

Edward Shorter's comment on Jack R. Foucher et al.'s Wernicke-Kleist-Leonhard phenotypes of endogenous psychoses: a review of their validity

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Our first follow-up response to Edward Shorter's comment on our recent review of Wernicke, Kleist and Leonhard (WKL) school (Foucher, Gawlik, Roth et al. 2020b) had to address the issue of IDC-DSM vs WKL concepts of catatonia as it is illustrative of the kind of misunderstandings that ensue the interpretation of the latter with the views of the former (and vice versa).

"I was dismayed to see "periodic catatonia" described as another of the "non-system schizophrenias." It has been with so much trouble that psychiatry has recently detached catatonia from schizophrenia and made it a disease of its own. Now, for the authors to reinsert catatonia in schizophrenia, and to claim that it is response to antipsychotics, is to weep. Antipsychotics are counter-indicated in catatonia; the remedies of choice are the benzodiazepines and convulsive therapy (Shorter and Fink 2018)."

This example embeds some of the most profound dissimilarities between the two frameworks which if unclarified might let the DSM and the WKL communities talking past each other, somewhat in the sense of an *incommensurability* (Kuhn 1996).

DSM-descriptive vs WKL-theoretical concepts

Indeed, as both research programs were looking for categorical pathological entities, these were defined in completely different ways. The developers of the DSM-III intended to be "*a-theoretical*" regarding the underlying structure of their consensual definitions: disorders aimed at providing mere phenomenological descriptions. This is in striking opposition with the WKL research program (WKL-RP) which explicitly embraced the disease-paradigm of the biomedical framework. By using the term "psychosis" these researchers made the strong *a priori* assumption that they had to look for homogeneous groups of patients that could be accounted for by *causes of major effects*, i.e., phenotypes. Some of these causes were already

known, i.e., “exogeneous” or secondary psychoses such as general paresis, pellagra, drug toxicity or withdrawal; but many remained unknown and were presumably related to an “*endogenous*” pre-disposition to be discovered in the endogenous psychoses of the WKL classification. Last, it was hypothesized that most of these causes might not directly affect the whole brain but only one domain or even only one functional system (parsimony principle), and these phenotypes were ordered accordingly.

The a-theoretical stance of the DSM and the theoretical embedment of the WKL-RP explain their radically different understanding of the word “catatonia.” In a DSM-formatted mind, the catatonia concept is merely *descriptive*, i.e., is defined by the presence of at least three symptoms from a checklist of 12. In in a WKL-formatted mind, the catatonia concept comes with *three biological hypotheses*:

- The phenotype is an endogenous psychosis, i.e., accountable for by a *biological cause*.
- The core disfunction impairs (a) *psychomotor* system(s), i.e., the one(s) that regulate(s) non-voluntary drive and high-level non-voluntary movements like orienting and emotional expression.
- Psychomotricity is not only quantitatively, but also *qualitatively* disturbed which goes together with a course having a *progressive* component: mostly progressive for system catatonias, mainly remitting-progressive with bipolar features for periodic catatonia. This evolution towards a residual state suggests that WKL-catatonias might come with neurodegenerative component which is likely to differ in nature according to the course and to the specific residual symptom-complex.

Operationalization: DSM-check-list vs WKL symptom-complexes

Ensuing the aforementioned WKL hypotheses, symptoms should not aggregate at random, but in definite clusters, forming specific *symptom-complexes** with specific evolution. The diagnosis of any catatonia-phenotype is based on a precise ascertainment and differentiation of cardinal psychomotor (primary) symptoms indicative for different kind of malfunctioning:

- Pure quantitative changes, i.e., hyperkinesia or akinesia, could be due to a defective regulatory system resulting in the excessive or reduced activity of psychomotor systems.

* We favor this label over the one of syndrome. Though the two terms had conveyed the same meaning at their origin, in the other field of medicine, “syndrome” rather refer to a symptom-complex related to the failure of an organ or a known system, e.g., pyramidal or extra-pyramidal syndrome, Horner's syndrome (upper sympathetic trunk)... In a way, a syndrome is a validated symptom-complex, as a disease is a validated phenotype. Unfortunately, the systems of which failure is supposed to account for most WKL-symptom-complexes remain speculative.

- Qualitative changes, i.e., psychomotor distortions such as parakinesia, mixity* or proskinesia, are supposed to be indicative for the impairment of one or several systems; hence auguring the progressive build-up of a residual state.

