Supplemental information n°1

# General Information Regarding the WKL Classification with Special Focus on Periodic Catatonia and Cataphasia

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### Overview of the WKL classification

The WKL phenotypes are consistent with the naturalist paradigm of traditional scientific medicine<sup>1</sup>. Although the failure of the international classifications, i.e. ICD and DSM, raised doubt about the adaptation of this paradigm to endogenous psychosis, the WKL school suggests that this failure is not due to the paradigm itself, but to the inappropriateness of the diagnostic entities. The only requirement for reliability<sup>2</sup> made researchers lose the perspective of what is the core of the traditional medical paradigm, i.e. the natural foundation of "morbid entities".

The Wernicke-Kleist-Leonhard school has proposed such natural phenotypes<sup>3</sup>. These have been elaborated on diachronic observations, using three variations of the principle of parsimony, to optimize the description process:

- 1. The elementary symptom principle, which calls for an interpretation of the symptomcomplex to distinguish elementary symptoms, close to the disordered process, from secondary symptoms, that result from them.
- 2. The longitudinal principle, which stipulates that whatever the polymorphic presentation, one patient can be affected by one phenotype only.
- 3. The family aggregation principle, which assumes that in multiplex families, members should be affected by the same phenotype.

This results in thirty-five major phenotypes (see table 1) of good reliability<sup>4</sup>, but also good predictive validity<sup>5</sup> and good differential validity on age of onset, inheritance, fetal event and treatment response<sup>3</sup>. International classifications did integrate the bipolar / unipolar concept of the WKL school although in a too much downgraded form to preserve its natural foundations. Please confer to our epistemological review article for a short account of the validity of this classification<sup>3</sup> and to the reference book<sup>6,7</sup> for clinical details. The following lines will focus only on two phenotypes: cataphasia and periodic catatonia.

Course	Familly	Psychic component				–Polarity
Course		Affect		Thougth	Psychomotricity	Polarity
Relapsing-remitting	Phasic affective psychoses	Pure depressions	Pure euphorias			
		Agitated D.	Unproductive E.			2
		Hypochondriacal D.	Hypochondriacal E.			Monopolar
		Self-tortured D.	Exalted E.			ğ
		Suspicious D.	Confabulatory E.			<u>e</u>
		Non-participatory D.	Non-participatory E.			Ĩ
		Pure melancolia	Pure mania			
		Manic-depressive psychosis				_
	Cycloïd psychoses	Anxiety-happiness psychosis		Excited-inhibited confusion psychosis	Hyperkinetic-akinetic motility psychosis	Bipolar
Relapsing progressive	Non system schizophrenias	Affective paraphrenia		Cataphasia	Periodic catatonia	
Progressive		(System) hebephrenias		System paraphrenias	System catatonias	
		Foolish H. Eccentric H.		Hypochondriacal P.	Parakinetic C.	Monomorphic
				Phonemic P.	Manneristic C.	
	System	Shallow H.		Incoherent P.	Proskinetic C.	ion
	schizophrenias	Autistic H.		Fantastic P.	Negativistic C.	Ĭ
		Combined H. (6)		Confabulatory P.	Speech-prompt C.	phic
				Expansive P.	Sluggish C.	
				Combined P. (15)	Combined C. (15)	

Table 1. Overview of the WKL phenotypes<sup>3</sup>. Only the 35 major forms are displayed, the 36 minor forms are two by two combinations of system-schizophrenias.

### Cataphasia

Follow the link for a more complete account on this phenotype : <u>http://www.cercle-d-excellence-psy.org/en/informations/classification-de-wkl/psychoses-endogenes/cataphasie/</u>

### Introduction

Cataphasia is one of the most common "schizophrenic" phenotype, accounting for about 7% of endogenous psychoses which gives an estimated prevalence of 0.1 to 0.2% in Germany<sup>8</sup>.

