

Motor impairment and developmental psychotic risk: connecting the dots and narrowing the pathophysiological gap

Running title: Motor impairment and developmental psychotic risk

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Abstract

The motor system in its manifold articulations is receiving increasing clinical and research attention. This is because motor impairments constitute a central, expressive component of the mental state examination and a key transdiagnostic feature indexing disease severity. Furthermore, within the schizophrenia spectrum, the integration of neurophysiological, developmental and phenomenological perspectives suggests that motor impairment is not simply a generic, extrinsic proxy of an altered neurodevelopment, but might be more intimately related to psychotic risk. Therefore, an increased understanding, conceptualization and knowledge of the motor system and its anomalies could empower contemporary risk prediction and diagnostic procedures.

The motor system in its manifold articulations is receiving increasing clinical and research attention, partly as a consequence of the empirical impulse induced by the RDoC initiative, with the related emphasis on multiple levels of explanation and dimensional approaches.¹ Indeed, as well-known to many clinicians in their daily practice, most of the neuropsychiatric disorders such as schizophrenia, obsessive compulsive disorders, autism, mood disorders and neurodegenerative conditions are characterized by various degrees of motor impairment. Those motor impairments constitute a central, expressive component of the mental state examination and a key transdiagnostic feature indexing disease severity.²

Motor impairment plays a special role in schizophrenia spectrum disorders, since early motor manifestations emerge already in premorbid and prodromal stages of the neurodevelopmental trajectory leading to overt, syndromic psychotic states. This is the case of later achievement of motor milestones in infancy, poor motor coordination, dyskinesia and neurological soft signs.²

Furthermore, besides motor delays and dys-coordination, several sub-types of motor abnormalities, including athetosis, chorea, dystonia, bradykinesia, tics, and stereotypies, are elevated in psychotic disorders, even among drug-naïve individuals. However, whereas, other motor symptoms clusters, such as catatonic symptoms, dystonia and stereotypies might become more pronounced in later clinical stages, dys-coordination and motor lags emerge relatively early in development.³ This is probably related to the different underlying neuropathological mechanisms subtending movement abnormalities in psychosis.

Accordingly given the continuous, gradient-like distribution of motor impairment along the neurodevelopmental progression to psychosis, motor impairment clearly warrants more prominence in contemporary psychosis prediction frameworks (e.g. within the ultra-high-risk paradigm) which mostly incorporate non-motoric features.

Needless to say, increased understanding, conceptualization and knowledge of motor impairment could empower contemporary diagnostic procedures of psychosis. Indeed, motor impairment profiling could complement other clinical assessment procedures (e.g. interviews addressing the patient's psychological processes)⁴ with psychomotor proxies amenable to innovative, digitally-enabled tracking (e.g. digital phenotyping of motoric patterns through accelerometer-based smart-wearables).^{5,6} Furthermore, motoric performances are likely to point to more specific and circumscribable functional circuits at a neurobiological level, whose neurodevelopmental pathways might be more easily mapped than those associated to neuro-psychological performances (e.g. social cognition and theory of mind).

However, although current empirical research provides extensive descriptions of specific motor circuits involved in distinct aspects of motor impairment within the schizophrenia spectrum (e.g. basal ganglia in excitation/inhibition abnormalities, cerebellar-subcortical circuits in sensory-motor dynamics and cortico-motor circuits in psychomotor organization and speed),⁷ the nature of the relationship between motor impairment and psychotic risk (or broadly speaking psychosis-proneness) is still unclear and perhaps under-conceptualized. Crucially, is motor impairment just an indirect phenotypic proxy of broad neurodevelopmental alterations putatively associated with prospective risk⁸ of developing psychosis (i.e. an epiphenomenic flag) – or, rather, is motor impairment a pathogenetically-central kernel (e.g. a direct manifestation of a latent pathophysiological mechanism causally involved in the neurodevelopment of psychosis)?^{9,10}