This is diametrically opposed to the ICD and DSM conceptions which define catatonia cross-sectionally and as the combination of a minimum number of various motor abnormalities depending on the authors and the instrument (Ungvari, Caroff and Gerevich 2010). This checklist approach ignores the *interrelationship between symptoms* and considers 4017 possible combinations[†] as equivalent, hence not taking advantage of specific symptom constellations in symptom-complexes. Last, qualitative and quantitative psychomotor disturbances are not distinguished, and the DSM-checklist makes no difference in this regard.

From the WKL perspective, this is a major impediment since only psychomotor abnormalities in the strict sense, i.e., not secondary to disorders of affect or thought, can provide a basis for a differentiated diagnostic classification of psychomotor psychoses beyond diagnostically unspecific catatonic features. Please find an illustration of this in box 1.

Box 1: Vignette of the WKL-diagnostic process

Because the WKL-phenotypes are defined at a more conceptual level, the diagnostic process is not the one of a recipe application but rather like a neurological reasoning (Foucher, Gawlik, Roth et al., 2020b). We will try to illustrate this with a clinical presentation fulfilling the DSM-catatonia diagnosis: the case of a motionless and mute patient having a slight resistance to passive mobilization.

Prevailing motor manifestations ≠ primary psychomotor involvement

The WKL diagnostic process gives little value to unitary symptoms. It rather aims at giving sense to their co-occurrence and their interrelationship. It attempts to capture a common underlying explanatory factor somewhat in a way of a latent variable. Hence symptom's saliency is much less important than the understanding of their coherent interplay when considering the full clinical picture. To that end, it is generally useful to find out whether one domain might be primary affected: looking for the elementary symptoms which might directly ensue the impairment of a specific neuropsychological domain (affect, thought or psychomotricity) and see if the other manifestations could be accounted for by secondary reactions to them. The formers are constant and constitute the core of symptom-complexes while the latter are more variable as they depend on the patient's temperament, personality, culture, and personal history, together as on the context.

Affect: the above-mentioned triad can be secondary to a primary overwhelming affect. Severe depression, anxiety, or ecstasy can paralyze mental and psychomotor activity: the

* Hyperkinesia and akinesia occurring together on different body segments.

[†] Considering that the diagnosis can be made for any combination of 3 or more of the 12 symptoms of the DSM check-list, the number of possible combinations is $N = \sum_{k=3}^{12} C_k^{12}$ (C stands for the binomial coefficient). In a way, by being defined by any of these 4017 combinations, the DSM-catatonia disorder could be viewed as a much less parsimonious proposal than the 22 WKL-catatonic phenotypes (periodic catatonia + 6 simple system catatonias + $C_2^6 = 15$ combined forms) or the 23 psychomotor ones (+ hyperkinetic-akinetic motility psychosis).

patient does not answer questions, does not move and resists to passive mobilization due to fears or the misunderstanding of the context. If we step back and consider the full clinical picture, the emotional state should be reflected in the patient's postures and facial expressions and on follow-up the patient should be able to recall it.

Thought and language: *alternatively, the triad could be secondary to a primary thought inhibition. Mutism would directly ensue while the patient might resist to passive movement again because he is no more able to understand the context or even misinterpret it as threatening. In such case, the reduction of motor behavior chiefly concerns voluntary actions and relatively spare automatic movements. The latter might be even increased due to a release phenomenon, e.g., stereotypies*. The whole clinical picture should be coherent with this interpretation: perplexed facial expression reflecting the patient's worrisome lack of understanding of his or her environment, poor or confused recall of the episode...*

Primary psychomotor inhibition *could for sure also account for the triad. In this case, the reduction of motor behavior should dominate on reactive and expressive movements, e.g., "empty" facial expressions, poor orienting towards the examiner etc. Conversely, voluntary movement tested by asking the patient to do simple actions might be slowed but relatively spared. Mutism can result from the blocking of verbal output[†], something that patients might be able to report at the end of the episode. Resistance can be either due to wariness in case of akinetic motility psychosis or can result from a psychomotor negativism which should be specifically tested (ambitendence induction) in case of a catatonic phenotype.*

Remark: *In case of severe acute state, the disturbances might be too widespread to conclude on the main affected domain. Patients should be at least reassessed while the acute state is abating as symptoms from the primarily affected domain are the last to remit. Alternatively they might not be one chiefly affected domain or it might change from one time to the next which would argue for a manic-depressive psychosis.*

Refining symptom-complexes and life-long phenotypical descriptions

With the benefit of hindsight, it is generally easy to distinguish the monomorphic, i.e., system catatonias, from the bipolar psychomotor phenotypes, i.e., motility psychosis and periodic catatonia. Passed the process phase, the clinical pictures of systemic forms remain stable. The description of their specific symptom-complexes continue to be surprisingly accurate as they are poorly modified by the treatments[‡].

