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# A brain imaging-based diagnostic biomarker for periodic catatonia

## Preliminary evidence using a Bayesian approach

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## Content

# 1. The concept of diagnostic biomarker in the perspective of the classical biomedical research program in psychiatry

A disease is a ***categorical*** construct because it is supposed to be underlaid by ***one cause of major effect***. When the cause is highly disabling, it is ***selected out*** from the normal population. Hence it is assumed to be rare, only present in patients[1]. Classically, the finding of a disease starts from the description of a ***phenotype***, i.e. a categorical construct endorsing the above-mentioned assumptions (bimodal distribution). Its biological cause can then be looked for by using objective measures indicative of various biological processes, i.e. ***biomarkers***. The finding of the specific biological cause accounting for a phenotype ***validates*** a ***model*** for its expression, a model that takes the name of "disease". Because the causal biological process is supposed to be highly different from the norm, its biomarker is necessarily strongly associated with the condition, validating the biological disorder on a patient per patient basis. Hence it can be used as a ***diagnostic biomarker***.

*Stricto sensu*, a ***biomarker*** is merely an objective measure indicative of a biological process. Yet, in the medical field, it is commonly equated with its clinical purpose, e.g. diagnosing, staging, prognosing, monitoring etc [2]. In the following lines, we shall focus on the ***diagnostic*** goal, meaning that a measure initially indicative of a biological process will become indicative of a diagnosis. This is a transitive reasoning which can only be true if the diagnosis is liable to the biological process in question. The problem is that this condition is only fulfilled by ***disease***-diagnoses but not by ***disorder***-diagnoses which is the current framework in psychiatry.

According to the classical ***biomedical paradigm***, a ***disease*** is a causal ***model***, hypothesizing that a single and specific ***biological dysfunction*** accounts for a typical set of clinical manifestations, i.e. a ***phenotype***[1]. It is the purpose of ***biological research***, to validate such disease-model. The ***first validation step*** is usually correlational: looking in what extent a measure of the putative dysfunctional process, i.e. its biomarker, is specifically, strongly and perhaps also linearly associated with the phenotype and its severity[1]. When a disease is modelized by its ***etiology***, the measure of its initial biological cause is a ***primary pathogenic*** biomarker, e.g. the number of CAG repeats in the huntingtin gene has been shown to correlate with Huntington's phenotype[3]. When a disease is modelized by its ***pathophysiology***, it is assumed that multiple primary causes converge towards a commune biological consequence measured by a ***secondary pathogenic*** biomarker. For instance, the striatal hypo-dopaminergic model of Parkinson's disease was initially validated by direct measurements of dopamine concentration in post-mortem tissues[4] and is now assessed *in vivo* by imaging radioligands of the dopamine transporter, e.g. DAT-scan[5]. But a biomarker can also be ***non-pathogenic***, i.e. a measure of a biological consequence that is unrelated to the causal chain leading to the symptoms. For example, the antibodies directed against intracellular antigens, e.g. anti-Hu or anti-Yo, that correlate with T-cell mediated encephalitis, are not implicated in the pathogenic process. They are the normal humoral response to the release of normally unexposed epitopes secondary to the T-cell-mediated neuronal injury[6]. This distinction between pathogenic and non-pathogenic biomarkers is crucial regarding the ***second validation step*** of the disease model: showing that the experimental manipulation of the causal biological process either reproduces or alleviates the phenotype (Tab. 1)[7]. Indeed, this can only be effective if the manipulated factor is pathogenic. Hence, in T-cell-mediated encephalitis, neither the induction nor the removal of auto-antibodies either induces or relieves the phenotype,

in contradistinction to antibody-mediated encephalitis, e.g. anti-NMDA[8].

