/10.1093/schbul/sbn146.

Merrill, R.M., Lyon, J.L., Matiaco, P.M., 2013. Tardive and spontaneous dyskinesia incidence in the general population. BMC Psychiatry 13, 152.

Mittal, V.A., Dean, D.J., Pelletier, A., Caligiuri, M., 2011. Associations between spontaneous movement abnormalities and psychotic-like experiences in the general population. Schizophr. Res. 132, 194–196. https://doi.org/10.1016/j.schres.2011.06.028.

Mittal, V.A., Walker, E.F., 2007. Movement abnormalities predict conversion to Axis I psychosis among prodromal adolescents. J. Abnorm. Psychol. 116, 796–803. https://doi.org/10.1037/0021-843X.116.4.796.

Mittal, V.A., Walker, E.F., Bearden, C.E., Walder, D., Trottman, H., Daley, M., Simone, A., Cannon, T.D., 2010. Markers of basal ganglia dysfunction and conversion to psychosis: neurocognitive deficits and dyskinesias in the prodromal period. Biol. Psychiatry 68, 93–99. https://doi.org/10.1016/j.biopsych.2010.01.021.

Nieoullon, A., 2002. Dopamine and the regulation of cognition and attention. Prog. Neurobiol. 67, 53–83. https://doi.org/10.1016/s0301-0082(02)00011-4.

Obeso, J.A., Rodriguez-Oroz, M.C., Stamelou, M., Bhatia, K.P., Burn, D.J., 2014. The expanding universe of disorders of the basal ganglia. Lancet 384, 523–531. https://doi.org/10.1016/S0140-6736(13)62418-6.

Pappa, S., Dazzan, P., 2009. Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review. Psychol. Med. 39, 1065–1076. https://doi.org/10.1017/S0033291708004716.

Park, S., Gooding, D.C., 2014. Working memory impairment as an endophenotypic marker of a schizophrenia diathesis. Schizophr. Res. Cognit. 1, 127–136.

Raine, A., 1991. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr. Bull. 17, 555–564.

Rosso, I.M., Bearden, C.E., Megginson Hollister, J., Gasperoni, T.L., Sanchez, L.E., Hadley, T., Cannon, T.D., 2000. Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. Schizophr. Bull. 26, 367–378.

Silver, H., Shlomo, N., 2001. Perception of facial emotions in chronic schizophrenia does not correlate with negative symptoms but correlates with cognitive and motor dysfunction. Schizophr. Res. 52, 265–273. https://doi.org/10.1016/s0920-9964(00)00093-1.

Snitz, B.E., Curtis, C.E., Zald, D.H., Katsanis, J., Iacono, W.G., 1999. Neuropsychological and oculomotor correlates of spatial working memory performance in schizophrenia patients and controls. Schizophr. Res. 38, 37. https://doi.org/10.1016/s0920-9964(98)00178-9.

Tarbox, S.I., Pogue-Geile, M.F., 2006. Spontaneous dyskinesia and familial liability to schizophrenia. Schizophr. Res. 81, 125–137. https://doi.org/10.1016/j.schres.2005.09.013.

Teulings, H.L., Contreras-Vidal, J.L., Stelmach, G.E., Adler, C.H., 1997. Parkinsonism reduces coordination of fingers, wrist, and arm in fine motor control. Exp. Neurol. 146, 159–170. https://doi.org/10.1016/0167-9457(91)90010-U.

Teulings, H.L., Maarse, F.J., 1984. Digital recording and processing of handwriting movements. Hum. Mov. Sci. 3, 193–217.

Walker, E.F., Savoie, T., Davis, D., 1994. Neuromotor precursors of schizophrenia. Schizophr. Bull. 20, 441–451.

Wechsler, D., 1997. Wechsler Adult Intelligence Scale, 3rd ed. Psychological, New York.

Whitty, P.F., Owoeye, O., Waddington, J.L., 2009. Neurological signs and involuntary movements in schizophrenia: Intrinsic to and informative on systems pathobiology. Schizophr. Bull. 35, 415–424.

van Harten, P.N., Walther, S., Kent, J.S., Sponheim, S.R., Mittal, V.A., 2017. The clinical and prognostic value of motor abnormalities in psychosis, and the importance of instrumental assessment. Neurosci. Biobehav. Rev. 80, 476–487.