The differential diagnosis between periodic catatonia and motility psychosis might be trickier, especially in the very first episodes. The qualitative changes allowing to orient the diagnosis towards periodic catatonia, e.g., mixity, parakinesia or psychomotor negativism, might be discreet and difficult to capture because they can be short lasting. Moreover, even after one or two episodes, the typical deficit symptom-complex of periodic catatonia is not easy to distinguish from the apathetic side-effects of antipsychotics to which motility

* This is a classical Jacksonian neurological reasoning: the defect of a high-level function is responsible for primary negative symptoms (decrease in voluntary movement) and by releasing its control over lower functional levels results in secondary positive symptoms (e.g., stereotypies).

† A primary psychomotor impairment does not mean that the patient is free from symptoms classically assigned to the other domains, e.g., in episodes of periodic catatonia, affective reactions are frequent and speech can be disorganized (yet in a different way than in cataphasia: impulsive short circuit speech vs logorrhea, agrammatic vs paragrammatic utterances...).

‡ System catatonias frequently allow to make sense out of cases who might be difficult to put in either DSM categories especially since the disappearance of the simple deteriorating disorder. This disorder remained in "Appendix B: Criteria Sets ... for Further Study" from the DSM-III to the DSM-IVR. It was intended to be the counterpart of ICD-8,9 and 10 simple-type schizophrenia. Unfortunately, it never found its way to be accepted as a definite category, partly due to a lack of research. The WHO endorsed DSM-5 decision in excluding simple-type schizophrenia from the 11th version of the ICD. Most of these patients might probably switch to the autistic spectrum disorders thanks to the considerable broadening of the concept.

psychosis are markedly sensitive. Sometime the definite diagnosis can only be secured after another episode or a longer follow-up.

It is perhaps one of the greatest achievements of the WKL school to provide ***complete phenotypical descriptions*** that go beyond the one of the clinical presentations (cross-sectional) or the clinical pictures (full episode). Their descriptions of the polymorphic forms, i.e., the seven bipolar ones, are *un tour de force* in being able to encompass the various clinical pictures that can be observed in the life course of these patients. Such comprehensiveness, integrating the evolution in the phenotype, is a considerable advantage as this is frequently the best way to secure a diagnosis. Yet, the other side of the coin is that it is quite impossible to make a definite WKL-diagnosis after a single detailed examination as it is possible to do with most DSM or ICD disorders thanks to their cross-sectional definition.

Diagnostic overlap in practice

With such dissimilarities in the definitions and the diagnostic processes, it can be awaited that most of DSM's catatonia-disorders are not WKL's catatonia-phenotype and vice-versa.

From DSM to WKL

DSM-catatonias might correspond to a large variety of WKL-phenotypes:

- Hyperkinetic-akinetic motility psychosis is likely to be most frequently diagnosed as DSM-catatonia.
- Yet, non-psychomotor phenotypes, e.g., manic-depressive illness, non-psychomotor cycloid psychoses, severely inhibited cataphasia might occasionally show DSM-catatonic features (as secondary symptoms).
- It is unclear to us whether some non-psychotic diagnoses could also be included in this entity, e.g., fear "freezing up" reaction, dissociative or malingering behaviors. Yet it is the case for some general medical conditions, e.g., epilepsy, intoxication, withdrawal...

The proportion of periodic-catatonia and system catatonias among these alternatives is unfortunately unknown. However, if secondary forms are included, they might account for less than ¼ of the DSM-catatonia diagnoses (figure 1A).

Considering that most (but not all) of the above-mentioned phenotypes are responsive to GABAergic interventions, e.g., benzodiazepines and ECT, and that hyperkinetic-akinetic motility psychosis is especially at risk of malignant side effect under first generation antipsychotics, we acknowledge that DSM-catatonia is a pragmatic (mainly treatment orienting) diagnosis.