It is the purpose of ***translational research*** to turn out valid disease-models into a ***disease-diagnoses*** suitable for ***clinical research***[9]. At this step, a measure initially indicative of a biological process will become indicative of a disease-diagnosis. Again, this implies that the phenotype is liable to the measured dysfunctional process, i.e. that the ***disease-model*** has some ***validity***. If clinical research demonstrates that the disease-diagnosis is amenable to more specific and effective therapeutic interventions, the biomarker will be of value as a predictor of the response and successfully used as a ***diagnostic-test*** when transferred in everyday ***clinical practice*** (table 1).

| | | Biological research | Translational research | Clinical research | Transfer regulation procedures | Clinical practice |
|---|---|---|---|---|---|---|
| | | **Disease-model** | | **Disease-diagnosis** | | **Clinical diagnosis** |
| **Observation** | | Phenotype optimization | | Disease-diagnosis | | ICD-diagnosis |
| **Correlation** | | Marker of a biological process | | Disease-diagnosis biomarker | | Diagnostic-test |
| **Experimental intervention** | **In animal** | Animal model (induction) | | Preclinical studies | | |
| | **In human** | Proof of concept (relief) | | Treatment development | | Approved therapy |

**Table. 1. Major steps for science-driven medical innovations** (adapted from ref. [1]). Fundamental or basic scientific research, i.e. biological research, relies on an epistemological framework to build realistic representations of normal and pathological conditions. Causal reductionism is central to the biomedical paradigm which is a continuous optimization process of disease-models, generally performed in an academic setting (see text). Translational research converts this knowledge into clinically usable tools: disease-models become disease-diagnoses, markers of a biological process become diagnostic biomarkers, animal models can be used for preclinical studies which could ultimately lead to human trials. Applied scientific research, i.e. clinical research, takes no advantage of any epistemological framework and is perfectly compatible with other kinds of diagnoses such as disorder-diagnoses. It is a pragmatic stage of medical innovation which comes with a major involvement of industrial R&D. Clinical research aims at demonstrating and optimizing the efficacy and safety of medical procedures and at providing the factual evidences on which regulatory agencies, medical associations or experts-consensus can acknowledge their transfer to clinical practice (evidence-based medicine).

Phenotypes and disease-models have not been investigated by psychiatric research for the last 40 years, which might account for its limited success in finding robust biological correlates, especially in the field of psychosis. Even though the ICD and the DSM define categorical diagnoses, these are diagnoses for ***disorders***, i.e. behavioral or mental conditions of clinical relevance[10]. As opposed to phenotypes, disorder-diagnoses are purely elaborated through ***consensus*** rather than by ***optimizing their natural foundations***. Moreover, in contradistinction with diseases, disorders remain ***atheoretical*** by definition[11]. Whereas clinical research can adapt to this consensual-atheoretical approach, this is not the case for biological research. From a clinical research perspective, using the disorder-diagnosis of schizophrenia would neither preclude the serendipitous discovery of chlorpromazine's antipsychotic properties nor impede to prove the therapeutic efficacy of other (Me-To) D2 blocking drugs[12]. However, from a biological research perspective, if schizophrenia is not an appropriate phenotype to start with, there will be no disease-model, and consequently no basic scientific finding to translate into clinical research[1].

The question of diagnostic ***validity*** that return to the front stage when the DSM-5 was put on the agenda, addressed the need to shift from disorder- to disease-diagnoses[13]. Whereas considering the usefulness of stable disorders-diagnoses for clinical research and practice, the DSM-5 and the ICD-11 finally did not endorse any change, basic research can now be published out of their diagnostic framework. Surprisingly however, major alternatives, such as DSM-5 section III[14], RDoCs[15], SyNoPsis[16] or HiTOP[17], refrain from resuming the biomedical paradigm, even in the field of psychoses. The sole research program that follows its line is the

***Wernicke-Kleist-Leonhard*** pathway (WKL)[18]. On a period spanning 3 generations, these clinicians empirically optimized credible ***phenotypes***, sorting out patients based on long-term catamnestic investigations and using symptom-complex, longitudinal, prognostic and family aggregation principles[1,19]. Instead of what is currently viewed as a schizoaffective continuum, they managed to discriminate 35 major phenotypes which are unsurprisingly poorly concordant with disorder-diagnoses ($\lambda$ = 0.4 - 0.56)[20]. Criticized for being too ***atomistic***, we rather view their ***splitting*** approach, i.e. defining rare but very coherent phenotypes, as more likely to lead to the discovery of potential biomarkers when comparing groups. Indeed, neurology provides us with many examples of its success relative to the ***lumping*** approach so popular in our discipline. Moreover, starting from an overly narrow phenotype does not preclude the description of its full clinical spectrum. Once the biomarker has been identified, it can be used to identify undiagnosed individuals enriching and expanding its clinical presentations in an ***inverted psycho-pathology*** - reverse phenotyping approach[21,22].

