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IMMUNOPSYCHIATRY OF INFECTED EARS, SINUSES, SKULLS, AND MENINGES: MAST CELLS, MOZART, VAN GOGH

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SUMMARY

Medical psychiatry acquires more prominence in the biological field by new anatomical insights into the wrappings of the brain: meninges, but also Meningo-Calvarial Channels (MCCs) connecting the former with the bone marrows´ also neuronally steered, functions. The skull-bone's meningeal arteries through migrating and orchestrating mast cells within a framework stressing their relations with arteries (Treviranus 2012-21) could explain enigmatic phenomena like migrainous and post-injury Cortical Spreading Depressions (CSD) or the Reversible Cerebral Vasoconstriction Syndrome (RCVS) escalating to "PRES". The skull might be accessed along chronic (para-)infectious paths resulting in Skull Bone Osteomyelitis (SBO) from the ear-nose-throat, dental and other microbiomes. Such paths seem promoted by compromised innate immune defenses: by "Mendelian" susceptibility, and/or acquired anti-INF-γ- or other auto-immunity or various microbial "Trojans" of e. g. meningeal myelo- and lymphocytes. These interact e. g. from the calvarial marrow niches onward. Hereby competing local and "intentional" intruding mast cells – by disturbing (or ingeniously boosting) cortical development and functioning – acquire relevance by interacting with arteries (Treviranus 2018, 2021). This predicts findings in behavior (Fitzpatrick & Morrow 2017) an "aortal" arterial biomechanical foundation of parasympathetic reverse arterio-intramural cerebro-interstitial drainage by CIMURAF/IPAD-2.0 (Treviranus 2018-21).

Here the recent physiological re-conceptions of the skull illuminate own case histories through a gamut of possibly relevant neuro(-surgico)-psychiatric challenges. Among these meningo-cerebral immune, vasospastic, and cystic processes some generate broad "experiential" hallucinations, which may slowly transit to true psychoses through "perfect crime lesions" of neurons and glia by tryptase-armed mast cells descending into parenchyma often congested by "push-back".

These emerging hypotheses coalesce in advancing an integrative macro-medical psychiatry and even the pathography of Van Gogh and Mozart stressing the benign and creative roles of mast cells.

Key words: *skull base osteitis - meningo-calvarial channels - infectious psychosis - Cortical Spreading Depression (CSD) - Intramural Peri-Arterial Drainage (IPAD) - Reversible Cerebral Vasoconstriction (RCVS) - Mendelian Susceptibility to Mycobacterial Disorders (MSMD)*

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THE WRAPPINGS OF THE BRAIN: SKULL AND MENINGES THE NEW PSYCHIATRIC FRONTIER?

"My only anxiety is, how can I be of use in the world? I am unable to describe exactly what is the matter with me: horrible fits of anxiety / emptiness and fatigue / melancholy / atrocious remorse / enthusiasm or madness or prophecy / great readiness of speech / terrible need of religion / intolerable hallucinations… to simple nightmare taking K+-bromide / undercurrent of vague sadness / fainting without remembrance."

Vincent Van Gogh symptoms from a letter to Theo

The present further exploration in anatomico-medical psychiatry concerns the brain's "wrappings" permeabilized through trajectories interacting with ORL-infections starting in early life due to plausible innate immunodeficiency - as suffered by several (!) own clients. These trans-disciplinarily bewildering , often subacute psycho-neuro-neurosurgical pathologies revealed by MRI-imaging spurs this proposal with two pathographic and three clinical vignettes (encoded as "V#[nr1,2,3],[gender],[YOBirth]"). Within text references here are mostly poly-authored and therefore don´t specify "et al.", while "&" connects two authors, and "." follows single authors.

Skull trouble starting from ears or sinuses: a Skull Base Osteomyelitis spectrum?

External otitis after persisting a week despite antibiotics can evolve into a «necrotizing» (EON) variant with micro-abscesses, cranial nerve disorders, gram-negative bacteria, often normal WBC and CT (1:6) or mysterious meningitis (Sideris 2022). EON can degenerate into 1:6-mortal "skull base osteomyelitis" (SBO) in various directions: anteriorly (2/3) as «typical» (TSBO; van der Meer 2022, Hutson & Watson 2019, Chapman 2021), through Huschke´s slit of 10% of external acoustic channels (Herreira-Ferrero 2020, Ribeiro 2021). «Atypical» central SBO instead stems e. g. from bacterio-fungal sphenoïdal sinusitis (Table 1). Both SBO can provoke meningitis and this plausibly through meningo-calvarial channels (MCCs), while smoldering bone marrow activations could – maybe on a spectrum – provide also neuropsychiatric etiologies e. g. for cortical hallucinations.