This phenotype has a relapsing-progressive course in about 80% cases. The remaining 20% cases are showing either a progressive development or look as if they didn't remit from the onset. During the episodes, the patients might show up a variety of affective and psychotic symptoms which explain why they can be labeled of whatever ICD / DSM diagnosis between mood disorders and psychotic disorders, including catatonia. However, the core symptomatology according to the WKL school<sup>9</sup> consists in a disordered logic, a sort of looseness of associations and a specific language disorder, involving both syntax and semantic. These symptoms remain discreet after the first episode, but progress with recurrences. The impairment of thought process is also mainframe to the clinical expression within the episodes with a bipolar feature as the thought process can be excited (35%) as well as inhibited (43%), and sometimes shows more mixed features (22%). The excited pole has been described by Kraepelin under the label "schizophasia"<sup>10, p.859</sup>. If the symptomatology is commonly dominated by one pole in one patient, the two poles can be seen in multiplex families. Indeed, it was the family aggregation principle that disclosed the relation between episodes of schizophasia and of the less characteristic clinical presentation dominated by thoughts' inhibition<sup>11</sup>. As the disease progresses, beside the typical "deficit" syndrome, there might be persistent psychotic symptoms, mostly as loose persecutory ideas due to a lake of understanding, as seen in aging or in partially remitted Wernicke aphasia<sup>12</sup>, or verbal hallucinations.

The language disorders are quasi-pathognomonic, although there might be some dialectal differences. German, for example, has a rigorous syntax which eases the detection of paragrammatical errors, whereas the same might be taken as a figure of speech in French. On the lexical side, German allows the buildup of new words by simple combinations of existing words. The use of a semantically close but inappropriate elementary word in a combination is easily detected as a neologism. While new word construction can also be seen in French, e.g. prefix or suffix added to the inappropriate word stem, the most frequent manifestations are word approximations or semantic paraphasias<sup>13</sup>. The "psychic experimental test", which is a general instrument used by the WKL school to assess thoughts and language disorders, greatly sensitize the detection of such errors<sup>8,13,14</sup>. However, their significance depends on the patient's language skills and thus are harder to detect in non-native speakers or low IQ patients. The TePEO-C used in this article is an operationalized version of this psychic experimental test, dedicated to the specific cataphasic signs<sup>13</sup>. Of note, there is certainly some trouble in understanding, but these are more difficult to evaluate<sup>15</sup>.

Cataphasic episodes improve well with classical neuroleptics in 78% of the cases<sup>16,17</sup>. Males are more frequently and more severely affected than females with a ratio of one woman for three men<sup>18</sup>, which might reflect sex differences in language vulnerability to brain lesion<sup>19</sup>. Disorganization, associated with emotional turmoil, appears to be particularly at risk for suicidal behaviors (52% of patients) and deaths by suicide (18% of patients)<sup>8</sup>. The phenotype shows familial aggregation, with 15 to 25% of affected first degree relatives, on top of which 12% of non-psychotic first degree relatives are also displaying the typical thought and language disorder<sup>8,20,21</sup>. Thus, if the core phenotype was defined by the mere residual symptoms, the cumulative amount of affected first degree relatives would be of 37%. This opens the possibility that the affective and psychotic

manifestations are only unspecific and variable brain reactions to an unknown brain damaging process in the same way than organic psychoses.

### Criteria

### Introductory remarks

We have no doubt that classical WKL diagnosis is exceeding the operational criteria we propose here. Their main purpose is to allow a way to replicate these results among different research groups, a requirement for scientific objectivity<sup>22</sup>. Indeed, it is unlikely that in the current competing context, clinicians and researchers will take the one to four years necessary for a clinician to be able to make reliable WKL diagnosis.

