Prog Neuropsychopharmaco Biol Psych 2018 Aug 30;86:363-369
doi: 10.1016/j.pnpbp.2018.03.008

A Double Dissociation Between Two Psychotic Phenotypes: Periodic Catatonia and Cataphasia

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Abstract:

Schizophrenia as a single liability model was confronted to the multiple psychotic phenotypes model proposed by the Wernicke-Kleist-Leonhard school, focusing on two: periodic catatonia (PC) and cataphasia (C). Both are stable and heritable psychotic phenotypes with no crossed liability and are coming with the buildup of specific residual symptoms: impairment of psychomotricity for PC and a specific disorganization of thought and language in C. Regional cerebral blood flow (rCBF) was used as a biomarker. We attempted to refute the single phenotype model by looking at relevant and specific rCBF anomalies for PC and C, that would exceed anomalies in common relative to controls (CTR), i.e. looking for a double dissociation. Twenty subjects with PC, 9 subjects with C and 27 matched controls had two MRI QUIPSS-II arterial spin labeling sequences converted in rCBF. One SPM analysis was performed for each rCBF measurement and the results were given as the conjunction of both analysis. There was a clear double dissociation of rCBF correlates between PC and C, both being meaningful relative to their residual symptomatology. In PC: rCBF was increased in the left motor and premotor areas. In C: rCBF was decreased bilaterally in the temporo-parietal junctions. Conversely, in both (schizophrenia): rCBF was increased in the left striatum which is known to be an anti-psychotics' effect. These evidences refuted the single schizophrenia model and suggested better natural foundations for PC and C phenotypes. They plead for further research on them and further research on naturally founded psychotic phenotypes.

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Key words: Schizophrenia; Endogenous Psychosis; Periodic Catatonia; Cataphasia; Regional Cerebral Blood Flow; Functional Brain Imaging.

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1. Introduction

The field of endogenous psychoses (1) is the one for which “cerebral diseases hypotheses” are the most likely in psychiatry. But the failure to validate schizophrenia as a model has generated a great skepticism against the traditional naturalist paradigm of scientific medicine which supposes the existence of “natural morbid entities”, i.e. diseases (2). According to this framework, a disease is a biological model of the "pathological dysfunction" able to account for a specific phenotype, i.e. clinical manifestations. The validation process of a disease model generally starts with the “correlation method” (3), looking for a robust and specific association of the putative phenotype with a biomarker. We questioned the “single” schizophrenia model and confronted it to the “multiple” psychotic phenotypes model proposed by the Wernicke-Kleist-Leonhard (WKL) school focusing on two of them: periodic catatonia (PC) and cataphasia (C).

As the other ICD / DSM diagnoses, schizophrenia and schizo-affective disorders were constructed by consensus, a procedure that only favors minimal common views. Following Carl Hempel, Rober Spitzer only focused on the strengthening of their reliability (4), not questioning their natural foundations as proposed by Eli Robin and Samuel Guze (5). Definitions of natural phenotypes are generally constructed by an optimization process consisting in a back and forth between observation and description, which could not go on if the definition remained fixed (6). To our knowledge, only the Wernicke-Kleist-Leonhard (WKL) school sustained this optimization effort over three generations, guided by three specifications of the principle of parsimony (1) (see S1). This ended up with the distinction of 35 major phenotypes which span from affective to psychotic disorders, with 22 of them being able to fulfill the DSM-5’s schizophrenia diagnosis (7). All have a good reliability (8), but also excellent predictive validity (9) and differential validity on age of onset, inheritance, fetal event and treatment response (1).

Previous attempt to select among the best categorical model used heritability as an external validator. The WKL framework outperformed the DSM-III in a twin study (10) and more recently the DSM-IV, ICD-10 and an exploratory latent class analysis in a multiplex family study for predicting heritability (11). We wanted to push the same question a little bit further in looking at brain correlates of these phenotypes.