Vignette: *V#1fS1972 of 3 siblings with possible familial MSMD-like susceptibility. After a severe Otitis Externa "Necrotisans" (EON) as a toddler, a silent sphenoïdal sinusitis after a swing-head injury evolved into a L-spreading ASOB with a sub-arachnoïdal cyst extending into the L-lateral ventricle (Figure 1). Age 31 she suffered a rotational head injury becoming*

Table 1. Trajectories of severe acute "typical" vs. "atypical" Skull Base Osteomyelitis as endpoints of an intermingling putative spectrum including abortive subacute diploic inflammatory states influencing CSF outles, meninges, vessels, cranial nerves, and brain (Mod. from Chapman 2020, Conde-Diaz 2017)

Typical TSBO by **Pseudomonas aeruginosa** (ant. TSBO) **(**85%) by *Aspergillus (temporo-occ.) dry hot climate* spreading from ...	**Atypical ASBO** by **Staphylococcus aureus ≥ Pseudomonas. aer.**, Fungi > Mycobacteria (Tbc, NTM) spreading from ...
Ext. Auditory Canal e.g. via Huschke`s hole ➔Ant.: Clinoid process, Sphenoïd lesser wing (fungal), Temporal bone (squamous & tympanic part), TM-Joint, Stylomastoïd foramen ➔Centr.: IntracranialTemporal bone (petrous mastoïd), jugular fossa, ➔Post.: (petro-clival synchondrosis), Clivus	**Sphenoid sinus, bloodstream** ➔Sphenoïd bone, central skull base, Clivus ➔Dura, ➔ Arachnoïd cyst (e. g. empty sella sits on Sphenoïd sinus roof) ➔ lateral Ventricle ➔?Temporal pole ➔ entorhinal Cx ➔ (HC) ➔Sigmoïd sinus & Jugular vein, Intracranial carotid artery.
Elderly, ? hidden in infants / children Otorrhea, severe otalgia, face / headache (90%)	Middle-aged, ? hidden in infants / children ? post-traumatic
T2DM > immune-compromised	T2DM = immune-compromised
Facial (60% C.N.VII, VIII), (Cranial Nerve I-V)	C.N.: ((I – V)), VI, IX, X (> VII) ((VII-XII)): palatal, arytenoïd e.g.; often multiple palsies
Contralateral spread, Intracranial Hypertension (IIH), papilledema, SIADH, TM-Joint or vasculitic infection, stroke, encephalopathy, fractures.	

