Published in final edited form as:

J Nerv Ment Dis. 2018 May ; 206(5): 356–361. doi:10.1097/NMD.0000000000000806.

Motor dysfunction as a risk factor for conversion to psychosis independent of medication use in a psychosis-risk cohort

Michael D. Masucci, MA^{1,*}, Amanda Lister, MA¹, Cheryl M. Corcoran, MD¹, Gary Brucato, PhD¹, and Ragy R. Girgis, MD¹

¹The Center of Prevention and Evaluation, New York State Psychiatric Institute, Columbia University Medical Center, 1051 Riverside Dr., New York, NY, 10032, USA

Abstract

The Structured Interview for Psychosis-Risk Syndromes (SIPS) contains criteria for the Attenuated Positive Symptom Syndrome (APSS), a period of subthreshold positive symptoms which predates full-blown psychosis. Motor abnormalities are often associated with these symptoms, but have not been adequately studied. We assessed a diverse sample of 192 APSS participants (27.1% female; 47.9% white; mean age=20.03 years) for motor dysfunction (SIPS G.3. score) at baseline, and conversion to psychosis every 3 months for up to 2 years. Fifty-nine (30.7%) participants converted to psychosis. Baseline G.3. score was significantly higher among converters than non-converters (mean difference=0.66; $t[95.929]=2.579$, $p<.05$). No significant differences in baseline G.3. were found between demographic groups or those with differential medication use. These results point to the utility of G.3. as a potential predictor of psychosis among APSS individuals, and potentially implicate the shared biological underpinnings of motor dysfunction in the APSS and full-blown psychotic illnesses.

Keywords

Attenuated psychosis; clinical high-risk for psychosis; prodromal psychosis; motor processes; dopamine

1. Introduction

The Structured Interview for Psychosis-Risk Syndromes (SIPS) defines an Attenuated Positive Symptom Syndrome (APSS; (McGlashan et al., 2001) a period of subthreshold positive symptoms thought to precede full-blown psychotic illness. APSS symptoms may include thought abnormalities (Addington et al., 2015), social withdrawal (Walker et al., 1998) and cognitive deficits (Silverstein et al., 2003). Of note, only approximately 35% of individuals who initially meet criteria for APSS convert to schizophrenia or a related psychotic disorder (Addington et al., 2012; Fusar-Poli et al., 2012). Thus, there is a need to identify more precise predictors of the transition to psychosis. Partly due to the overlap between the neural substrate believed to underlie both dyskinesia and psychotic symptoms

*Corresponding author: Michael Masucci, Mailing Address: 643 West 172nd St., 56, New York, NY 10032., Phone: (315) 281-7205, masucci.mike@gmail.com.

(Walker, 1994), it has been suggested that movement abnormalities in the APSS may prove predictive of psychosis. Indeed, abnormal movements are highly prevalent among individuals at clinical high-risk (CHR) for psychosis (Mittal & Walker, 2007), particularly spontaneous dyskinesias (Callaway et al., 2014; Dickson et al., 2012; Rosso et al., 2000; Schiffrman et al., 2004). However, to date, these have not been adequately explored.

Abnormal movement has been detected in the early stages of schizophrenia (Kindler et al., 2016; Mittal & Walker, 2007), in first-episode psychosis (Walther & Strik, 2012), and in chronic schizophrenia, regardless of medication history (Cunningham-Owens & Johnstone, 1980; Fenton et al., 1995; Walther & Strik, 2012). Walker *et al.* have observed abnormal movements as early as infancy in pre-psychotic individuals (Walker et al., 1994), and Mazzoni *et al.* found diagnoses related to motor dysfunction, such as elimination disorders, to be frequent in adolescents at clinical high-risk for psychosis (Mazzoni et al., 2009). Elevated movement abnormalities, specifically dyskinetic movements, in CHR individuals have been found to be related to psychosocial functioning (Mittal et al., 2011b). These findings support the possibility that abnormal movement may help predict poor psychosocial functioning, and may be a key indicator of potential for conversion to psychosis. However, these studies are also hampered by small sample sizes. Given this evidence, additional research is warranted to determine the role motor abnormality plays in psychosis-risk and diagnosis in a larger, more diverse population. Thus, the aims of the current study are to characterize motor dysfunction in individuals meeting criteria for the SIPS APSS, and determine how movement abnormalities relate to prospective APSS outcomes in a large single-site sample