## 2. Periodic catatonia

***Periodic catatonia*** (PC) is one of the WKL-phenotypes with the highest construct validity and for which a disease-model is supported by some evidences, i.e. validity *per se*. The ***prevalence*** of PC in patients referred to psychiatric hospitals for endogenous psychoses has been consistently estimated to be about ***10%*** (n = 438/4433, 4 German university centers)[23–26]. PC has a ***progressive-remitting*** course in ***98.5%*** of the cases[23] which episodes are diagnosed as affective or psychotic disorders, specified as having catatonic features in a minority of cases: 6% of first hospitalized patients, 20% after an average of 13 years of evolution[27]. From a WKL perspective, the term of "catatonia" indicates that the core dysfunctional domain is ***psychomotricity*** and that it will be impaired on the long run. Psychomotor functions account for the coherent coupling between drive, affect and behavior and their most direct readouts are expressive movements[28]. During PC-episodes, these can be either mainly excited or mainly inhibited, with both kinds being reported in ***86%*** of cases on the long run, corresponding to a ***bipolar*** feature from a WKL standpoint[23]. Most typically, the two poles occur at the same time resulting in hyperkinetic body segments while the others are akinetic. This combination is responsible for a stiff and awkward motor aspect and for distorted face and body expressions up to grimacing and parakinesia. The residual state of PC progressively builds-up after each relapse and consists in persistent mild psychomotor anomalies together with varying amount of abulia and affective blunting [29]. PC is a phenotype with high ***construct validity***: it is reliable, even when compared to other WKL-psychomotor phenotypes (inter-rater agreement $\kappa$ = 0.93)[30], it is life-long consistent ($\kappa$ = 0.79 at 30 years interval)[31]. It also demonstrates an interesting differential validity on several outcomes among which the most striking are its familiality and its therapeutic response. Actually, ***27%*** of PC ***first-degree relatives*** are affected by the same phenotype without cross liability[25]. Hence, ***60%*** of index cases have an affected sibling, parent or even child[30], and 15.4 % of the pedigrees extend over 3 generations[32]. Regarding its therapeutic response, antipsychotics[33,34] and all interventions that reinforce cortical inhibition, e.g. benzodiazepines[35] and electroconvulsive therapy[36], are effective in PC but not in the other WKL-catatonic phenotypes that are called system catatonias[33–36].

The etiological genetic model for PC suggested by its autosomal dominant inheritance with incomplete penetrance is supported by the replication of a chr15q14-15 locus[37,38]. Unfortunately, gene-findings were precluded by the genetic heterogeneities of the

phenotype, not only different mutations but also different genes seemed to be implicated in different pedigrees. Yet, these might converge towards a pathophysiological bottleneck. The co-occurrence of hyper and hypo-kinetic features and their responsiveness to GABAergic interventions fostered the hypothesis that PC could be accounted for by defective lateral inhibition in sensorimotor regions and premotor cortices either medial, i.e. supplementary motor area (SMA), or lateral (LPM). This pathophysiological model was first supported by the reduced binding for $GABA_A$ receptors radioligand in the left sensorimotor cortex of schizoaffective patients having ≥3 catatonic symptoms[39]. New evidence came from the increase of cerebral blood flow (rCBF) in the SMA and the left LPM (L-LMP), when patients with acute DSM-schizophrenia having ≥2 catatonic symptoms were compared to those with 1 or less[40]. Considering the 10% prevalence of PC relative to the 20% prevalence of patients with ≥2 catatonic symptoms[41], it can reasonably be assumed that PC might have chiefly contributed to these results. This interpretation was further supported by a study specially focusing on the PC-phenotype during its residual state, in which a large left-sided network of sensorimotor and premotor regions was hyper-perfused regardless of the comparison group, whether it was healthy controls or non-PC patients with schizophrenia spectrum disorder diagnosis under the same medication regimen[42]. The disregard of PC phenotype might not only be accounted for by the current distrust in categorical approaches. Its diagnosis remains difficult to assure as it relies on clinical skills that have been left aside for four decades. The core psychomotor signs of PC are commonly overlooked either because they are taken for antipsychotics side-effects or because they are considered less relevant than the more familiar and hence salient affective or psychotic manifestations. Hopefully, this state of affairs might change with the revived interest in motor disturbances driven by key opinion leaders[43,44] and the recent RDoC's adoption of a sensorimotor domain[45]. Yet, the development of a diagnostic biomarker for PC would help the diffusion of this phenotype-diagnosis for biological and clinical research.