We performed a *systematic review* of case reports mentioning the diagnosis of “periodic catatonia” (Pubmed from 1939 to July 2018). Of the 32 retrieved reports, 16 (50%) explicitly referred to Gjessing’s account (Gjessing 1974). Yet this is the same as defining periodic catatonia as the mere recurrence of DSM or ICD catatonic episodes which was indeed the case for all publications. From the description of the cases, we could find compelling evidence for WKL periodic catatonia in only six of them (19%) while at least 16 (50%) could be confidently diagnosed as motility psychoses due to the long follow-up with multiple episodes without residuum. This makes the *WKL-diagnosis of motility psychosis three times more likely than the one of periodic catatonia in the case of recurring DSM-catatonic episodes!*

From WKL to DSM

The name “periodic catatonia” is unfortunately misleading if understood in the ICD-DSM sense: *only 20% of WKL-periodic catatonia are diagnosed as ICD-catatonia* after an average of six episodes and 13 years of evolution (Krause 2012). Indeed, the core features of this phenotype are likely to be overlooked during the acute states, especially in instances of too salient, yet inconstant and unspecific schizoaffective features. In the deficit state, the psychomotor anomalies are clearer but viewed as treatment side-effects by the DSM-reading grid: reduction of drive and emotional expressions while psychotic manifestations are typically lacking.

For sure, our account of antipsychotic response might sound inappropriate if periodic catatonia is understood as recurrences of DSM-catatonic episodes but would it still be the same if we remind that $\frac{1}{2}$ to $\frac{3}{4}$ of these patients are diagnosed for psychosis according to the ICD or DSM nomenclature respectively at the first episode and 13-years follow-up (see figure 1B) (Krause 2012)? *Periodic catatonia is an illustration of the kind of misunderstandings that can result from the WKL-DSM commensurability mismatch.*

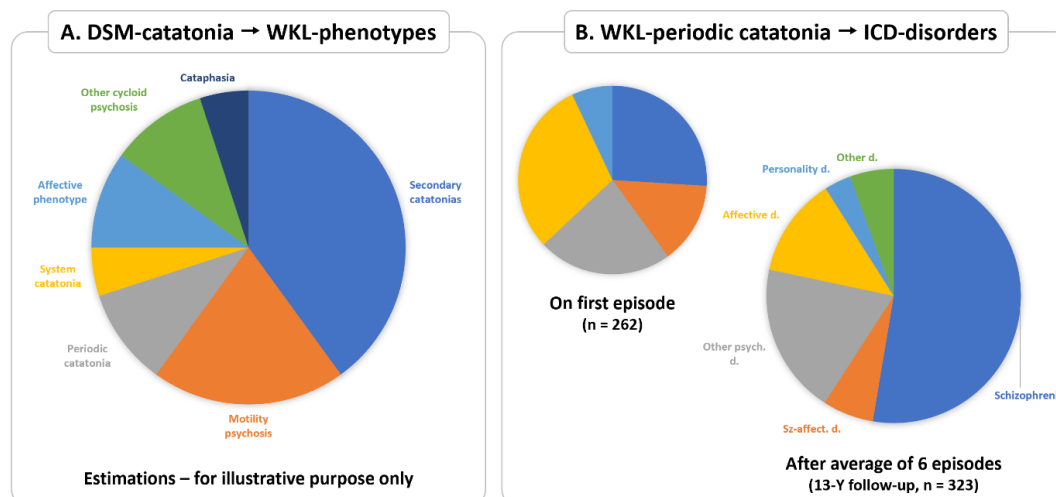


Figure 1: Commensurability mismatch between DSM-ICD-catatonias and periodic catatonias diagnoses. **A.** Starting from a DSM-catatonias diagnosis, estimations for the different WKL-phenotypes that might account for. Unfortunately, no empirical data are currently available, so the relative proportions are just estimated. **B.** Starting from WKL-periodic catatonias, the proportions of ICD-disorder diagnoses are given at first episode and after an average of 13 years follow-up.

The problem might be the same for WKL-system catatonias. Their proportion given the diagnosis DSM-catatonias is unknown, but at least 4 of them are unlikely to fulfil DSM-criteria, i.e., parakinetic, pseudo-compulsive, absentminded and short-circuit speech catatonias*. All these phenotypes are chronic forms. Hence, their poor responsiveness to any therapeutic attempt, including ECT and benzodiazepines (Ungvari, Chiu, Chow et al., 1999), might come less as a surprise if we adopt the DSM-reading grid.