2. Method

2.1 Participants

The Center of Prevention and Evaluation (COPE) at the New York State Psychiatric Institute (NYPPI)/Columbia University Medical Center (CUMC) (Brucato et al., 2017) recruited 200 help-seeking individuals, ages 13–30, between May, 2003 and July, 2016, all of whom met criteria for the SIPS APSS. Written informed consent was provided by those 18 or older. Minors gave written assent, with written informed consent provided by a parent or legal guardian. Separate consents and assents were signed by eligible individuals who wished to participate. The study was preapproved by the NYSPI's Institutional Review Board.

Exclusion criteria included age of <13 or >30 years; non-proficiency in English; current or past psychosis; I.Q. < 70; a DSM disorder better accounting for symptoms; medical conditions affecting the central nervous system; significant risk of harm to self or others; or current Substance Abuse or Dependence. Individuals taking antipsychotic medications required clear evidence of attenuated psychosis at medication onset.

2.2 Clinical assessments

The SIPS (McGlashan, et al., 2001; Miller et al., 2002; Rosen et al., 2002) semi-structured interview probes for past and current attenuated versus threshold psychotic symptoms. All participants met criteria for the aforementioned APSS, in which participants score greater

than three but less than six on at least one item of the positive symptom subscale. Participants were also given the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I; (First et al., 2002), or the K-SADS-PL for participants younger than 16 years of age (Kaufman et al., 1996), to rule out the possibility that symptoms are better accounted for by another disorder.

While motor dysfunction does not factor directly into diagnosis of the syndromes proposed in the SIPS, it is tapped by the third item on the “General” scale (item G.3.) Participants are asked if they have noticed any clumsiness, awkwardness, or lack of coordination in their movements. The clinician is asked to consider their self-reported motor dysfunction in conjunction with observed catatonia, motor rituals, and dyskinetic movements to rate the participant’s motor dysfunction on a scale from 0 (“Absent”) to 6 (“Extreme”), with a rating of 6 corresponding to evident loss of natural movement, motor blockages, echopraxia or dyskinesia, and a rating of 3 (moderate) corresponding to poor coordination and difficulty performing fine motor movements (McGlashan, et al., 2001; Miller, et al., 2002; Rosen, et al., 2002). The following anchor point descriptions are provided as guidelines to aid in raters’ scoring (McGlashan et al., 2001):

1. Absent
2. Questionably Present: Awkward
3. Mild: Reported or observed clumsiness
4. Moderate: Poor coordination. Difficulty performing fine motor movements
5. Moderately Severe: Stereotyped, often inappropriate movements
6. Severe: Nervous habits, tics, grimacing. Posturing. Compulsive motor rituals.
7. Extreme: Loss of natural movements. Motor blockages. Echopraxia. Dyskinesia.

All clinical raters were certified to conduct SIPS ratings through training with Yale’s PRIME clinic. This training has been shown to improve interrater reliability on the entire SIPS measure across CHR clinics, with post-training interrater reliability in “excellent” range ($r_{icc} > .75$) for 17 of 19 items, and $r_{icc} = .70$ and $.72$ for the remaining items, across 6 sites (Miller et al., 2003). To promote interrater reliability within this study, all ratings went through a consensus process in which a second certified clinical rater verified the initial ratings based on the notes of the primary rater. Discrepancies in scoring were discussed between these raters until a consensus rating was reached.