Recent neuroscientific research in the field seems to confer further plausibility to the pathogenetic relevance. For example, Feinberg¹¹ suggested that impairments in corollary discharges (CD) may underpin psychotic experiences, and more recently, we suggested that they may represent a specific pathophysiological link between motor impairment and longitudinal psychotic risk.¹²

Across the animal kingdom, this basic neural mechanism allows all species to distinguish between sensations coming from external sources (e.g., pressure on a nematode's head from an approaching predator) and self-generated sensations (e.g., pressure on its head from swimming forward).¹³ It both tags sensations as coming from "self" and minimizes the resources needed to process the sensations in multiple sensory domains (e.g. visual, auditory).^{13,14} Vocalization studies in primates show that responses in auditory cortex are relatively inhibited during self-initiated vocalizing and excited during passive listening,¹⁵⁻¹⁷ likely reflecting the successful action of the corollary discharge mechanism. Also, the CD contributes to perceptual stabilization, and at the motor level, it enables fluid motor sequencing and motor learning, contributing to the subliminal scaffolding of the experiential field.¹⁸ [see figure 1]

From a developmental perspective, a pivotal pathophysiological role of CD in linking motor impairment to psychotic risk, is not implausible. Indeed, first, neonates are already by two months of age able to discriminate precisely between self- and exogenous-stimulations:¹⁹ as the integrity of CD mechanisms is crucial for such discrimination, CD mechanisms are likely to have an early onset in human development.

Second, motor coordination impairment in childhood (i.e. dyspraxia) is presumed to be subtended by co-potentiating impairments in two key basic processes involving movement circuits: CD mechanisms and the sensory feedback to estimate actual body states.²⁰ The sensory-motor remapping in dyspraxic children is marked by a larger discrepancy between sensory and motor signals in order to maintain continuous learning and adaptation; i.e. these children have difficulties in processing error signals used for adjusting action that arise from comparing sensory feedback to CD. The deficiencies in error signal processing may be due to noisier/inefficient sensory feedback and impaired CD mechanisms, both of which have been directly documented in this condition.²¹⁻²³ Another cognitive model of Developmental Coordination Disorder, the internal

deficit model,²⁴ suggests that these children have difficulties in generating or using predictive estimates of body position as a means of correcting actions in real time: this would affect also their ability to learn new internal models or modify existing ones. Thus, even within the internal deficit model, impaired CD mechanisms may be causally involved.

Third, childhood motor impairment is longitudinally associated with an increased risk of psychosis²⁵⁻²⁸ and schizotypy,²⁹ and the anamnesis of psychotic subjects is characterized by later achievement of motor milestones and subsequent motor impairment.^{2,3} Moreover, genetic risk for schizophrenia spectrum disorder is associated in childhood with phenotypic impairments at the motor level, as highlighted by familial high-risk studies on offspring of subjects with diagnosis of schizophrenia.³⁰ Importantly, clinical-high risk youth have a documented abnormality in suppressing cortical responsiveness to sensations resulting from their own motor actions, specifically during talking.^{31,32} This has also been seen in people with schizotypy,³³ further underscoring the sensitivity of CD abnormalities to psychosis across the wellness spectrum.

Finally, CD are altered in psychosis in multiple sensory systems^{34,35} and CD impairments may be involved in the pathogenesis of specific psychotic states.^{11,12,36} This is due to the pivotal role of CD for the primitive, immediate experience of self-agency (i.e. the direct, implicit sense of being the author/volitional agent of an ongoing action). That is, when a predicted sensation matches an actual sensation it contributes to the concrete subjective experience of volitionally controlling our own acts. However, psychotic states may be associated with the external misattribution of self-generated actions.¹¹ In the emergence of prototypical schizophrenia-spectrum psychotic phenomena, misattributions of self-generated actions may take place in terms of delusional-hallucinatory agency disturbances. This might be the case of (1) passivity delusions (e.g. experiencing one's own thoughts, feelings or actions as under external control), and (2)

auditory verbal hallucinations, such as hearing one's thoughts spoken aloud or externalized commenting "voices".