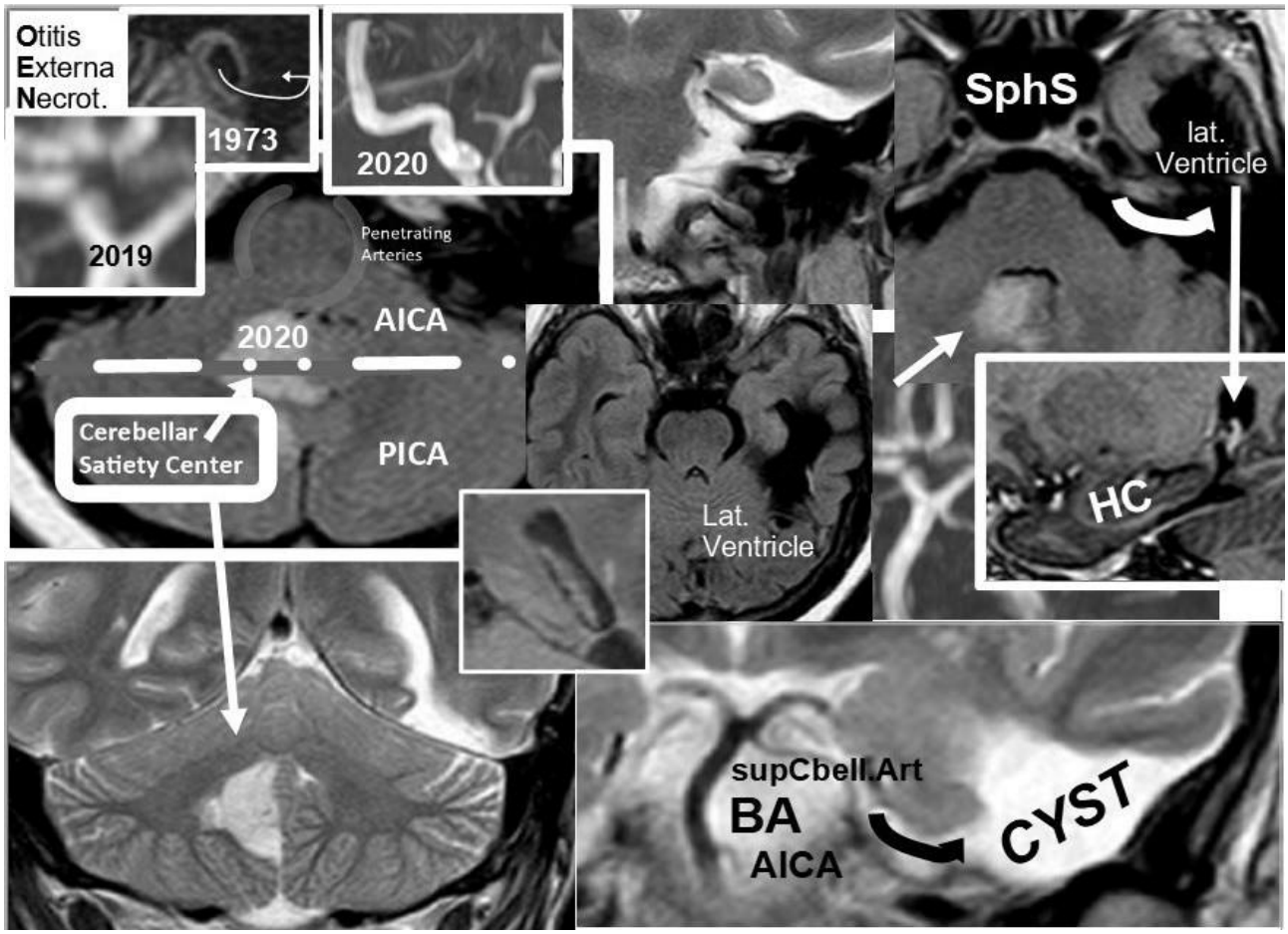

Figure 1. V#1fS1972: The external ear channel defect "1973" allowed the Otitis Externa Necrotisans" to spread as ASOB with a CYST expanding beneath the hippocampus (HC) with the L-lateral ventricle. On a MRI of "2019" a constriction of the R PICA – likely from a MC degranulation in a CIMURAF-"sliding chamber" – was not considered, and "2020" a slow stroke of a putative "cerebellar satiety center" had stopped a hyperphagia since an RTA (2003). Her daughter suffers from hyper-satiety but refused MRI. Fatigue stems from choroid plexus (center) permeabilization promoting intracranial hypertension

severely hyperphagic and obese from damage to a cerebellar satiety center (Low 2021). On MRI performed for vertigo age 47 a constriction of the R PICA was not retained and at age 48 a slow stroke of the cerebellar satiety center area apparently stopped her hyperphagia.

She is a hyperthymic janitor, strong, emotionally intelligent, yet crippled by fatigue. Her brother A. is treated for retinal vasculitis. Her brother R. suffers from bipolar disorder-2 like herself, severe epileptoïd hallucinations, fatigue, meandering intestinal and bodily pain - also from abuse of codeïn and anti-mycobacterial pro-autophagy zolpidem (Moraski 2015). Her daughter suffers from hyper-satiety.

Pathographies of Mozart and Van Gogh expanded on

The above SBO also sheds light on the pathographies (Wikipedia) of Mozart`s temporal fracture (Figure 2) and Van Gogh`s self-severed external ear channel (Figure 3), wherefrom the below (non-subjunctive) narratives result, on how the two geniuses hereby were shaped in not only tragic ways (Akiskal & Savino 2005, Jamison 1989).

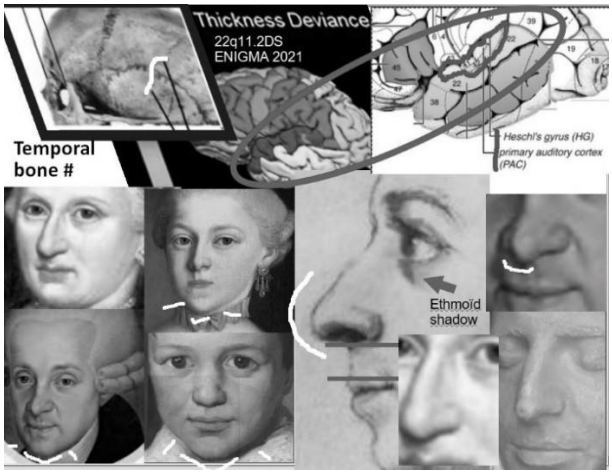

Figure 2. The physiognomies of Wolfgang, who suffered a temporal bone fracture (white) and had rings pointing to ethmoïdo-orbital exsudates, (besides a long philtrum) in his physiognomy, like his sister Anna, and both parents except for bulbous tips of elongated noses and marked chins presented no features of 22q11.2 D, which nevertheless strengthens cortical areas beneath meningeal arterial branches as often found in musicians