Because negative results might be mostly due to heterogeneity in the patient's group, these criteria favor specificity over sensitivity. Accordingly, they do not account for the full spectrum of cataphasia, and some genuine cataphasic patients might not be diagnosed as such using them. As an example, the requirement for a relapsing-progressive course is just an easy way to limit the risk of including other phenotypes, mostly system schizophrenia, even though this criterion will be only filled by 80% of cataphasic patients. Thus, they are not adapted for epidemiologic or genetic research which should keep on with the classical WKL approach.

These criteria remain work in progress. Especially, they have not been validated in other groups than ours, and as such, we cannot guaranty that they will work as well for non-WKL trained investigators.

These criteria are inspired from those put forward by the Würzburg school, those of Sigmund<sup>23,24</sup> and DRC Budapest-Nashville<sup>25,26</sup>. Although the specific language distortions are well characterized in German and French, they might have to be refined in English and other language.

Finally, as this study was not concerning epidemiology, heredity or genetics, we also included the family aggregation principle as a minor criterion.

### Using the criteria

The background idea is simply to combine typical symptoms, i.e. qualitative disturbance of thought and language, with a typical course, i.e. of relapsing-progressive type. Since the former is rarely reported in ICD / DSM oriented case-notes, the criteria require prospective observation. When symptoms are too poorly characteristic, a cataphasic first-degree relative is required. Here are the different scenarios:

- 1. Previous episodes are compatible + Observed episode with typical symptoms + Observed remission with typical OR non-typical residuals symptoms.
- 2. Previous episodes are compatible + Observed remission with typical residual symptoms ± Observed episode with non-typical symptoms.
- 3. Previous episodes are compatible + Observed episode with non-typical symptoms + Observed remission with non-typical residual symptoms + affected first degree relative.

### Compatible previous episode(s)

For patients with a(many) previous episode(s) that was(were) not observed with the WKL classification in mind, the compatibility of previous episode(s) shall be assured.

#### Inclusion criteria

The following ICD diagnosis are compatible:

- Affective psychosis (anxiety, depression, mania or other kind of bipolar episode), no necessary psychotic feature.
- Psychotic episode of any kind except purely delusional.

### Exclusion criteria

At least one episode not secondary to:

- drug use or withdrawal.
- a general medical condition.
- a severe stressor, i.e. no reactive psychosis.

### Observed episode with non-typical symptoms

Must be prospectively collected or retrospectively assessed on videotaped interview as it is very unlikely that ICD / DSM oriented case-notes can be helpful. The current episode can fulfill any of the ICD diagnosis criteria mentioned in the "compatible episode" section.

### Criteria for the inhibited phase

At least, two items present during a sufficient amount of time:

- Extreme slowing of thought and speech up to mutism.
- Slowness predominating on movements requiring reflection relative to reactive and expressive movements.
- Patient's facial expression is dazed (hebetude), reflecting his inability to figure what is going on around him.

### Criteria for the excited phase (schizophasia)

Both criteria must be present (logical AND) at least during a significant amount of time:

- Logorrhea without pressure of speech (fill silences, no affectively driven pressure of speech).
- Various forms of disorganized speech (discourse): looseness of associations, derailments, digressions.

### Exclusion criteria

Not secondary to:

- Drug use or withdrawal.
- A general medical condition.
- A severe stressor, i.e. no reactive psychosis.

### Observed episode with typical symptoms (core symptoms)

Must fulfill the "Observed episode with non-typical symptoms" and at least two of the following criteria, prospectively assessed by the psychic experimental test:

- Syntactic disorders, i.e. paragrammatic sentences.
- Lexical disorders, i.e. word approximation, paraphasic errors up to neologism.
- Logical disorder and / or conceptual confusion, i.e. a special form of inability to converge toward the distinction between two concepts, e.g. difference between a child and a dwarf, between a river and a lake.

### Observed residual state

Although full or nearly full recovery can be observed after the first episode, residual symptoms should be present in case of > 2 relapses, either typical or non-typical.