Periodic catatonias vs system catatonias

The differentiation between periodic catatonias and the group of system catatonias was shown to be highly reliable with a quite considerable stability of the diagnoses (Franzek and Beckmann 1992; Pfuhlmann, Franzek, Stöber et al. 1997). Various published catamnestic case records and video documentations in regular psychopathology workshops of the International Wernicke-Kleist-Leonhard-Society illustrate that the catatonic phenotypes identified by Leonhard are still observable in everyday clinical practice.

Epidemiological studies support the naturalistic kindness of this differentiation by showing a strikingly significant reverse balance between familial and environmental factors (Stöber and Reis 2009):

- System catatonias appeared in most cases to be sporadic, i.e., 86%, and mostly associated with neurodevelopmental risk factors, e.g., mid-gestational maternal infections in more than $\frac{1}{3}$ of the cases, +10% risk if born in early spring.
- In contrast, periodic catatonias shows a clear familiarity with 60% of index cases having at least one affected relative while it is poorly related with environmental risk factors, e.g., mid-gestational maternal infections in only 8%, inverse seasonality of birth effect with -6% risk.

* The three latter were formerly referred to as manneristic, sluggish and speech-prompt catatonias.

Periodic catatonia on the road to validity?

Periodic catatonia has a low prevalence in Europe. It is globally estimated to be about 1‰, and its genetic forms would be about 0.5 ‰, i.e., it could be considered as a *rare phenotype*. Yet these patients have been reported to account for up to 10% of the patients laid up in acute wards of several European University hospitals.

Evidence for genetic etiology

As reminded, periodic catatonia is one of the most heritable WKL-phenotypes with no cross-liability (Beckmann, Franzek and Stöber 1996). Its inheritance pattern is *autosomal dominant with partial penetrance*: 21-27% of affected first degree relatives have the full psychotic phenotype (Stöber 2001), 32-41% if relatives with *formes frustres* are included, i.e., residual symptoms but no past-record of affective or psychotic episodes (Franzek and Beckmann 1999; Leonhard 1975). Again, this is in sharp contrast with other WKL psychomotor phenotypes: motility psychosis (4.3%) and system catatonias (3.1%) (Stöber 2001). The heritability of full periodic catatonia phenotype was estimated to be $H^2 = 0.63$ (Franzek and Beckmann 1999). The linear genotype-phenotype concordance argues for a *single gene* to be implicated *within a pedigree* (Franzek, Schmidtke, Beckmann and Stöber 1995). Last, we could recently replicate the *anticipation phenomena* as the offspring have earlier onset and more severe forms than their affected parent in 93% of periodic catatonia pedigree (Stöber, Haubitz, Franzek and Beckmann 1998; Foucher, Gawlik et al. work in progress).

While two linkage studies did already point toward a *major locus on Chr15q* accounting for about 2/3 of the pedigrees (OMIM 605419) (Stöber, Saar, Rüschen-dorf et al. 2000), it is only very recently that a genome-wide association study could refine the location to a non-coding region upstream of GCOM1 (Gawlik et al. unpublished material). Interestingly, the combination of an anticipation phenomenon with half-penetrance is suggestive for an *unstable mutation* mechanism, i.e., expansion of a repeated sequence from a pre-mutation which could account for the relatively high prevalence of PC (Mantere, Kersten and Hoischen 2019). Thanks to the recent advance in whole genome sequencing, these expansions are increasingly discovered in non-coding regions in association with a variety of slowly progressing neurodegenerative diseases (spinocerebellar ataxias, fronto-temporal dementia and/or amyotrophic lateral sclerosis, familial epilepsy with cortical tremor) (Aydin, Dekomien, Hoffjan et al. 2018; Corbett, Kroes, Veneziano et al. 2019; Florian, Kraft, Leitão et al. 2019; McFarland, Liu, Landrian et al. 2015; Rafahi, Szmulewicz, Bennett et al. 2019; Seixas, Loureiro, Costa et al. 2017; Zeng, Zhang, Wang et al. 2019). Hence an ongoing study is looking for *expansions*, especially in the non-coding region between *CGNL1 and GCOM1 complex*

locus. However, that might only account for the Chr15q hotspot reported in $\frac{2}{3}$ of the pedigree and the phenotype is likely to be genetically heterogeneous, e.g., Chr21q locus (Stöber, Seelow, Rüschemdorf et al. 2002).