Wolfgang Amadeus Mozart´s malady

Amadeus had suffered boys´ parapharyngeal peritonsillitis (Dawson 2010), from an intracellular persistent rash-causing *Streptococcus pneumoniae* (*SP*; Rohde & Cleary 2016, Weinzimer 1998, Han & Kerschner 2001, Castagnini 2015, Klug 2017) to which, lacking GH for full size beyond 160 cm (as 1:6000, or 4% of 22q11.2DS: 1:1400´000; Weinzimer 1998), he was susceptible genetically (Farhat 2018) and/or from a secondary sub-arachnoïdal empty-sella-cyst (Carosi 2022) on the sphenoïdal roof. He died at age 35 (Meia 2013) having suffered a left squamous temporal skull-fracture (Kanat 2019) a year (of bad headaches from chronic subdural hematoma) before, in a recurrent syncope from his life-long ASBO (see Table 1). This had started very early (Gülhan 2019) from a persisting sphenoïd *SP*-sinusitis with headaches (Yap 2022). Degranulating optical nerve *mast cell* (Levin 1993) – collaborators of *SP* (van den Boogaard 2014) and possibly in the context of a central 22q11.2DS (Matsuoka 2018) – caused his prolonged amaurosis fugax (Antonelli 1893) – not «smallpox» (McEntire 2021). He was ultimately bedridden with fever, generalized edema, and palpable rash from a rare recurrent adult (Tsapenko 2011) post-acute *SP-streptococcal* glomerulonephritis (Odaka 2015). Ecstatic laughter attacks - prominent in Milos Forman (1984) and Peter Shaffer`s (1979) «Amadeus» were related by a lady: "When this man wo had composed such a divine music started to laugh, he resembled more an animal than a human being.». Unnatural fits *can* occur with adequate humor (Unnwongse 2010, Roodakker 2020) as in cortical aura (Datta 2013, Mathew 2016).

Figure 3. The physiognomies of Vincent, Theo, and his mother Anna (with three foreign portraits) besides bulbous nose tips and marked chins on photos share attentive, worried bewilderment, but no further dysmorphic features

Mozart to Costanze of a bipolar disorder (Brown 2009, Huguelet & Perroud 2005) had described his lows: "It is a certain emptiness - which accordingly hurts me - a certain longing, that is never satisfied, consequently never stops - always continues to grow, yes, from day to day." triggering, in a final slide, his Requiem – truncated by aprosody – in moribund premonition to be “deadly poisoned”.

High intelligence comes with high neuro-immunomorbidity (Karpinski 2018, Breitenfeld 2007); possibly this includes rare central Chr22-breaks. Of 1:4000 births with 22q11.2 deletion of which twice <8% are of two

less compromising *central* kinds. 15% are (usually maternally) inherited, but here both parents show suggestive «drop» noses. The 46 «halfed» genes increase cortical thickness including parts of the neo-Heschl areas, *multiplied* in almost all musicians (Forsyth 2021, Tanaka 2018, Benner 2017): here even less-hearers hallucinate (Marschall 2020). Could there have been an imbalance-generated (Cantonas 2022) ingenious variant of auditory processing?

Vincent Van Gogh's malady

«Engineer» Vincent - «one wonderfully gifted, delicate and gentle, the other proud, selfish and hard» - died from his gun-wound after ablating his L «ear as a source of his ills» including vertigo (Arenberg 1990). He had pejorated, as did his hospitality for Gauguin (self-portrayed with an ethmoïditis!). In this the role of shame in a «replacement child» predicting unrelenting unsuccessfulness (Meissner 1996, Taghipour 2019), reinforced the above *broad*-symptomatic «intermittent» TL-epilepsia-like disorder, less caused by foci than by *general* factors - like a disturbance of the pterygopalatine ganglion (PPG) plausibly governing the brain-drain *and* the shame-reflex (Treviranus 2012, 2021). Since Himmelhoch (1984) such constitutes «bipolar-II with psychotic symptoms disorder» – whispered as an alternative to schizo-affectivity – being «archetypal» for another genius with putative ASBO (Cooper & Agius 2018, Jänisch & Nauhaus 1986). His gastritis besides ethanol and MCs points to H. pylori often disrupting the BBB (Haorah 2005, Fedwick 2005).