For the purpose of this study, both schizophrenia and schizo-affective disorders, as operationalized in the DSM-5, were considered together as being part of the “single” schizophrenia model, which was confronted to the WKL “multiple” phenotypes model. Only two of the phenotypes that are regularly taken for schizophrenia were used because of their frequency: C and PC. Both have an estimated prevalence between 0.1 and 0.2% of the West-European population (12). Depending on the episode, both phenotypes generally fall within the schizoaffective and schizophrenic disorders according to ICD / DSM criteria although other diagnosis such as depressive, bipolar, or non-otherwise specified bipolar or psychotic disorders might be determined for an episode (13). Both typically have a bipolar relapsing-progressive course. This means that both excited and inhibited phases can be observed and that their respective specific residual symptoms will progressively increase especially after each relapse. Both phenotypes are among the most hereditable WKL “psychotic” phenotypes, with affected first degree relatives’ percentage, ranging between 15-26% depending on the study (12,14,15). PC has a major susceptibility locus on chromosome 15q15 (MIM 605419)(15). Importantly, C and PC appear to be independent phenotypes as there is no crossed inheritance (12,14). The core residual symptoms of the cataphasic phenotype consist in a disordered logic or incoherence and a specific language disorder, affecting both syntax and semantic (7). This is especially present during the episode, variably associated with unspecific affective or psychotic features, but it is also more and more apparent between the episodes while the phenotype progresses. Conversely, the core residual symptoms of PC consist in a quantitative and qualitative disorder of psychomotricity (7).

This study intends to confront the single schizophrenia model to the PC and C independence model, using a comprehensive biological marker, the whole brain regional cerebral blood flow (rCBF). We anticipated two main issues. 1) PC and C show the same rCBF changes in the same brain regions relative to controls (CTR), without any phenotype-specific changes. This would validate schizophrenia as a

single liability model, especially if the changes had some relevance for psychosis proneness. 2) PC and C have specific anomalies, and these anomalies are relevant with their core symptoms. This would refute, in the Popperian sense, the single schizophrenia model and provide some validation to PC and C as independent phenotypes. Specificity was operationalized as a double dissociation between PC and C (16), which means that PC had to differ from CTR in the same regions than it differed from C and vice versa.

2. Material and methods

2.1. Participants

Thirty-one patients were recruited by WKL-trained psychiatrists (MR, OM, SW, FB, JF) from the non-invasive neuromodulation center and the university psychiatric ward of Strasbourg, by convenience sampling method. They had to be right-handed, aged between 18 and 65 years, in outpatient setting, stabilized for more than a month and fulfill the double diagnoses of DSM-5's schizophrenia or schizo-affective disorder (17) and WKL's periodic catatonia (PC) or cataphasia (C). Although the screening was based on the original description of these phenotypes (7), for replicability, patients also had to fulfill operationalized criteria for these phenotypes designed to favor specificity over sensitivity (see S1). Exclusion criteria included MRI contraindication, neurological history, current drug abuse except nicotine and past electroconvulsive therapy. Twenty-eight controls subjects were included, matched by age, sex and year of education with the patients' group. Exclusion criteria were the same but adding any significant personal or family psychiatric history using both the screening level 1 instrument proposed in the DSM-5 (17) and medical interview. The study protocol complies to the declaration of Helsinki (18) and was approved by the local ethic committee. Each participant signed informed consent and received compensation for their participation.

All subjects were appraised for handedness by the Edinburgh inventory (19), IQ was estimated using the French National Adult Reading Test or fNART (20) and the Mill Hill Vocabulary Scale synonym section (part B) as a rating of conceptual ability (21). Patients' general psychopathology was evaluated using the positive and negative syndrome scale (PANSS)(22), with a special attention to depressive symptoms using the Calgary Depression Scale (CDSS)(23) and according to the eight dimensions of the Clinician-Rated Dimension of Psychosis Symptom Severity (CRDPSS)(17). Specific catatonic symptoms were evaluated using the Bush and Francis Catatonia Rating Scale (BFCRS)(24) whereas specific cataphasic symptoms were evaluated using the French version of the psychic experimental test operationalized for Cataphasia (TePEO-C)(25), an operationalized version of the test used by the WKL school for thought and language disorders. Antipsychotics doses were converted to olanzapine equivalent (OLZ)(26), and benzodiazepines doses were converted to diazepam equivalent (DZP)(27).