In sum, CD is likely a key domain – or at least an informative neurophysiological window – to better understand the link between some features of childhood motor impairment and developmental liability to psychosis. Such connection might be mechanistically due to an early onset of CD abnormality in neonates and to its snow-ball-like progressive interference early in development (e.g. childhood motor impairment and subtle trait-like anomalies of the sense of self-agency), slowly progressing toward more characteristic vulnerability features (e.g. schizotaxic-schizotypal traits), ultimately increasing the chance of incurring in a psychotic state.

Indeed, moving bottom-up from a neurophysiological to a cognitive/subjective level, the contribution of CD mechanisms to self-agency and to the perceived continuity of the experiential stream, could explain why their alterations may play a role in the development and gradual consolidation of a multidimensional vulnerability to psychosis. CD mediate sophisticated sensorimotor and neurocognitive operations (e.g. perceptual stabilization, motor sequencing and sensorimotor learning) and contribute to the subliminal scaffolding of the experiential field;^{18,37} at a neural level they enable the implicit sense of mineness of psychomotor experience and lend coherence and fluidity to our immediate interaction with the surrounding world, which are often compromised in schizophrenia and related vulnerability states. Therefore, early CD mechanism impairments unavoidably reverberate into subtle, inchoate distortion of the sense of agency: this might prompt the emergence of those subtler, subclinical modes of altered subjective experience (a.k.a., Self-disorders)³⁸⁻⁴⁰ that precede (often by several years) the onset of positive symptoms. Self-disorders are trait-like, non-psychotic anomalies of subjective experience that have been recursively corroborated as schizophrenia spectrum vulnerability phenotypes. They encompass varieties of depersonalization, derealization and similar distortions of the subjective experience,

characterized by a diminished sense of existing as an embodied, coherent subject, vitally immersed in the world and author of his own actions. Self-disorders are clinically closer to initial disturbances of the sense of agency than overt psychotic symptoms and might constitute a more robust (and developmentally earlier) phenotype to anchor the investigation of basic physiological processes as CD mechanisms conferring premorbid (schizotaxic) vulnerability to psychosis.

Therefore, closer attention to early alteration of CD mechanism and to their longitudinal, neurodevelopmental impact, might illuminate possible pathogenetic and pathophysiological connections between motor development (and its impairments) and broad vulnerability to mental disorders (e.g. psychotic risk) [see figure 2]. For example, an early CD mechanism impairment would interfere with the processing of error signals for the adjustments of ongoing motor actions, phenotypically resulting in a childhood clinical picture of motor coordination impairment. Along development, the early alteration of CD mechanism may longitudinally impact the ontogenetic development of the sense of agency, subjectively experienced as fleeting, yet disturbing Self-disorders. Therefore, the same mechanism that is early involved in motor coordination impairment, in a more long-term perspective, is also involved in the development of those trait-like subjective experiences indexing the longitudinal liability to psychosis. Moreover, we should also consider possible developmental changes in CD mechanisms, that could capture brain maturational trajectories associated to age-specific windows of vulnerability to schizophrenia spectrum disorders. In this perspective, the early alteration of CD mechanisms presumably present since childhood could be worsened by additive alterations in age-specific processes of brain development, as detected for example by oculomotor control tasks.⁴¹ Abnormal synaptic pruning⁴² and myelination⁴³ during adolescence could cause further delay of already altered CD that, interacting with other possible neural alterations,⁴⁴ may contribute to explain the peak of psychotic risk during peri-adolescence.

However, given that childhood motor impairment is not necessarily associated with adult psychosis (and, conversely, adult psychosis is not systematically preceded by childhood motor impairment), other physiologically and temporally intermediate mechanisms need to be considered in the developmental cascade from early motor impairment to later psychotic risk. In this sense developmental psychopathology framework could empower the heuristic resolution of the multiple-levels of enquiry thematized in the RDoC approach.^{1,7} Indeed, in line with the multifinality principle of developmental psychopathology,⁴⁵ several protective/risk factors as well as other variables may morph the developmental trajectory leading to increased cumulative risk of psychosis over time. Overall, this coheres with some degree of motor impairment described in other adult psychopathological conditions outside the psychosis spectrum² (although further investigation is needed to establish their possible developmental origins).