Meaningful patterns are sought in the manifestations of 22q11.2 DS (Motahari 2019) which concerns 4.7:100´000 (Blagojevic 2021) - possibly caused by mast cells` transgranulations (Wilhelm 2005).

Meningeal lymphatic vessels (MLVs) and Meningo-calvarial channels (MCCs).

While the parenchymal drainage occurs *separately* through the walls of arteries by the "aortic" muscular engine - as the Cerebral IntraMUral-Reverse-Arterial-Flow (CIMURAF)-model suggested before IPAD (Albagorthy 2018) refuting glymphatics-1.0 (Iliff 2012, Treviranus 2018) - meningeal MLVs (Aspelund 2015, Louveau 2015) drain some «surrounding» CSF along emissary veins, by *bypassing* the main CSF outflow through the cribriform plate to the cervical lymph nodes (Jacob 2022). In parallel arachnoïd granulations may drain into dural veno-petal lymphatics or into the bone marrow diploë, as do the sagittal system`s protrusions (Yagmurlu 2021, Rustenhoven 2021, Ringstad & Eide 2022) transmitting CSF-to-marrow signals.

The MCCs connect the meninges with nearby bone-marrow niches (Cai 2018, Pulous 2022, Mazzitelli 2022), which provide – also through vastly interacting (Gri 2012) MCs or e-immunology (Abraham & St. John 2010, Grune 2021) – the brain with new myeloid cells, like ambivalent neutrophils (Herison 2018, Brioschi 2021, Cugurra 2021, Arts & Kuijpers 2018). While MCs instruct effector T-cells (Stelekati 2009), such incite myeloid cells (Jain 2020). Lymphocytes too have their (peri-)-cerebral tissue distributions, and the dura produces exclusive B-cells (Schafflick 2021) while T-cell patrol the CSF (Schläger 2016, Kivisäkk 2002). MS-simulating Th17-cells shape B-cells before their descent into the parenchyma (Hartlehnert 2021). Rodent AT-II-hypertension´s artificial microglial inflammation starts after hyper-sympathetic bone-marrow-productions of myeloid cells (Santisteban 2010, Calvillo 2019, Ahmari 2019).

Meningeal arteries "unseal" (via mAChR maybe on intramural MCs) – but don't "enlarge" when e-stimulating the Pterygo-Palatine-Ganglion (PPG, Delépine & Aubineau 1997) – or the trigeminal nerve (Buzzi 1992): maybe through trigeminally eliciting the "shame-reflex" via PPG (Suzuki 1989); such could muscarinically degranulate MCs (Shelukhina 2017). Thus via the basilary artery (Roloff 2016) the PPG could open brainstem barriers and provoke sudden death (Pasi 1992) in nose-down flu-babies or adult SUDEP – refuting "brainstem CSD" (Aboghazleh 2021).

Cortical spreading depression: advancing a too far-reaching agenda?

Since "CSD" (www.cosbid.org) – Cortical (jointly) Spreading (metabolic) Depolarization (& EEG-Depression) - & oligemia - appears as a variously vasomotive (trans-zoological) 4mm/min "wave in the gray matter, *regardless* of functional divisions or arterial territories" (Cozzolino 2018) - restricted to *sub-calvarial* cortex - answers might be provided by the MCC-transmission of speculative inciting vasomotive "marrow-fire-waves" starting from diploïc meningeal arteries (ignited by MCs ascending vertically from the aortic arch´s lymphatic crossroad), the more as specific vessels orchestrate cell-producing niches (Zhang 2021). Under CSD the healthy brain is more perfused (possibly by musculo-plegia) - and then lastingly less (plausibly because of mural swelling from IPAD/CIMURAF-failure; Treviranus 2020). The ensuing energy-crisis (with failing glutamate) via cation influx and GABAA lets "beading" dendritic neurons swell – slowly restored by Na^+/K^+-pumps. Severe TBI/SAH triggers (70%) "trauma-CSDs", which ketamine (likely acting on the PPG) lowers 14-fold (Carlson 2018).