2.2. Imaging Protocol

The scanner was a 3 Tesla VERIO with a 32-channel head receiver antenna (Siemens, Erlangen, Germany). All scanning session took place in the morning, and participants were instructed to have a good night before, not taking more than one cup of coffee and not more than the nicotine equivalent of two cigarettes before the scanning session. After the acquisition of a 3D T1-weighted (MP-RAGE), a FLAIR 3D anatomical volume and a field map, participants passed two sets of arterial spins labeling images covering the whole brain using an EPI based QUIPSS-II sequence (28) both acquired while subjects were in different cognitive sets (see below). The first was a "pure ASL" sequence, thanks to a short TE of 9.7 ms, while the second was an "ASL-BOLD" sequence by using a long TE of 21 ms (27). Except for the number of volumes and acquisition time (101 vol in 5 min for pure ASL, 405 vol in about 20 min for ASL-BOLD), all imaging parameters were kept the same: TR = 3000 ms, TI1 = 600 ms, TI2 = 1325 ms, flip angle = 90°, resolution = 4 x 4 x 4 mm. The ASL signal was computed after rigid registration of the EPI series and converted in rCBF (27).

2.3. Cognitive Tasks

Different tasks were performed in each ASL sequence to constrain the subjects' cognitive states but also to ensure that our results were not dependent from them. During the pure ASL sequence, the subjects were asked to watch videos of real fall or car accidents which luckily did not entails casualties. During the ASL-BOLD sequence, subjects were confronted with six different tasks of intermingled box-car presentation, separated by short periods of rest, and requiring answers from the

participants, using a three-button box: evaluating emotional videos, assessing inner-feelings, mental calculation, reading, episodic and verbal working memory.

2.4. Data Pre-Processing and Analysis

All anatomical scans were visually inspected to discard any significant anatomical anomaly and ASL volume to discard artifacts. All pre-processing and analyses were performed with Matlab12 (Mathworks, Natick, MA, USA), using the SPM12 Toolbox (30).

The rCBF images of each subject were first unwarped using the fieldmaps then spatially normalized using the deformation field computed on the 3D-T1 anatomical volume of each subject. Images were resliced at 2 x 2 x 2 mm resolution and smoothed with a Gaussian 3D filter of 8 x 8 x 8 mm. Two statistical parametric analysis were performed on the whole brain, one for each ASL sequence. Subjects' rCBF were mathematically projected on the design matrix composed by the three regressors for the groups (CP, C, CTR), one regressor for the age, and regressors for the global blood flow value. Groups were compared by a Student t-test for groups of unequal variances.

Assuming that schizophrenia-related changes should be the same whatever the WKL-group, these were defined as the regions commonly different from the CTR by both groups, i.e. as a conjunction of the (CTR vs. CP) ^ (CTR vs. C).

To claim for CP specific changes, these had to be the same regardless the group with which the comparison was made, i.e. a conjunction of (CP vs. CTR) ^ (CP vs. C). The same rule was applied for C specific changes, defined as the conjunction (C vs. CTR) ^ (C vs. CP). Using an uncorrected $\alpha = 0.05$ per elementary statistical parametric map, this gives a first level conjunction map at $\alpha^2 = 0.0025$. To avoid a possible artefact or a possible interaction with the task, only voxels that were commonly significant in the pure-ASL and the ASL-BOLD sequences were retained, that is second level conjunction, which threshold is thus $\alpha^4 = 6.25\ 10^{-6}$ and using extension of k = 125 vx (1 cm^3).

To assess the correlation between the significant regions of the above-mentioned SPMs and patients' characteristics, the rCBF values were extracted from these regions and averaged. To minimize the number of tests, rCBF values measured with both sequences were also averaged. Planned correlations were between rCBF value for the significant clusters and medication daily intake converted in OLZ and DZP equivalent, catatonic symptoms given by the BFCSR score and cataphasic symptoms evaluated by the TePEO-C.