In any case, even if childhood motor impairment is to be considered a simple, distal risk factor for psychosis, it is crucial to realize that its prognostic value increases along the premorbid and early clinical risk stages. That is, the presence of motor impairment in at-risk/prodromal phases has an increased prognostic weight than in previous, premorbid ones.^{46,47} This clearly strengthens the rationale for including developmental motor impairment features in multivariate models of psychotic risk calculators.⁴⁸

In conclusion, the integration of neurophysiological, developmental and phenomenological perspectives suggests that motor impairment is not simply a generic, extrinsic proxy of altered neurodevelopment, but might be more intimately related to psychotic risk. In this respect, the potential impact of altered CD systems for the early development of an unstable sense of self-agency (i.e. a perturbation of basic self-awareness and my-ness of experience which might confer liability to schizophrenia spectrum conditions) is an attractive direction of research.¹² This conception may fit alternative (although not necessarily mutually exclusive) extant models of

motor dysfunction in psychosis,^{7,49} and strongly suggests investigating clinical implications of motor impairment outside the motor domain.

Furthermore, current technology-enabled tools for laboratory (e.g. eye tracking)⁴¹ and daily life settings (e.g. accelerometers and other tracking sensors built into ubiquitous portable devices) make the prospect of generating multimodal, high-resolution motoric profiling concrete and unobtrusive,^{5,6} with the ultimate goal of defining gradients along a number of kinematic dimensions. This might be the enabling step for an improved stratification and subtyping of subtle motor anomalies, including those – so called micro-movements⁵⁰ - that may elude traditional clinical observation. Finally, given their central adaptive function and long evolutionary history across species, these sensori-motor mechanisms (such as CD systems), provide a unique translational bridge for the neurophysiological exploration of their alterations.

References

1. Garvey MA, Cuthbert BN. Developing a motor systems domain for the NIMH RDoC program. *Schizophr Bull.* 2017;43:935-936.
2. Peralta V, Cuesta MJ. Motor abnormalities: from neurodevelopmental to neurodegenerative through functional (neuro)psychiatric disorders. *Schizophr Bull.* 2017;43:956-971.
3. Fatemi SH, Folsom TD. The neurodevelopmental hypothesis of schizophrenia, revisited. *Schizophr Bull.* 2009;35:528-548.
4. Schiffman, J. Motor issues in the clinical high risk phase of psychosis. *Schizophr Bull.* 2017;43:937-938.
5. Insel T. Digital phenotyping: technology for a new science of behavior. *JAMA.* 2017;318:1215-1216.

6. Raballo A. Digital phenotyping: an overarching framework to capture our extended mental states in the digital world. *Lancet Psychiatry* 2017; 5: 194-5.
7. Mittal VA, Bernard JA, Northoff G. What can different motor circuits tell us about psychosis? An RDoC perspective. *Schizophr Bull.* 2017;43:949-955.
8. Burton, BK, Thorup AE, Jepsen JR, et al. Impairments of motor function among children with a familial high risk of schizophrenia or bipolar disorders at 7 years old in Denmark: an observational cohort study. *Lancet Psychiatry.* 2017;4:400-408.
9. Raballo A., Lundgren E, Leuci E, Fontò S, Maggini C. Self-centrality, psychosis and schizotaxia: a conceptual review. *Acta Biomed.* 2006;77:33-39.
10. Grivois H. Coordination et subjectivité dans la psychose naissante. In H. Grivois, et J. Proust (Eds). *Subjectivité et conscience d'agir, approches clinique et cognitive de la psychose.* Paris, Presses Universitaires de France, 1998, 35-73.
11. Feinberg I. Efference copy and corollary discharge: implications for thinking and its disorders. *Schizophr Bull.* 1978;4:636-640.
12. Poletti M, Gebhardt E, Raballo A. Corollary discharge, self-agency and the neurodevelopment of the psychotic mind. *JAMA Psychiatry.* 2017;74:1169-1170.
13. Crapse TB, Sommer MA. Corollary discharge across the animal kingdom. *Nat Rev Neurosci.* 2008;9:587-600.
14. Straka H, Simmers J, Chagnaud BP. A new perspective on predictive motor signaling. *Curr Biol.* 2018;28:R232-R243.
15. Eliades SJ, Wang X. Sensory-motor interaction in the primate auditory cortex during self-initiated vocalizations. *J Neurophysiol.* 2003;89:2194-2207.
16. Eliades SJ, Wang X. Dynamics of auditory-vocal interaction in monkey auditory cortex. *Cereb Cortex.* 2005;15:1510-1523.