Probably PPG-derived myelinated perivascular nerves aggravate CGRP-trigeminal pain (Koroleva 2019). Without meningeal lymphatics the PPG seems to lack trigeminal signals via Suzuki`s link, delaying (Patel 2019) its drainage of parenchyma by CIMURAF. In fact, only cephalic noxa promote dural trigemino-neurogenic inflammation (Filipović 2014).

The threefold immuno-processes of: the tight arachnoïd bag around bouyant CSF, the skull's logistically

hyperconnected dural, and the brain´s pial meningeal layers usually host lasting inflammations and precede parenchymal processes (Rua & McGavern 2018). All arterial parenchymal suppliers running through the subarachnoïdal space, their interaction with MCs is also key after (Arac 2019) - or even *before* stroke. The (fenestrated) duro-calvarial 3 meningeal arteries – stemming via the aortic arch from its lymphatic crossroad especially on the *left* should receive by CIMURAF (Treviranus 2014, 2019) incoming adventitial destination-driven MCs from the *entire lower* body (the gut-brain-axis e.g.) - which might then descend into the brain. In fact, meningeal MCs change morpho-spatio-temporally in *left*-lateralized ways (Michaloudi 2007). Brain`s MCs are unique as local influencers (Silver & Curley 2013, Cocchi 2022) in that these BBB-opening long-lived sophisticated guardians (Theoharides 1990, 2007) intrude into the sane brain. There MCs also destroy oligodendrocytes´ cytoskeleton (Medic 2010) through vesicle-carried tryptase. By generating C4a from neuron`s C4-coating the latter plausibly also drill schizophrenogenic MAP-pores (Treviranus 2020, Fukuoka 2008, Rey 2020, Druart 2021, Hatzimanolis 2022) - maybe by bypassing a need for C2 (Laich 2022) - while C2-*deficiency* promotes SLE-psychoses (Matsuura 1983). The tryptase-to-C4-link is supported by postpartal AFE (Busardò 2021) or psychoses (Melbourne 2018, Prasad 2018), including confusional «Cycloïd psychoses» (Pfuhlmann 1998) along *just one* of the three median dyn4TAM-loops – maintained plausibly by *limited* thalamic MCs-vasculitis *and* NMDAR(NR1)-Ab (Giné Servén 2021) - produced within skull-draining lymph-nodes and teratomas, which via D816H-(not D816V) mutation in c-kit (Mitchell 2017) over-activate - also depressogenic (Moura 2011) - MCs.

The epileptoïd psycho-sensorial spectrum towards “cortical psychosis”.

“Abundant” subsyndromal epileptoïd symptoms – described since long (Lepois 1618) - as defined by a threshold of 4 entry symptoms from a modified ISSE (Feiner 1998) were found in 13.1% (F) and 11.6% (M) among 494 own out-patient clients (Figure 3), which matched previous 15% (Himmelhoch 1984). Scores decreased linearly with age confirming previous studies (Chapman & Mensh 1951, Richardson & Winokur 1967), thus calming etiological “kindling” (Silberman 1985, Post 2007) (Figure 4).

Affective psychoses mellow soon, but others not in years (Winokur 1985). Inpatients describe auditory > somatic > visual hallucinations – diminishing from SCZ (61%) via bipolar mixed states several-fold to MDD (Abo Hamza 2021). Hallucinators sustain *broad* hyper-oxidative (Maes 2020) connectivity disruptions (Schutte 2022, Hwang 2021), related less to traumatic, than to fantastical contents (Giesbrecht 2007). The loss of intra-*cortical* myelination with age points to neutrophils (Zuo 2022).

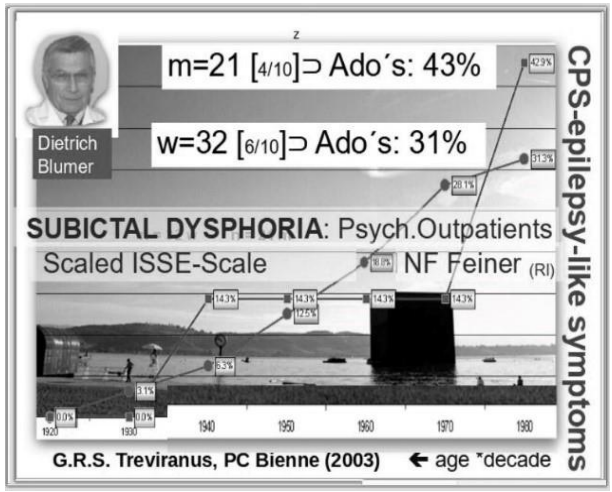

Figure 4. A near-linear age-correlated loss of “abundant” broad epilepsy-like symptoms inspired from (Blumer 2000) - defined after 4 entry items through a 4-graded version of ISSE (N. Feiner 1987-98) among 494 own out-patient clients (F20: 140; F25: 40; F33: 59; F38/F31: 30; other: 235; Treviranus, not publ., 2003

Vasospams from mast cell degranulations by arterio-intramural push-back?