2.3 Statistical Analyses

2.3.1 Demographic Analyses—Descriptive and inferential statistics were calculated using SPSS version 22 (Corp., 2013). First we sought to determine the effect of demographic factors on baseline G.3. score, regardless of conversion status. Independent-samples t-tests were used to investigate group differences in G.3. for two-factor demographic variables, including sex (1=male, 2=female), and education stats (1=did not graduate high school, 2=graduated high school). One-way ANOVA was used to look at group differences in G.3. for multi-factor variables, including race/ethnicity (1=White/

Caucasian, 2=African-American, 3=Multiracial, 4=other), and a bivariate Pearson correlation was calculated to look at the relationship between participant age and G.3. score.

2.3.2 Clinical Analyses—Second, we looked at how baseline clinical factors were related to G.3. score. Bivariate Pearson correlations were calculated between G.3. and the other SIPS variables. Differences in G.3. between medication groups at baseline were analyzed using a one-way ANOVA (1=no medication, 2=antidepressants only, 3=antipsychotics only, 4=both antidepressants and antipsychotics), and difference in baseline G.3. between converters and non-converters was analyzed using an independent-samples t-test. An additional independent-samples t-test of the difference in G.3. score between converters and non-converters was run while excluding individuals on neuroleptics to determine if the effects of motor dysfunction on conversion risk are independent of the motor effects potentially produced by neuroleptics.

2.3.3 Differences between converters and non-converters—Third, we sought to unpack how G.3. score may be related to interactions between conversion status and clinical/demographic factors by performing the aforementioned analyses separately between the converting and non-converting participants.

2.3.4 Analysis of G.3. as a categorical variable—Finally, in the previous analyses, G.3. was treated as a continuous variable with values of increasing severity from 0–6. However, it is possible that the anchored scores provided as guidance by the SIPS could be discreet categories of pathology, rather than lying on a continuum of severity. These categories may have differential relations to, for example, conversion to psychosis, that is not captured by using the instrument continuously. To investigate this, we re-ran the original analyses with G.3. as a categorical variable, performing Pearson Chi² tests between G.3. score and clinical/demographic groups.

3. Results

3.1 Demographic differences

Of the 200 original participants, 8 (4%) were excluded from analyses due to lack of available G.3. score. Demographic information about the sample is displayed in Table 1. No significant differences in baseline G.3. severity were found between White and Non-White participants ($t[190]=-0.564$, $p=.573$), between males and female ($t[190]=0.247$, $p=.805$), or between those who did and did not complete high school ($t[189]=1.183$, $p=.238$). Additionally, no significant correlation was found between G.3. and age of admittance ($r=-0.059$, $p=.415$). Further demographic comparisons between converters and non-converters are found in a study by Brucato and colleagues, using the full sample of 200 participants (2017).

3.2 Clinical analyses

Baseline G.3. was found to be highly correlated with a large number of symptoms from each of the SIPS subscales (see Table 2). Between-group differences at baseline for converters and non-converters were assessed; Baseline G.3. was significantly higher among converters (mean=2.37, sd=1.73) than non-converters (mean=1.71, sd=1.46; $t[95.93]=2.579$, $p=.011$).

Additional analyses were run to determine if antidepressant or antipsychotic use, or the use of both in tandem, was related to baseline G.3. severity. No significant differences were found for those using antidepressants ($t[177]=1.127$, $p=.261$), antipsychotics ($t[177]=.383$, $p=.702$) or both ($t[177]=.921$, $p=.305$). Furthermore, no difference was found between those on any of the aforementioned medications and those not on medication ($t[177]=1.370$, $p=.172$). In addition, there is the potential that those on neuroleptics are more likely to be farther along in the development of the prodrome, or have their motor coordination affected by medication. For a final sensitivity check, individuals on neuroleptics were excluded from analysis for an independent-samples t-test looking at baseline G.3. between converters and non-converters. The difference remained significant ($t[83.908]=2.231$, $p=.028$, mean difference=.621).

3.3 Differences between converters and non-converters

To address the possibility that demographic characteristics differentially impacting G.3. between converters and non-converters, the aforementioned demographic and clinical analyses were run separately for converters and non-converters. The results of these analyses are presented in Table 3; no significant differences or relationships in G.3. score emerged between demographic subgroups (age gender, race, education status) or clinical subgroups (medication status) in either the converting or non-converting sample.