17. Eliades SJ, Wang X. Neural substrates of vocalization feedback monitoring in primate auditory cortex. *Nature*. 2008;453:1102-1106.
18. Sun LD, Goldberg, ME. Corollary discharge and oculomotor proprioception: cortical mechanisms for spatially accurate vision. *Annu Rev Vis Sci*. 2016;2:61-84.
19. Rochat P, Hespos SJ. Differential rooting response by neonates: Evidence of an early sense of self. *Early Dev. Parent*. 1997;6:105-112.
20. Gomez A, Sirigu A. Developmental Coordination Disorder: core sensori-motor deficits, neurobiology and etiology. *Neuropsychologia*. 2015;79:272-287.
21. Katschmarsky S, Cainery S, Maruff P, et al. The ability to execute saccades on the basis of efference copy: impairments in double step saccade performance in children with developmental coordination disorder. *Exp. Brain Res*. 2001;136:73-78.
22. Wilson PH, Ruddock S, Smits-Engelsman B, Polatajko H, Blank R. understanding performance deficits in developmental coordination disorders: a meta-analysis of recent research. *Dev Med Child Neurol*. 2013;55:217-228.
23. Wilson PH, Smits-Engelsman B, Caeyenberghs K, et al. Cognitive and neuroimaging findings in developmental coordination disorder: new insights from a systematic review of recent research. *Dev Med Child Neurol*. 2017;59:1117-1129.
24. Adams JL, Lust JK, Wilson PH, et al. Compromised motor control n children with dcd: a deficit in the internal model? – A systematic review. *Neurosci Biobehav Rev*. 2014;47:225-244.
25. Mittal VA, Walker EF. Movement abnormalities predict conversion to Axis I psychosis among prodromal adolescents. *J Abn Psychol*. 2007;116:796-803.
26. Schiffman J, Sorensen HJ, Maeda J, et al. Childhood motor coordination and adult schizophrenia spectrum disorders. *Am J Psychiatry*. 2009;166:1041-1047.

27. Schiffman J, Mittal V, Kline E et al. Childhood dyspraxia predicts adult-onset nonaffective–psychosis-spectrum disorder. *Develop Psychopathol.* 2015;27:1323-1330
28. Burton BK, Hjorthoj C, Jepsen JR, et al. Research Review: Do motor deficits during development represent an endophenotype for schizophrenia? A meta-analysis. *J Child Psychol Psychiatry.* 2016;57:446-456.
29. Filatova S, Koivumaa-Honkanen H, Khandaker GM, et al. Early motor milestones and schizotypy in the northern Finland birth cohort study 1966. *Schizophr Bull.* 2017; Dec 9 Epub ahead of print; DOI:10.1093/schbul/sbx165
30. Hameed MA, Lewis AJ. Offspring of parents with schizophrenia: a systematic review of developmental features across childhood. *Harv Rev Psychiatry.* 2016;24:104-117.
31. Mathalon DH, Roach DJ, Ferri J, et al., Deficient auditory predictive coding during vocalization in the psychosis risk syndrome and in early illness schizophrenia. *Psychol Med.* submitted.
32. Perez VB, Woods SW, Roach BJ, et al. Automatic auditory processing deficits in schizophrenia and clinical high-risk patients: forecasting psychosis risk with mismatch negativity. *Biol Psychiatry.* 2013;75:459-469.
33. Oestreich LK, Mifsud NG, Ford JM, et al. Cortical suppression to delayed self-initiated auditory stimuli in schizotypy: neurophysiological evidence for a continuum of psychosis. *Clin EEG Neurosci.* 2016;47:3-10.
34. Ford JM, Mathalon DH, Heinks T, et al. Neurophysiological evidence of corollary discharge dysfunction in schizophrenia. *Am J Psychiatry.* 2001;158:2069-2071.
35. Ford JM, Mathalon DH, Roach BJ, et al. Neurophysiological evidence of corollary discharge function during vocalization in psychotic patients and their nonpsychotic first-degree relatives. *Schizophr Bull.* 2013;39:1272-1280.