Reversible Cerebral Vasoconstriction Syndrome (RCVS; Chen 2018) denotes a vaso-constrictio-(dilatation) plausibly of one or many sliding «1-chamber-rings» wringing out the CIMURAF (Treviranus 2019, 2020) with delayed segmental 6-fold, always concentric, balloonings of arterial walls (Mossa-Basha 2017). One trigger is C. jejuni meeting MCs in IBS (Shariati 2018, Huayanay 2020). RCVS (in 1/3 angio-negative) starts with broad mastocyto-vegetative processes and ensuing bilateral sagittal spreading (1-180)-min-headaches (and migraine in 1/3), followed by (≤1:3) punctuate convexial hemorrhages (Otiniano-Sifuentes 2021), and some seizures or focal deficits (Kikui 2020). RCVS precedes (in 85%) the 15%-lethal near-ubiquitous, not merely «”Posterior” Reversible Encephalopathy Syndrome» with 2-in-3 convulsions, hallucinations, visual changes, cortical blindness. PRES is imputed to arterioles, and strongly related to autoimmunity (Fugate 2010), hypertension, not merely peri-partal women (Meyer & Zenclussen, 2020), migraine (Delaruelle 2018), and depression (Topcuoglu 2016). RCVS/PRES (and migraines) are probably well explainable by (parieto-occipital) MCs degranulating within the strictly mural sliding chambers draining the brain through CIMURAF in a thus segregated inflammation (Koyuncu Irma 2019, Malhotra 2016). This is visualized by Vessel-Wall-MRI (Mazzacane 2020) or causing edematous watersheds on FLAIR-MRI e. g. along the rear superior frontal sulcus (Johnson 2017), paralleling the pericallosal long-track, were CIMURAF acts maximally, or from the calvario-meningeally irritated lepto-meningeal arteries receiving «push-backs» into bland arterioles from PPG-failure (Treviranus 2020).