# 3. Pseudo-compulsive catatonia (pCC)

pCC belongs to system catatonias. These are not really considered as possible "different diseases" but rather as phenotypes related to the impairment of ***different neuropsychological systems*** possibly accounted for by the same cause(s), as strokes, multiple sclerosis or degenerative diseases can lead to various clinical manifestations depending on the location of the neuronal damage. "***System***" should be understood here in its neurological sense, i.e. as a specific ***brain functional network***.

All system schizophrenias, to which system catatonias belong, have been conceptualized like ***encephalitic processes***. Accordingly, a process and a residual phases are described. During the ***process phase***, neuronal damages are supposed to progress due to an unknown pathological mechanism which is further responsible for various ***accessory symptoms***, not necessarily related to the affected system, e.g. psychotic or affective disorders. This active pathological process is hypothesized to abate after 2-3 years, making the transition with the ***residual phase***. Here, the brain lesions are supposed to be fixed. This is supposed to account for the stable and monomorphic clinical picture during this phase in which the symptom-complex remains unchanged until the end of patient's life, except for modest variations in intensity.

pCC follows this typical course and is one of the final residual states that can ensue. Its first core features are the occurrence of rituals, i.e. ***compulsive-like*** complex behavior and/or omissions, i.e. avoidance of specific behaviors. As opposed to obsessive-compulsive disorders, these are "pure" compulsive-

like behaviors, unsupported by congruent obsessive ideas and the anxious reactions that ensues. This doesn't mean that the patient is never anxious, but that his anxiety is not focused and not evoked when prompting the patient to stop his rituals or to do his omissions. These demands rather trigger irritation. Pseudo-compulsions are not associated with egodystonic feelings and the symptoms are mostly accepted even if patients might recognize them as meaningless (incomplete insight). There is no spontaneous attempt to fight against them.

The second core feature of pCC is the ***progressive stiffness and rigidity*** of posture and movements mainly on affective and reactive motor behaviors.

While many other catatonic symptoms might occur during the process phase, they are not part of the residuum, i.e. there are no parakinesia, verbigeration, negativism (differential diagnosis with omissions which can grow up to complete motor arrest), stereotypies or short-circuit responses.

***Remarks***

- Rituals and omissions were originally referred to as "mannerism" in the original textbook, hence the original label of manneristic catatonia to name it. Considering the gap between the pCC concept and the current understanding of this term, the WKL international society has decided to change its English name in pseudo-compulsive catatonia.
- Operational criteria have been elaborated but remain under evaluation (see http://www.cercle-d-excellence-psy.org/en/informations/classification-de-wkl/psychoses-endogenes/manneristic-catatonia/).
- pCC generally comes with a much more severe chronic impairment than PC.