3.4 Analyses of G.3. as a categorical variable

As the diagnostic criteria for each point of G.3. are dissimilar and not necessarily continuous (i.e., they do not necessarily fall along a continuum), we also considered the possibility that additional findings would emerge by analyzing the scores categorically. A chi-square test found that individuals with G.3. scores of 4 (Moderately Severe – Stereotyped, often inappropriate movements; adjusted residual = 2.1) or 5 (Severe – Nervous habits, tics, grimacing, posturing, compulsive motor rituals; adjusted residual = 2) at baseline were significantly more likely to convert to psychosis ($\chi^2[5, N=192] = 16.629$, $p=.005$; see Table 4).

4. Discussion

The results of this study provide further support for motor dysfunction as an indicator of psychosis-risk. In line with Mittal et al. (Mittal, et al., 2011b), baseline motor dysfunction was significantly higher among those who would eventually convert to psychosis, independent of medication status. We also found that baseline G.3. was correlated with many of the other risk factors for psychosis measured by the SIPS (see Table 2), indicating that motor symptomatology may go hand-in-hand with the cognitive and perceptual changes associated with the progression toward psychosis. Specifically, motor dysfunction that can be observed and assessed in a diagnostic interview (as opposed to a neuropsychological interview) can be used to anticipate conversion potential and risk severity. Participants with visibly demonstrated gross motor dysfunction (reflecting scores of 4 and 5 on G.3.) were more likely to convert to psychosis. These scores encompass motor dysfunction that is commonly associated with schizophrenia spectrum disorders, including stereotyped

movements, posturing, and tics. Scores of 3 or below, which would generally reflect participant-reported clumsiness, were not related to psychosis conversion potential.

Interestingly, the distribution of motor dysfunction was not significantly different between genders, races, those with differing education levels, and independent of medication status. Other indicators of psychosis-risk have been shown to differ between genders (Brucato, et al., 2017), ages (Gerstenberg et al., 2016), and socioeconomic statuses (Hur et al., 2015). The stability of motor dysfunction between demographic and medication groups in this study supports G.3. as an indicator of psychosis-risk that is potentially more consistent and less biased by sociocultural and biochemical factors.

Motor dysfunction has been implicated as a risk factor for an adult schizophrenia diagnosis when present in early childhood (Cannon et al., 1999; Clarke et al., 2011). One mechanism that has been proposed to explain these motor effects in schizophrenia is basal ganglia dysfunction (Mittal, et al., 2011b). Abnormalities in the basal ganglia, such as a larger putamen (Chemerinski et al., 2013), have been demonstrated in individuals with schizophrenia (Mueller et al., 2015; Williams, 2015) and psychosis (Farid & Mahadun, 2009). Another area of the basal ganglia, the caudate nucleus, has been found to be misshapen (Levitt et al., 2009) or undersized (Koo et al., 2006) in participants with schizotypal personality disorder, which is theorized to be underlain by similar genetic and biological mechanisms to schizophrenia (Siever & Davis, 2004). In populations at risk for psychosis, but who have not yet developed fully psychotic symptoms, dysregulated dopamine synthesis may be a cause for the motor function abnormalities preceding psychosis (Blanchard et al., 2010) and psychotic-like experiences (MacManus et al., 2012; Mittal et al., 2011a). Some research suggests that both dyskinesias and psychotic symptoms arise from similar dopaminergic pathways (DeLong & Wichmann, 2007; Mittal et al., 2008; Walker et al., 1996). Imaging studies have demonstrated dysregulated dopamine synthesis in the striatum of individuals with schizotypal personality disorder (Abi-Dargham et al., 2004), populations who are at risk for psychosis (Allen et al., 2012), and prospectively in those who would eventually develop psychosis (Howes et al., 2011).