3. Results

3.1. Population Characteristics (table 1)

One patient and one CTR did not complete the study and one patient had to be discard because she didn't fill the appropriate WKL diagnoses. From a DSM5 perspective, there were 20 schizophrenia patients and 9 schizo-affective disorder patients, equally distributed in the PC and C groups. No patient fulfilled the ICD-10 or the DSM-5 diagnosis for catatonia in any of their previous episode. Groups were not different in terms of age, sex and years of education. Patients' groups did not differ in terms of illness' duration since the first symptoms and number of episodes. Patients underperformed in the Mill Hill Vocabulary Scale synonym section relative to CTR, but this effect was mostly accounted for by C patients who had significantly lower score relative to PC and CTR. The same was true for the fNART IQ evaluation.

The PANSS total, positive and negative scores were not significantly different between PC and C patients. The two patients' groups did not differ on depressive symptoms according to the CDSS. Patients' groups significantly differed on three dimensions of the CRDPSS (see S2): speech disorganization (PC < C, 0.3 ± 0.1 vs 1.4 ± 0.3, p = 0.004), psychomotricity (PC > C, 1.7 ± 0.2 vs 0.6 ± 0.2, p = 0.002) and negative symptoms (PC > C, 2.4 ± 0.2 vs 0.9 ± 0.4, p = 0.007).

In accordance with their residual symptoms, PC patients had a significantly higher BFCRS score relative to C (4.7 ±3.0 vs. 2.0 ±2.6, p = 0.029), whereas the latter scored higher at the TePEO-C (6.9 ±3.3 vs. 28.9 ±3.6, $p = 1.2\ 10^{-7}$).

All but three patients were treated with antipsychotics. There were no significant differences in antipsychotic and benzodiazepine dosage between the two groups.

		Patients (SZ)		Controls	Significance	
		PC	C	CTR	SZ vs CTR	PC vs C
Characteristics	Number	20	9	27		
	Age (years)	38 ±13	38 ±7	39 ±9	ns	ns
	Sex (F/M)	10 / 10	5 / 4	14 / 13	ns	ns
	Academic years	13.4 ±2.6	13 ±2.7	14.3 ±2.3	ns	ns
	IQ (fNART)	106.3 ±5.6	102.4 ±3.8	106.6 ±7.0	ns	0.049
	Mill-Hill part B	15.7 ±3.5	13.5 ±2.5	16.9 ±7.0	0.029	0.068
	Edinburgh (manuality)	76 ±39 %	81 ±31 %	83 ±27 %	ns	ns
Clinical	SA / SZ	6 / 14	3 / 6			ns
	Duration (years)	15.6 ±12.7	14.4 ±6.4			ns
	Nb episodes	3.3 ±2	4.1 ±2.9			ns
	PANSS total	65.7 ±13.9	66.7 ±16.1			ns
	PANSS positive	11.7 ±4.4	16.8 ±5.7			ns
	PANSS negative	19.6 ±5.5	16.8 ±5.7			ns
	CDSS (depression)	3.0 ±3.8	4.7 ±4.9			ns
	BFCRS (catatonia)	4.7 ±3.0	2.0 ±2.6			0.029
	TePEO-C (cataphasia)	6.9 ±3.3	28.9 ±3.6			$1.2 \cdot 10^{-7}$
TTT	OLZ equivalent (mg)	13 ±10.9	12 ±5.9			ns
	DZP equivalent (mg)	4.1 ±6.7	7.8 ±20			ns

Table 1. Population Characteristics. OLZ: antipsychotics doses are given in olanzapine equivalent (in mg); DZP: benzodiazepines doses in diazepam equivalent (in mg).

3.2. Imaging Results

3.2.1. Schizophrenia Related rCBF's Changes (table 2, figure 1 in green)

To consider PC and C as belonging to the same SZ group, they had to come with similar differences relative to CTR. The conjunction map was significant for an increase of rCBF in the left putamen and the left somatosensory cortex. There were no significant common rCBF decreases.

There was no significant correlation between rCBF in the putamen and antipsychotic dosage according to OLZ equivalent (r = - 0.09, n.s.) or DZP equivalent (r = 0.15, n.s.).

3.2.2. Periodic Catatonia-Specific rCBF Changes (table 2, figure 1 in red)

PC patients had a higher rCBF than CTR and C in their left precentral gyrus ranging from the posterior Broca area up to the supplementary motor area (SMA), their left prefrontal cortex, and in their middle part on the medial cingulate cortex. The reverse contrast did not give significant results.