# 4. Additional figures

## Figure 1

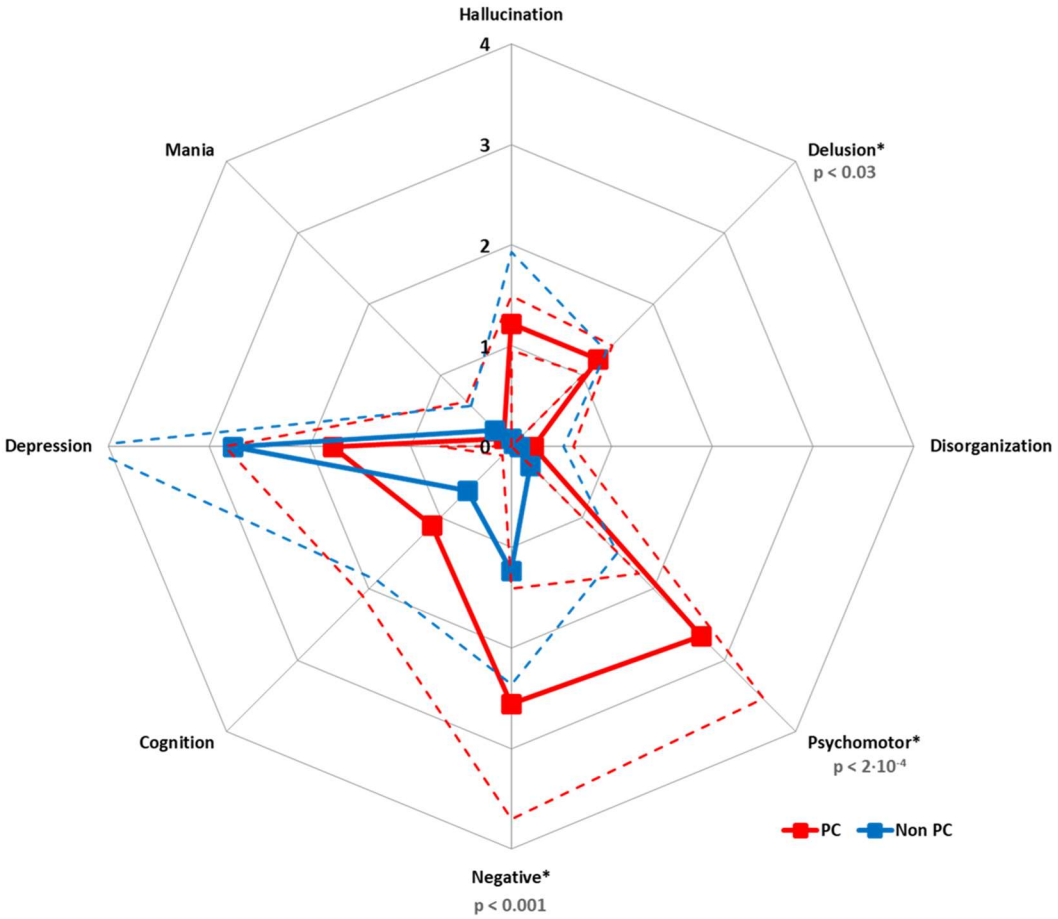


***Figure 1. Clinician-Rated Dimension of Psychosis Symptom Severity***. Mean values for PC (red) and non-PC (blue) in solid lines and standard deviations in dotted lines. The two groups significantly differed for the delusion, psychomotor and negative symptoms dimensions (2-sided t-test, p-value in gray).