### Exclusion criteria (out of the episode)

- Staring in the middle position or true catatonic symptoms according to WKL, i.e. parakinesia, true negativism (i.e. with ambitendance), waxy flexibility (with posture maintenance) ...
- Systematized chronic paranoiac delusion with a designated persecutor OR a delusion purely connected to affect/passion, i.e. erotomania, jealousy.
- Grossly disorganized behavior, i.e. there should be a striking difference between speech disorganization and the ability of the patient to behave rather normally in a familiar environment.

### Observed residual state with typical symptoms (core symptoms)

Should not have exclusion criteria for "observed residual state" + at least two of these symptoms:

- Syntactic disorders, i.e. paragrammatic sentences.
- Lexical disorders, i.e. word approximation, paraphasic errors up to neologism.
- Logical disorder and / or conceptual confusion, i.e. a special form of inability to converge toward the distinction between two concepts, e.g. difference between a child and a dwarf, between a river and a lake.

### Residual state with non-typical symptoms and an affected first-degree relative

Should not have exclusion criteria for "observed residual state" + one of these symptoms:

- Various forms of disorganized speech (discourse): looseness of associations, derailments, digressions.
- Incomplete insight.

+ An affected first-degree relative.

### Periodic Catatonia

Follow the link for a more complete account on this phenotype: <u>http://www.cercle-d-excellence-psy.org/en/informations/classification-de-wkl/psychoses-endogenes/catatonie-periodique/</u>

### Introduction

Periodic catatonia is roughly as common as cataphasia, also accounting for about 7% of endogenous psychoses suffering patients.

During the episodes of WKL periodic catatonia, affective and psychotic symptoms might dominate the clinical presentation. This explains why the ICD / DSM catatonia diagnosis is rarely done in these cases despite the name. Most frequently these patients are diagnosed with depressive, bipolar, schizoaffective, schizophrenic, or non-otherwise specified psychotic disorders<sup>27</sup>. During the episodes, it is very unlikely to be able to distinguish periodic catatonia from cataphasia using a mere dimensional approach since these patients may also have severe disorganized speech. However, this disorganization is qualitatively different as it is secondary to the disordered psychomotricity, e.g. agrammatic chunk of sentences, changing topics without logic... In the WKL perspective, the core of the phenotype is the combination of quantitative and qualitative changes in psychomotricity. These changes are not only within the episode, but also persist in between as residual symptoms<sup>9</sup>. Quantitative changes are bipolar as they can show up both poles: akinesia, hyperkinesia but also most frequently a mix of the two, e.g. fixe gaze and facial stiffness associated with stereotyped movement and impulsive actions. Qualitative changes are typical, although not pathognomonic, but are frequently transient, e.g. parakinesias<sup>9</sup>. These mostly affect expressive movements which appear clumsy, awkward, bizarre, resulting in grimacing facial expressions. The course of periodic catatonia is typically relapsing-progressive in more than 90% of the cases and purely progressive in the others. Residual symptoms are discrete at the beginning but progress with episode's repetition. They are dominated by aboulia and reduced emotional expression occasionally accompanied by more specific motor disorganization, e.g. grimacing or parakinesias<sup>9</sup>. Residual psychotic symptoms are rare and social or occupational impairment is intermediate with an average GAF of 60 ±20<sup>28</sup>. John Forbes Nash and his affected son, John Charles Martin Nash, respectively illustrate a residual and mildly excited state of this phenotype (follow this link: http://www.cercle-d-excellence-psy.org/en/clubpsychose/cas-cliniques/celebrites/john-f-nash/).