There was no significant correlation between rCBF in the abovementioned regions with catatonic symptoms according to the BFCRS (r = - 0.02, n.s.) or with any treatment (OLZeq: r = -0.07, n.s.; DZP = - 0.14, n.s.).

3.2.3. Cataphasia-Specific rCBF Changes (table 2, figure 1 in yellow)

Group C showed a decrease in blood flow in comparison with CTR and with PC in the upper temporal gyrus level bilaterally and a lateral rightward decrease at the angular gyrus level (Table 2 and Figure 1 - yellow). The reverse contrast did not give significant results.

There was a significant negative correlation between rCBF in the TPJ with cataphasic symptomatology according to the TePEO-C (r = - 0.68, p = 0.012). There was no correlation with treatment doses (OLZ: r = - 0.11, n.s.; DZP: r = 0.12, n.s.).

4. Discussion

This study aimed to confront the single schizophrenia model to the multiple phenotypes model of the WKL school, although limiting its investigation to two of them, i.e. PC and C.

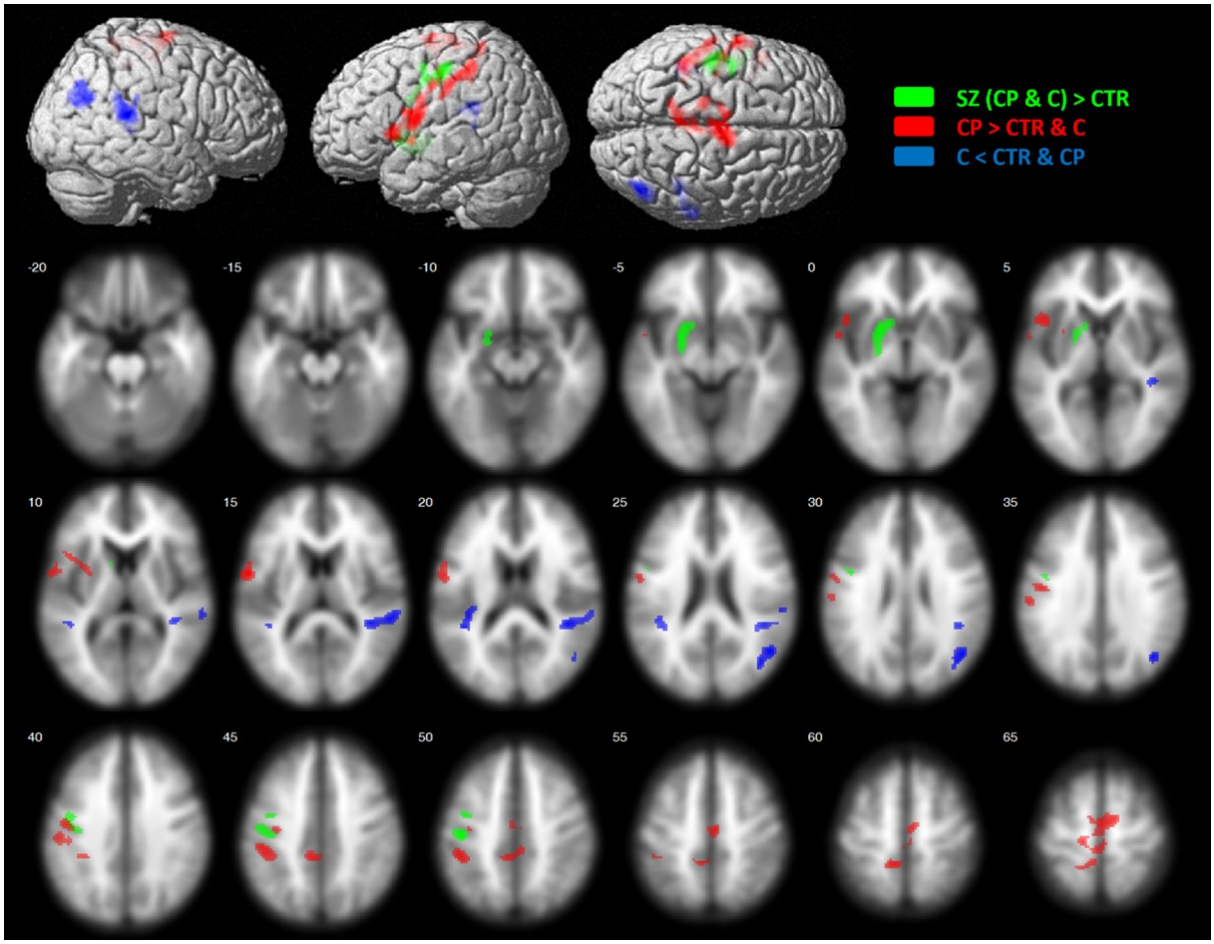

Figure 1. Imaging Results. In Green: schizophrenic patients (SZ) related changes, regions with common rCBF increase in periodic catatonia (PC) and cataphasia (C) relative to Controls (CTR). In red: PC-specific changes, regions with rCBF increase in PC relative to CTR and to C. In blue: C-specific changes, regions with rCBF decrease in C relative to CTR and to PC. Conjunction threshold of 6.25 10^{-6}, with extension of 125 vx (1 cm^3).

		Cluster size		Min single SPM		Conjunction SPM		Position (mm)		
	Side	k (vx)	vol (cm^3)	p_{unc}	T	p_{unc}	T	x	y	z
Schizophrenia (+)	**(CTR < PC) ^ (CTR < C)**									
Premotor cortex	L	320	2.6	0.0015	3.1	$5.3 \cdot 10^{-12}$	8.6	-44	-22	50
Putamen	L	435	3.5	0.0020	3.0	$1.5 \cdot 10^{-11}$	8.3	-20	6	0
Periodic catatonia (+)	**(PC > CTR) ^ (PC > C)**									
Precentral gyrus	L	377	3.0	0.0004	3.5	$3.2 \cdot 10^{-14}$	10.0	-58	0	14
Paracentral lobule	L	280	2.2	0.0037	2.8	$1.9 \cdot 10^{-10}$	7.6	-10	-46	62
Pre- and post-central gyri	L	343	2.7	0.0039	2.8	$2.9 \cdot 10^{-10}$	7.6	-46	-38	50
Operculum	L	175	1.4	0.0044	2.7	$3.9 \cdot 10^{-10}$	7.4	-48	14	4
Supplementary motor area	R/L	521	4.2	0.0050	2.7	$6.3 \cdot 10^{-10}$	7.3	10	-10	68