Evidence for a specific pathophysiological model

Accordingly, the whole phenotype might be better accounted for at the pathophysiological level. Building on older proposals (Ferguson and Gao 2018), the current working model for periodic catatonia is an *acquired deficit of intra-cortical inhibition* (Foucher, Gawlik, Roth et al. 2020b). This could ensue a defective neuroprotection of GABA-interneurons by Gcom1. The reduction of this NMDA-receptor associated protein seems to increase their vulnerability to excitotoxicity, resulting in their apoptotic death (Foucher, Elowe and Berna 2020a; Roginski, Lau, Santoiemma et al. 2018). Though the defect is probably widespread, it might be especially detrimental in the premotor cortices as they are naturally poor in GABAergic interneurons (Zilles and Palomero-Gallagher 2017).

The first evidence for inhibition-deficits in catatonia came from the reduction of GABA_A receptors binding in the left-premotor cortices of these patients (Northoff, Steinke, Czervinka et al. 1999). More recently, the same cortices were found to be hyperactive both in acute catatonia (Walther, Schäppi, Federspiel et al. 2017) and in remitted periodic catatonia (Foucher, Zhang, Roser et al. 2018b). The replicability of this finding by two independent groups led us to the question of its usability as a diagnostic biomarker. In a first proof-of-concept study, this left-premotor hyperactivity was shown to be sensitive = 98% [76-100%]_{95CI} (95% credible interval) and specific = 96% [82-100%]_{95CI} for periodic catatonia even when confronted to pseudo-compulsive catatonia, i.e., a systemic form (Foucher, de Billy, Jeanjean et al. 2019). Recently, the Bayesian update confirmed these findings on a larger population though with a slight decrease in sensitivity = 82% [64-94%]_{95CI} while specificity remained at 95% [81-100%]_{95CI} (de Billy et al., submitted). However, due to the relative rarity of periodic catatonia, the samples remain scarce ($n_{PC} = 23 / n_{non-PC} = 32$) and we are currently looking for collaborations to replicate these findings. We take the opportunity of this post to encourage willing researchers to contact us.

The last argument for a defective intra-cortical inhibition is the good response of acute episodes of periodic catatonia to GABAergic interventions, e.g., benzodiazepines (Ungvari, Leung, Wong and Lau 1994) and electroconvulsive therapy (Ungvari, Chiu, Chow et al. 1999). A further appealing evidence recently came from an interim analysis of an ongoing proof-of-concept trial using personalized transcranial stimulation or TMS (RETONIC - NCT03116425). In this study, patients' specific hyperactive regions could be selectively modulated thanks to

the robotic positioning of the TMS coil under the control of a neuronavigation device (Zorn, Renaud, Bayle et al. 2012). The selective reinforcement of left-premotor internal inhibition over a 5-day protocol resulted in clinically significant improvement of the residual symptoms (predominantly on the drive deficit) in nine out of 10 patients while only two of them responded to the classical left dorsolateral prefrontal target (Foucher, de Billy, Mainberger et al. 2018a). Up to now, these results could be replicated as left-premotor inhibition was effective in six out of seven patients from another group (de Billy et al. submitted).

Conclusion

The case of periodic catatonia is paradigmatic of the kind of misunderstandings that are due to the mismatch between DSM and WKL conceptual frameworks. If we missed our goal to clarify this in our paper, we are happy to be able to discuss that further thanks to Edward Shorter's comment.

Periodic catatonia is also illustrative for the added value of WKL differentiated psychopathology regarding the prognosis and the treatment of patients with prominent motor manifestations. It further nicely shows that the biomedical research program is still promising in the field of psychiatry to delineate sufficiently homogeneous groups of patients to share the same neurobiological anomalies.

Last, periodic catatonia also allows us to exemplify how the kind of progress that Edward Shorter was calling for, could be implemented. Building on the biomarker, we are currently trying to refine the description of early onset variants in a reverse phenotyping approach (Schulze and McMahon 2004). Indeed, patients who are developing their first symptoms before 12 years of age (< 5% of cases) frequently have atypical features making them difficult to diagnose, e.g., they quickly progress to a residuum, lack the classical bipolar course and are more likely to present uncharacteristic features like pseudo-obsessions on the foreground. It might be that pheno-biotypical definition could allow us to define even more homogeneous groups of patients to ultimately find out their etio-pathophysiological cause.

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