**Figure 2**

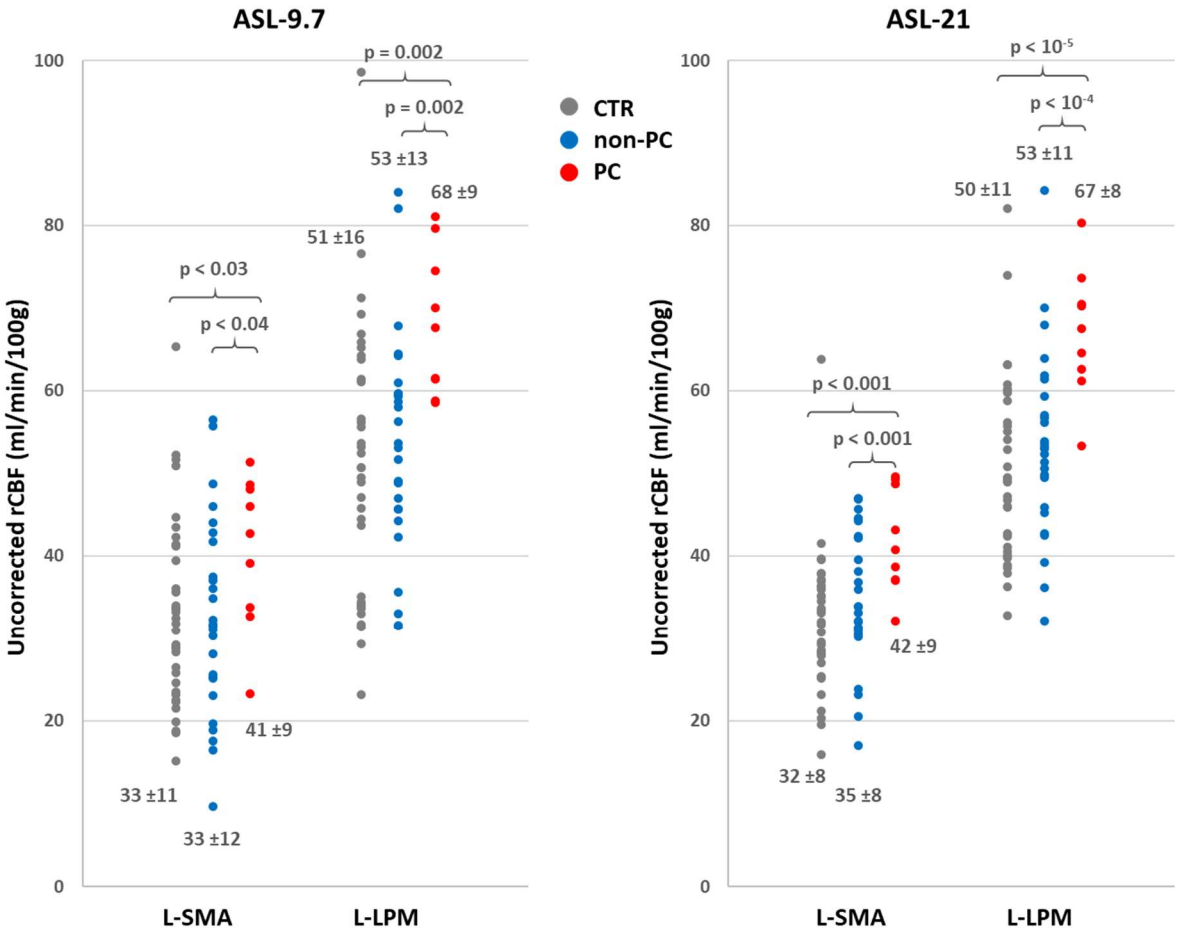


***Figure 2. Absolute rCBF values in ml/min/100g***. Values are uncorrected for global rCBF and age. Values for controls (grey), non-PC (blue) and PC (red) are given for ASL-9.7 (left) and ASL-21 measurements (right). Means ± standard deviations of each group are written in grey. PC had higher raw rCBF values either compared to non-PC patients or controls (1-sided t-test).

# 5. Additional tables

**Table 1**

| | ASL-9.7 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Se** | **CI** | **$P_{Se}$ > 0.5** | **Sp** | **CI** | **$P_{Sp}$ > 0.5** | **Youden's J** | **AUC** |
| L-SMA | 66% | 35% - 89% | 0.84 | 92% | 78% - 98% | 1 | 0.58 | 0.78 |
| L-LPM | 98% | 76% - 100% | 1 | 91% | 78% - 98% | 1 | 0.89 | 0.97 |
| L-SMA ∨ L-LPM | 98% | 76% - 100% | 1 | 84% | 68% - 95% | 1 | 0.82 | 0.97 |
| | **ASL-21** | | | | | | | |
| L-SMA | 55% | 25% - 83% | 0.63 | 95% | 83% - 100% | 1 | 0.50 | 0.88 |
| L-LPM | 87% | 58% - 99% | 0.99 | 84% | 68% - 95% | 1 | 0.71 | 0.96 |
| L-SMA ∨ L-LPM | 98% | 58% - 99% | 0.99 | 88% | 72% - 97% | 1 | 0.86 | 0.97 |
| | **ASL-9.7 ∧ ASL-21** | | | | | | | |
| L-SMA | 55% | 25% - 83% | 0.63 | 99% | 90% - 100% | 1 | 0.54 | 0.78 |
| L-LPM | 98% | 76% - 100% | 1 | 92% | 78% - 98% | 1 | 0.90 | 0.99 |
| L-SMA ∨ L-LPM | 98% | 76% - 100% | 1 | 96% | 83% - 100% | 1 | 0.94 | 0.99 |

***Table 1. Re-computation of discriminant performances*** after discarding the 5 patients with significant MRI or motor anomalies on examination (excluding patients RD05, 08, 10, 13 and 23).