Cataphasia (-)	**(C < CTR) ^ (C < PC)**									
Superior temporal gyrus	R	484	3.9	0.0016	3.1	$6.9 \cdot 10^{-12}$	8.5	58	-38	14
Angular gyrus	R	255	2.0	0.0026	2.9	$4.7 \cdot 10^{-11}$	8.0	48	-64	26
Superior temporal gyrus	L	148	1.2	0.0069	2.6	$2.2 \cdot 10^{-9}$	7.0	-40	-44	22

Table 2. Statistical Parametric Mapping Results. The cluster size is given in number of voxels (k) or in volume (cm3). Significance is given as the minimal value for each individual map as p-value uncorrected for multiple testing (p_{unc}) and t-value (T). But considering that this was the smaller p-value of the 4 SPMs, the conjunction p- and t-values are given in the "Conjunction SPM" columns. Coordinates x,y,z, are given in mm in the MNI space.

Using rCBF as a biological marker, there is strong support for a double dissociation between the two phenotypes. Results also suggest putative pathophysiological account for their clinical manifestations.

4.1. Schizophrenia Related rCBF's Changes

The only common differences between PC and C, when compared to CTR, were the increases in rCBF in the left putamen and the left central gyrus. As this was a correlation study, and that all patients but three were under antipsychotics, there is no perfect way to disentangle between a disorder or a medication effect. Striatal involvement has been described in drug-naïve psychotic patients, however this refer to dopamine occupancy, dopamine synthesis, D2 receptor density (31) and BOLD slow oscillation connectivity studies (32). However, we are not aware of any report about changes in rCBF in drug naïve patients whereas there are ample evidences from the literature showing antipsychotics to induce an unspecific increase of rCBF in both structures in patients (33,34) and normal controls (35). In the striatum, this comes with increases in metabolic consumption (36) and grey matter volume (37) in relation with synaptic sprouting (38). Nevertheless, the absence of correlation between putamen's rCBF and antipsychotic dosage should temper this interpretation. We have no reasons to believe that benzodiazepines might have played any role in these differences.