More recently, decreased connectivity between the cerebellum and cortex has been linked to motor dysfunction (increased postural sway) and negative symptom severity in CHR patients, potentially related to the eventual cerebellar changes and increased postural sway of individuals with schizophrenia (Bernard et al., 2014). Another study has found differences in body movement (Dean et al., In press) between CHR participants and healthy controls, but no relationship to symptom severity in any domain. In the current study, motor dysfunction was correlated with nearly all symptoms on the SIPS, except for suspiciousness, grandiosity, occupational dysfunction, dysphoric mood and impaired stress tolerance. However, the SIPS G.3. measure of motor dysfunction is broader than specific aspects of motor movement like postural sway, encompassing general clumsiness to tics and temporary catatonia. Additional studies may benefit from looking at the specific movement abnormalities indicated by the SIPS and how they correlate with specific symptom domains. The results of this study are in line with previous research identifying motor dysfunction as common among CHR individuals, and point to the need for further exploration of the causal mechanisms leading

from hyperdopaminergic activity in APSS to the brain abnormalities associated with psychosis.

5. Conclusion

This large-sample, single-site study highlights the importance of recognizing motor dysfunction as an indicator of psychosis risk. However, it is important to note that a limitation of the SIPS as a clinical interview used for assessing motor dysfunction is that the anchored ratings on the SIPS do not necessarily distinguish between voluntary motor rituals and involuntary motor movements like tics and dyskinesias. From the data for this study, it is not possible to determine which specific types of severe motor dysfunction are related to conversion to psychosis. While this study is limited insofar as it did not code motor movements based on video or neuropsychological assessment, the scores yielded by a combination of participant report and clinical observation yielded results similar to those of previous studies with regard to the ability of overall, observable motor dysfunction to distinguish those who will eventually convert to psychosis. Although the study did not compare motor dysfunction of APSS participants to healthy controls, it has revealed a large amount of variety within an extremely diverse psychosis-risk population and demonstrated that those with higher motor dysfunction at baseline are at higher risk for conversion to psychosis. While the date of emergence and trajectory of motor abnormalities is unknown in the current study, it is possible that participants have demonstrated motor dysfunction in childhood, demonstrating higher psychosis risk prior to meeting the criteria for APSS as in previous literature (Cannon, et al., 1999; Clarke, et al., 2011). Future studies should further clarify the relationship of early motor dysfunction to specific psychosis-related diagnoses and conversion potential by investigating how trait-based disorders related to schizophrenia, such as Schizotypal Personality Disorder, may yield trait differences in motor dysfunction, and how these differences relate to affective expression and other symptom domains. Additionally, the high correlations between G.3. score and other symptoms of the SIPS (see Table 2) signify that motor dysfunction is related to the cognitive-perceptual changes characteristic of the progression toward psychosis – particularly, the negative symptom of Ideational Richness (N.5.; $r=.343$) and the disorganization symptom of Odd Behavior or Appearance (D.1.; $r=.326$). Further research is needed to clarify the relationship of G.3. to these other symptoms. Finally, additional research is needed to determine if the motor dysfunction evident in APSS has the same biological and neurochemical underpinnings as that of schizophrenia spectrum disorders, and if the trajectory of motor dysfunction across these conditions is related to increasing symptom severity over time.

Acknowledgments

Conflicts of Interest and Sources of Funding: This study was funded by NIMH grants K23MH106746 and R01MH093398 (R.R.G.), R01NIMH107558 (C.M.C.) and the New York State Office of Mental Hygiene. R.R.G. discloses research funding from Allergan, Otsuka, Genentech, and BioAdvantex. For the remaining authors, none where declared.

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Table 1

Demographic and sample information in relation to G.3. score (n = 192)