**Table 2**

| Condition | PC prev. | PPV | NPV |
|---|---|---|---|
| Psychotic inpatient | 10% | 73% | 100% |
| ↳ No affected 1$^{rst}$ deg. relative | 6% | 61% | 100% |
| ↳ ≤ 1 relapse | 1% | 20% | 100% |
| ↳≥ 2 relapses | 8% | 68% | 100% |
| ↳Bipolar | 13% | 79% | 100% |
| ↳≥ 2 catatonic Σ | 18% | 84% | 100% |
| ↳≥1 affected 1$^{rst}$ deg. relative | 18% | 84% | 100% |
| ↳≤ 1 relapse | 2% | 33% | 100% |
| ↳≥ 2 relapses | 23% | 88% | 99% |
| ↳Bipolar | 34% | 93% | 99% |
| ↳≥ 2 catatonic Σ | 43% | 95% | 98% |
| ↳ORC for PC | 64% | 98% | 96% |

***Table 2. Re-computation of predictive values*** inferred from the discriminant performances of the combo test computed after discarding the 5 patients with significant MRI or motor anomalies on examination (Se = 98% and Sp = 96%, see table 1).

**Table 3**

| | ASL-9.7 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Se** | **CI** | **$P_{Se}$ > 0.5** | **Sp** | **CI** | **$P_{Sp}$ > 0.5** | **Youden's J** | **AUC** |
| L-SMA | 66% | 35% - 90% | 0.84 | 87% | 65% - 97% | 1 | 0.53 | 0.76 |
| L-LPM | 98% | 76% - 100% | 1 | 99% | 86% - 100% | 1 | 0.97 | 1 |
| L-SMA ∨ L-LPM | 98% | 76% - 100% | 1 | 87% | 66% - 97% | 1 | 0.85 | 0.99 |
| | **ASL-21** | | | | | | | |
| L-SMA | 55% | 26% - 83% | 0.63 | 93% | 74% - 99% | 1 | 0.48 | 0.94 |
| L-LPM | 87% | 58% - 99% | 0.99 | 87% | 66% - 97% | 1 | 0.74 | 0.95 |
| L-SMA ∨ L-LPM | 98% | 76% - 100% | 1 | 81% | 58% - 94% | 1 | 0.79 | 1 |
| | **ASL-9.7 ∧ ASL-21** | | | | | | | |
| L-SMA | 55% | 25% - 83% | 0.63 | 99% | 86% - 100% | 1 | 0.54 | 0.85 |
| L-LPM | 98% | 76% - 100% | 1 | 98% | 86% - 100% | 1 | 0.96 | 0.98 |
| L-SMA ∨ L-LPM | 98% | 76% - 100% | 1 | 98% | 86% - 100% | 1 | 0.96 | 0.99 |

***Table 3. Re-computation of discriminant performances*** after discarding the 3 patients with system catatonia (pCC01, 02 and 03) and the 5 patients with significant MRI or motor anomalies on examination (RD05, 08, 10, 13 and 23).

**Table 4**

| Condition | PC prev. | PPV | NPV |
|---|---|---|---|
| Psychotic inpatient | 10% | 84% | 100% |
| ↳ No affected 1$^{rst}$ deg. relativ | 6% | 76% | 100% |
| ↳ ≤ 1 relapse | 1% | 33% | 100% |
| ↳ ≥ 2 relapses | 8% | 81% | 100% |
| ↳ Bipolar | 13% | 88% | 100% |
| ↳ ≥ 2 catatonic Σ | 18% | 91% | 100% |
| ↳ ≥1 affected 1$^{rst}$ deg. relative | 18% | 91% | 100% |
| ↳ ≤ 1 relapse | 2% | 50% | 100% |
| ↳ ≥ 2 relapses | 23% | 94% | 99% |
| ↳ Bipolar | 34% | 96% | 99% |
| ↳ ≥ 2 catatonic Σ | 43% | 97% | 98% |
| ↳ ORC for PC | 64% | 99% | 96% |

***Table 4. Re-computation of predictive values*** inferred from the discriminant performances of the combo test computed after discarding the 3 patients with system catatonia and the 5 patients with significant MRI or motor anomalies on examination (Se = 98% and Sp = 98%, see table 3).

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