36. Feinberg, I. Guazzelli M. Schizophrenia – a disorder of the corollary discharge systems that integrate the motor systems with the sensory systems of consciousness. *Br J Psychiatry*. 1999;174:196-204.
37. Cavanaugh J, Berman RA, Joiner WM, et al. Saccadic corollary discharge underlies stable visual perception. *J Neurosci*. 2016;36:31-42.
38. Raballo A, Sæbye D, Parnas, J. Looking at the schizophrenia spectrum through the prism of self-disorders: an empirical study. *Schizophr Bull*. 2011;37:344-351.
39. Raballo A, Parnas J. The silent side of the spectrum: schizotypy and the schizotaxic self. *Schizophr Bull*. 2011;37:1017-1026.
40. Raballo A, Pappagallo E, Dell’Erba E, et al. Self-Disorders and clinical high-risk for psychosis: an empirical study in help-seeking youth attending community mental health facilities. *Schizophr Bull*. 2016;42:926-932.
41. Thakkar KN, Diwadkar VA, Rolfes M. Oculomotor prediction: a window into the psychotic mind. *Trends Cogn Sci*. 2017;21:344-356.
42. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res*. 1982/1983;17:319-334.
43. Whitford TJ, Ford JM, Mathalon DH, et al. Schizophrenia, myelination and delayed-corollary discharges: a hypothesis. *Schizophr Bull*. 2012;38:486-494.
44. Whitford TJ, Oestreich LKL, Ford JM, et al. Deficits in cortical suppression during vocalization are associated with structural abnormalities in the arcuate fasciculus in early illness schizophrenia and clinical high risk for psychosis. *Schizophr Bull*. 2017; Nov 29 Epub ahead of print; DOI: 10.1093/schbul/sbx144

45. Franklin JC, Jamieson JP, Glenn CR et al. How developmental psychopathology theory and research can inform the research domain criteria (RDoC) project. *J Clin Child Adol Psychol.* 2015;44:280-290.
46. Hirjak D, Meyer-Lindenberg A, Kubera KM et al. Motor dysfunction as research domain in the period preceding manifest schizophrenia: a systematic review. *Neurosci Biobehav Rev.* 2018;87:87-105.
47. Dean DJ, Walther S, Bernard JA, et al. Motor clusters reveal differences in risk for psychosis, cognitive functioning, and thalamocortical connectivity. Evidence for vulnerability subtypes. *Clin Psychol Sci.* 2018; 31 May Epub ahead of print; DOI: [10.1177/2167702618773759](https://doi.org/10.1177/2167702618773759).
48. Cannon TD, Yu C, Addington J, Bearden CE et al. An individualized risk calculator for research in prodromal psychosis. *Am J Psychiatry.* 2016;173:980-988.
49. Walther S, Mittal VA. Motor system pathology in psychosis. *Curr Psychiatry Rep.* 2017 19:97.
50. Nguyen J, Majmudar U, Papatomas TV, et al. Schizophrenia: the micro-movements perspective. *Neuropsychologia.* 2016;85:310-326.