Episodes respond to classical neuroleptics only in 60% of the cases<sup>16,17</sup>, but it is the phenotype in which the switch to clozapine and perhaps olanzapine give the greatest benefit<sup>29,30</sup>. Periodic catatonia has repeatedly been shown to be heritable, with 21-26% of affected first degree relatives<sup>20,21,31</sup>, which is significantly larger than the more severe system catatonias (3%), another WKL family of catatonic disorders<sup>32</sup>, and also more than the more benign hyperkinetic-akinetic motility psychosis (5% - cf. warning). Episodes can be discreet and some patients might be taken for a schizotypal personality while some relatives may show the typical residual psychomotor symptoms, especially the non-psychotic obligate carriers. If such non-psychotic relatives<sup>33</sup>. A striking feature in multiplex families is the anticipation phenomenon with children sometimes starting the illness before the parents<sup>34</sup>. A genome-wide linkage study found evidence for a major susceptibility locus on chromosome 15q15 in most of the pedigrees assigning this phenotype to MIM 605419 in the Mendelian Inheritance in Man catalogue<sup>35,36</sup>. However, there are evidences for genetic heterogeneity as at least one other locus has been reported on chromosome 22q for a small set of pedigrees not related to chromosome 15<sup>36</sup>.

*Warning:* The WKL concept has a misleading homonym in the literature with which it is frequently confused, i.e. Gjessing's periodic catatonia<sup>37</sup>. Yet, it should be distinguished from the WKL phenotype. Gjessing's entity is merely characterized by periodic bouts of pure akinesia which fill ICD / DSM criteria for catatonia. It mostly corresponds to another WKL phenotype: hyperkinetic-akinetic motility psychosis, which belongs to the cycloid psychoses family. This phenotype is characterized by pure quantitative changes in psychomotricity, has a purely relapsing-remitting course and thus have a more benign outcome. It is most likely caused by slight brain damage acquired during the fetal development while its hereditary burden is not significantly different from controls.

### Criteria

### Introductory remarks

Although the same general remarks seen for cataphasia operational criteria prevail for periodic catatonia, there are some specific features.

Firstly, there is no doubt that the classical WKL diagnosis is superior to the following operational criteria. Their main purpose is to propose a way to replicate our results by clinicians unfamiliar with the WKL classification.

To preserve group homogeneity, these criteria favor specificity over sensitivity and thus do not cover the full symptomatic spectrum of periodic catatonia. The requirement for a relapsing progressive course is a good example of the limits of these criteria. Such course will not consider the 10% of genuine periodic catatonic patients with purely progressive development. Yet, it is practical for avoiding confusion with system catatonia. In the other way, periodic catatonia without persistent symptoms after  $\ge 2$  relapses will be discarded to avoid misdiagnosis with motility psychosis. Although this might be rarely observed for trained clinicians, it might be more frequent for investigators unfamiliar with this phenotype. Of note, we warn clinicians not to use the following criteria for epidemiologic or genetic researches.

These criteria remain work in progress. We work hard to make them operative and to validate them, but we cannot guaranty their direct usability by non-WKL trained investigators. Specifically, the detection of parakinesia might require a minimal formation.

The criteria are inspired from those put forward by the Würzburg school, those of Sigmund<sup>23,24</sup> and DRC Budapest-Nashville<sup>25,26</sup>. We urge researchers not to apply the misleading logic of recurrent episode of ICD / DSM catatonia = periodic catatonia. As stated previously, this might be more typical for hyperkinetic-akinetic motility psychosis. Since qualitative distortion of psychomotricity and psychomotor negativism exclude this diagnosis, they should be especially look for. Considering that the latter is not a mere ICD / DSM negativism. We can only advise clinicians and researchers to get trained on videos and supervised in clinical settings.

Finally, as this study was not concerning epidemiology, inheritance or genetics, we also included the family aggregation principle as a minor criterion.

### Using the criteria

The background idea is simply to combine typical symptoms, i.e. qualitative disturbance of psychomotricity, with a typical course, i.e. of relapsing-progressive type. Because the former is rarely reported in ICD / DSM oriented case-notes, the criteria require their direct observation by the evaluator. When symptoms are too poorly characteristic, an affected first-degree relative is required.