In contradistinction, expected rCBF decreases, especially in the prefrontal cortex, could not be observed despite their frequent report in perfusion, metabolic and anatomic studies (39–41). This might be due to the recruitment of PC and C as schizophrenic patients. In classical imaging studies, the need for the patient consent bias the sample towards milder WKL's phenotypes, i.e. cycloid psychoses. They accounted for more than 70% of the schizophrenic patients in one of our previous imaging study while representing no more than 20% of endogenous psychoses (36). These are the phenotypes that come with prefrontal anomalies such as reduced rCBF (43) together as enlarged lateral ventricles (44) and cortical defects (45), the two latter being absent in PC and C (44,45).

As an intermediate conclusion, the patient's group effect, i.e. effect common between PC and C, might be better accounted for by the medication, rather than the disorder, i.e. providing no argument for schizophrenia to be a homogeneous "single" entity.

4.2. Periodic Catatonia-Specific rCBF Changes

PC-specific perfusion increases were observed in the left primary motor, pre-motor and Broca areas, together with the SMA, bilaterally. This could not be due to the antipsychotics or benzodiazepines as PC and C were treated with similar doses. A phenotype effect is thus very likely. A swiss group in Bern reported a similar SMA and left sided premotor hyper-perfusion pattern in a catatonic subgroup of schizophrenic patients as defined by two positive items in the BFCRS vs. patients without catatonic symptoms (46). Considering that persistent catatonic features are mostly seen in periodic catatonia and the six systems catatonias phenotypes (7) but that the latter are generally too impaired to be enrolled in a study, it is very likely that the Bern's team (46) might have compared a group enriched with PC to a group enriched with "other" schizophrenic phenotypes. The clear left-sided changes are harder to understand, but might be related with the even larger left-sided laterality for psychomotricity than for language, as demonstrated by ideomotor apraxia (47).

The absence of correlation between rCBF in motor-premotor cortices and BFCRS score could be due to the lack of specificity of this scale. The BFCRS is a mere aggregation of psychomotor distortions symptoms (22), many of which being only seen in system catatonias and never observed in PC (7). Conversely, parakinesia, a major sign in PC, is not considered as well as attenuated quantitative psychomotor disturbances, which are taken for negative symptoms.

This increased base-line activity concerns regions involved in programming, control and monitoring of motor functions. This good agreement with the core residual symptomatology of this phenotype sheds new lights on the pathophysiology of the clumsiness, the parakinesias and the mix of retarded and excited psychomotor symptoms. These could be interpreted as a reduction of the signal-noise ratio, that would also explain why catatonic patients had a lower BOLD signal in the motor cortices during a finger tapping task (48). Both perfusion increase and lower signal-noise ratio could be underpinned by the reduction of $GABA_A$ receptors, binding in the primary motor

cortex of catatonic patients (49). This hypothesis of a defective inhibition is further supported by the anti-catatonic effect of $GABA_A$ positive modulator, e.g. benzodiazepines (50), barbiturates (51), and electroconvulsive therapy (52,53). There is also evidence showing that such reduced cortical inhibition is compensated by antipsychotics (54), with a potentially larger effect of clozapine (55), a treatment that might be especially effective in PC (56).

4.3. Cataphasia-Specific rCBF Changes

The C-specific rCBF decreases bilaterally in the temporo-parietal junctions (TPJ) is in accordance with a previous report of a reduced BOLD activity in the left TPJ when patients had positive formal thought disordered speech during the scanning session (57). Again, this result could not be accounted for by the medications as C and PC were under similar doses of antipsychotics and benzodiazepines.