<i>Age at Admission, Years</i>					<i>Comparison Statistics</i>	
	Male	Female	Total		<i>r</i>	<i>p</i>
Mean (SD)	20.03 (3.84)				-0.059	0.415
<i>Sex</i>					<i>df</i>	<i>T</i>
n (%)	140 (72.9%)	52 (27.1%)	192 (100%)		190	0.247
G.3. Mean (SD)	1.93 (1.62)	1.87 (1.46)	1.91 (1.57)			
<i>Race</i>	White	African-American	Other	Multiracial	<i>df</i>	<i>F</i>
n (%)	92 (47.9%)	42 (21.9%)	15 (7.8%)	43 (22.4%)	3	1.166
G.3. Mean (SD)	1.98 (1.54)	1.86 (1.57)	2.47 (1.77)	1.69 (1.56)		
<i>Education Status</i>	Did not graduate HS	High school graduate			<i>df</i>	<i>T</i>
n (%)	86 (44.8%)	105 (54.7%)			189	1.183
G.3. Mean (SD)	2.07 (1.63)	1.80 (1.52)				
<i>Conversion to Psychosis</i>	Converted	Did not convert			<i>df</i>	<i>T</i>
n (%)	59 (30.7%)	133 (69.3%)			95,929	2.579 *
G.3. Mean (SD)	2.37 (1.73)	1.71 (1.46)				
<i>Medication Status</i>	None	Antidepressants	Neuroleptics	Both	<i>df</i>	<i>F</i>
n (%)	136 (70.8%)	25 (13.0%)	11 (5.7%)	20 (10.4%)	3	1.988
G.3. Mean (SD)	1.82 (1.53)	2.56 (1.69)	2.18 (1.94)	1.60 (1.35)		

* p < .05

Table 2

Bivariate Pearson correlations between G.3. score and other SIPS scores (n = 192)

SIPS Symptom	Correlation with G.3. (r)
<i>Positive Symptoms</i>	
P.1. Unusual Thought Content/Delusional Ideation	.279 **
P.2. Suspiciousness/Persecutory Ideas	0.069
P.3. Grandiose Ideas	0.085
P.4. Perceptual Abnormalities	.196 **
P.5. Disorganized Communication	.328 **
<i>Negative Symptoms</i>	
N.1. Social Anhedonia	.196 **
N.2. Avolition	.189 **
N.3. Expression of Emotion	.254 **
N.4. Experience of Emotions and Self	.207 **
N.5. Ideational Richness	.343 **
N.6. Occupational Functioning	−0.04
<i>Disorganization Symptoms</i>	
D.1. Odd Behavior or Appearance	.326 **
D.2. Bizarre Thinking	.263 **
D.3. Trouble with Focus and Attention	.271 **
D.4. Impairment in Personal Hygiene	.163 *
<i>General Symptoms</i>	
G.1. Sleep Disturbance	.227 **
G.2. Dysphoric Mood	−0.104
G.4. Impaired Tolerance to Normal Stress	0.077

**
p < .01*
p < .05

Comparison of analyses of demographic effects on G.3. between converters and non-converters (n = 192)

Table 3

	Non-Converters (n = 133)			Converters (n = 59)		
	<i>r</i>	<i>p</i>		<i>r</i>	<i>p</i>	
Age	0.004	0.959		-0.188	0.154	
	<i>df</i>	<i>T</i>	<i>p</i>	<i>df</i>	<i>t</i>	<i>p</i>
Sex	131	0.552	0.582	57	0.544	0.589
Education Status	130	0.392	0.696	57	1.297	0.582
	<i>df</i>	<i>F</i>	<i>p</i>	<i>df</i>	<i>F</i>	<i>p</i>
Race	3	0.485	0.694	3	1.085	0.363
Medication Status	3	0.757	0.52	3	1.894	0.141

Table 4

Baseline SIPS G.3. Score and Conversion Status Crosstabulation (n = 192)

	SIPS G.3. Score					Total
	0	1	2	3	4	
	Absent	Questionably Present	Mild	Moderate	Moderately Severe	Severe
<i>Did not convert to psychosis</i>						
Count	34	32	29	23	7	8
Expected Count	30.5	32.6	22.2	25.6	10.4	11.8
Adjusted Residual	1.3	-0.2	2.9	-1	-2	-2.1
<i>Converted to psychosis</i>						
Count	10	15	3	14	8	9
Expected Count	13.5	14.4	9.8	11.4	4.6	5.2
Adjusted Residual	-1.3	0.2	-2.9	1	2	2.1
Total Count	44	47	32	37	15	17
χ^2	<i>df</i>					192
Pearson Chi-Square	16.63*					0.005

p < .01