- 1. Previous episodes are compatible + Observed episode with typical symptoms + Observed remission with typical OR non-typical residuals symptoms.
- 2. Previous episodes are compatible + Observed remission with typical residual symptoms ± Observed episode with non-typical symptoms.
- 3. Previous episodes are compatible + Observed episode with non-typical symptoms + Observed remission with non-typical residual symptoms + affected first-degree relatives.

### Compatible episode(s)

For patients with one or many previous episode(s) not observed with the WKL classification in mind, the compatibility of previous episode shall be assured.

### Inclusion criteria

The following ICD diagnosis are compatible:

- Affective psychosis (anxiety, depression, mania or any other bipolar episode) no necessary psychotic feature.
- Psychotic episode of any kind except purely delusional.

### Exclusion criteria

At least one episode not secondary to:

- Drug use or withdrawal.
- A general medical condition.
- A severe stressor, i.e. no reactive psychosis.

### Observed episode

Must be prospectively collected or retrospectively assessed on videotaped interview as it is very unlikely that ICD / DSM oriented case-notes can be helpful.

The current episode can fulfill any of the ICD diagnosis criteria mentioned in the "compatible episode" section.

#### Criteria for the akinetic pole

Both criteria must be present (logical AND):

- Akinesia OR stiff, empty facial expression OR stupor.
- Strange postures OR mutism OR depressive or anxious mood.

#### Criteria for the hyperkinetic pole

Both criteria must be present (logical AND):

- Hyperkinesia OR psychomotor restlessness non-influenced by external stimulation.
- Elated mood OR impulsive actions or talking OR purposeless aggression

#### Exclusion criteria

Not secondary to:

- Drug use or withdrawal.
- A general medical condition.
- A severe stressor, i.e. no reactive psychosis.

### Observed episode with typical symptoms

Must fulfill the diagnosis for "observed episode" + the intermittent presence of one of these symptoms. It may last only an hour in an episode of several months:

- Mixed motility disorder: some segments or limbs or face are akinetic while others are hyperkinetic.
- True psychomotor negativism, i.e. with evoked ambitendency.
- Parakinesia.
- Distorted facial expression (inappropriate gesture/expression).
- Waxy flexibility OR true catalepsy, i.e. not simple "Haltungsverharren".

### Observed episode with non-typical symptoms

Must fulfill the diagnosis for "observed episode" + the intermittent presence of one of these symptoms:

- Fixed gaze.
- Motor or speech perseverations.
- Stereotypies or iterations neither caused by affective tension nore by thought inhibition, i.e. not a mere release phenomenon.

### Observed residual state

Although full or nearly full recovery can be observed after a first episode, residual symptoms should be present in case of > 2 relapses either typical or non-typical.

### Exclusion criteria

- Illogicality or blurring of concepts OR syntactic or semantic disorder of language persisting between episodes.
- Systematized chronic paranoiac delusion with designated persecutor OR a delusion purely connected to affect/passion, i.e. erotomania, jealousy, persisting out of the episodes.
- Features of system catatonia: echolalia, echopraxia, proskinesia (forced grasping, non-resistance to pressure or limb positioning).

### Observed residual state with typical symptoms

Must fulfill the diagnosis for "observed residual state" + the intermittent presence of one of these symptoms at least at a mild degree:

- Staring.
- Parakinesia.
- Grimacing.
- Slight psychomotor negativism.

### Residual state with non-typical symptoms and an affected first-degree relative

Must fulfill the diagnosis for "observed residual state" + one of these symptoms:

- Abulia OR apathy not caused by depression or too high D2 blockade.
- Reduction of expressive movements, mild akinesia up to a robotic aspect not part of antipsychotic extrapyramidal syndrome, i.e. rigidity to passive movement absent or clearly insufficient.
- Emergence, i.e. not previously existing, of stiffness, clumsiness or distortion of movements.

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• Incomplete insight.

+ An affected first-degree relative.

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