Such observations give some cues for the pathophysiology of core cataphasic symptoms. The posterior part of left superior temporal and angular gyri are known to play a crucial role in understanding and language production, with clinical pictures of fluent aphasia emerging from their lesion, i.e. Wernicke aphasia, and transcortical sensory aphasia (58,59). Both come with a classical logorrhea in acute setting and persistent paraphasias, paragramatism and difficulties in understanding language, which are responsible for distrust of the environment (59,60). Comprehension may be further impaired by the involvement of the right TPJ, which supports the construct of a contextually related coherent meaning of language including paralinguistic aspects, such as understanding emotional intonation, metaphor, irony, and social cognition (61). These features are very consistent with schizophasia and residual cataphasic symptoms (7).

The relationship between core cataphasic symptoms and rCBF decreases in the TPJ is further strengthened by the significant negative correlation between perfusion of both TPJ and the TePEO-C score. Conversely to the BFCRS, the TePEO-C has been especially developed to measure the specific cataphasic symptoms such as conceptual loosening and the above-mentioned lexical and semantic distortions. This might be related to the significantly lower scores in fNART and Mill Hill of C patients. These are generally interpreted as crystallized intelligence, but considering the roughly similar number of academic years in C relative to PC and CTR, these results could also be interpreted as a pathology-related loss in language abilities.

To conclude from the two last parts, we observed a clear double dissociation between PC and C with specific rCBF changes. Perfusion anomalies are not only diametrically opposed, i.e. increase in PC vs. decrease in C, but also in separated brain regions, compatible with the core residual symptoms, i.e. motor and pre-motor areas for the phenotype marked by dysfunctional psychomotricity (PC) and temporo-parietal junctions bilaterally for the phenotype manifesting specific disorganization of concepts and language (C).

4.4. Limitations

Although the initial plans were to recruit as much C than PC patients with an objective of 15 or more in each group, the number of C subjects remained below our expectations. The distrust that frequently comes with the residual state of cataphasic patients made them harder to recruit. The use of the conjunction between the pure ASL and ASL-BOLD sequence cannot be considered as a reproduction. This procedure only limits the risk of methodological artifact and ensures that the group difference was intrinsic and not related to any specific cognitive state. A replication study, including new participants remains desirable. It could further extend these results by including cycloid psychoses such as confusion and motility psychoses, which might have close albeit distinguishable clinical manifestations, in comparison to both C and CP, and also a more benign purely relapsing-remitting course (7).

Finally, the “schizophrenia”-group effect remains difficult to interpret because of the tight correlation of the medication factor with it. This should temper our interpretation of an absence of a schizophrenia effect. Importantly however C- and PC-specific rCBF anomalies were much more striking than their similarities and could not be accounted for by the medications since both antipsychotics and benzodiazepines were at the same doses in both groups and that no correlation could be seen with treatment dosage. This report of selective and permanent regional functional changes, associated with PC and C is only the first step for validating both phenotypes as “syndromes”, i.e. residual symptoms congruent with the functions supported by these brain regions. This might be mere final common

pathways responding to different etiologies. Indeed, there are already evidence for PC to be related to different loci (62).

5. Conclusion

The relevance of this functional double dissociation between PC and C contrasted with the unspecific and probably treatment-related nature of PC and C functional commonalities. According to our premises, these results come along the better prediction in heritability (10,11) to suggest that WKL phenotypes might be closer to natural kinds than ICD or DSM and should deserve further attention. They also provided some cues for future validation of the PC and C phenotypes considering the accordance of the function supported by their functionally abnormal regions with their respective core symptomatic features. Such causal models could be validated by controlled experiments, e.g. by correcting their regional functional anomalies using personalized transcranial magnetic stimulation (63) in order to test the improvement of their respective core residual symptoms.

Acknowledgments

The authors want to thank Mrs Corinne Marrer, Mrs Annabel Schneider, Celine Behrendt and Mr Gregory Johais for data collection and gathering, and Mr Christophe Panzer for the English correction. Funding: This work was supported by the Programme Hospitalier de Recherche Clinique “Connectivité” and the “Plateforme d’imagerie in vivo” of the iCube Laboratory

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Supplement 1. General information regarding the WKL classification with special focus on periodic catatonia and cataphasia.

Supplement 2. Radar plot of Clinician-Rated Dimension of Psychosis Symptom Severity for periodic catatonia (red) and cataphasia (blue).