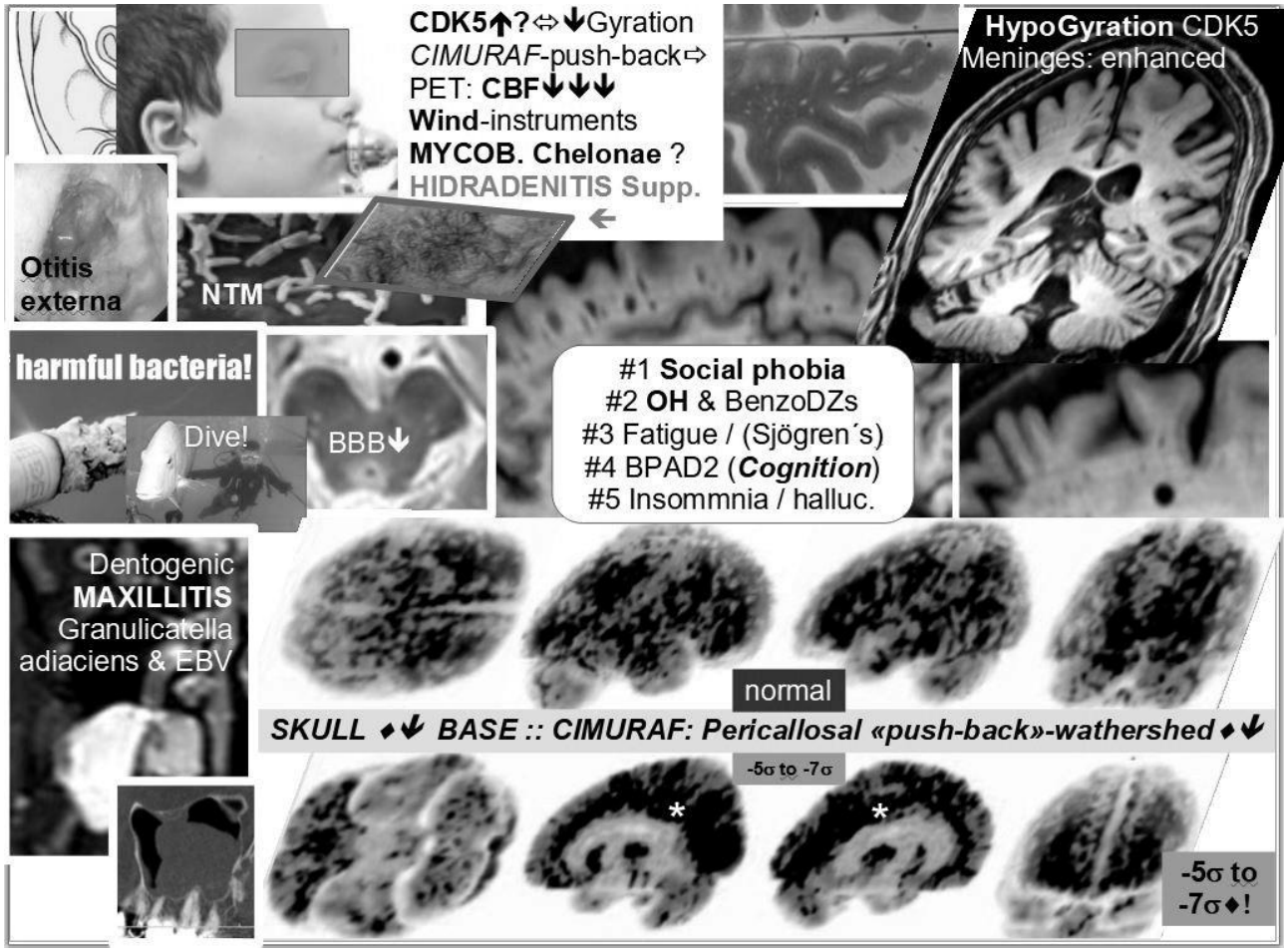

Figure 5. V#2mF1965: A MRI revealed a) Laplacian "wind-boilers" from impaired drainage of WM , b) hypo-gyration from likely genetic CDK5-hyperfunction and c) via PET-FDG unsuspected severe fine-speckled hypometabolism (-3 to (-5) -7 s): Bilaterally maximal (grey) at ventral thalamus, cerebellum, temporal poles and sides, central region, SPG, with spared precuneus. No correlated atrophy (MRI 2015/16). Stars (*) point to 90°-branches from pericallosal artery being occluded by intoxicating "push-back" by failing CIMURAF (Treviranus 2020), also touching basilary artery (Roloff 2016).

HOW TO DEAL WITH INNATE IMMUNO-LOOPHOLES IN PSYCHIATRY

The cruelly successful Mycobacterium tuberculosis (Mtb) informs about host-microbe relations also of other Non-Mtb (NTM)-myco- and other bacteria in general.

Vignette: *V#2mF1965 as a boy trumpet soloist became increasingly plagued by social phobia, urinary urge and hidradenitis suppurativa pointing (as his mother´s recurrent gut-abscess) to rare NTM like M. chelonae colonizing wind-instruments (Tichenor 2012, Møller 2017). From a rural working-class upbringing he made his career as an IT-manager, founding a family, which - after EBV triggered a Sjögren's syndrome with odontogenic maxillitis - ended through persistent fatigue also from typical hyperthymic anxiolytics and alcohol consumption (Figure 5).*

Inflammatory maladies of the meninges and arteries: tuberculosis teaches

The 1% CNS-cases provide 1/6 of extrapulmonary tuberculosis (Tbc). Its often under-five meningitis, which may cause psychosis, remains largely unexplained (Creswell 2021). Besides "parenchymal initiations" the bloodstream supposedly carries Mtbs to both meninges, where Rich's delayed single rupture of meningeal /sub-cortical granulomas contaminates sub-arachnoid spaces (Rice & McCordock 1933, Donald & Schoeman 2004) promoting e. g. purulent basal meningo-cerebritis. Yet tuberculomas transverse the skull and/or cause also, misleading (Lyndon 2019) meningioma-like histologies (Aggarwal 2016).

A meningeal contamination through intra-myelocyte Mtbs intruding through MCCs has not yet been considered. In Mtb-meningitis thrombotic infarcts (1:2) in the young hit *within* subcortical tuberculomas, but spare (supposedly disseminating) other arteries and the veins altogether - while contraction of *all* arteries still occurs (Kalita 2018).

Within "syndemic" Tbc-depression (Sweetland 2017) switches under tubercolo-statics (Van Rensburg 2020) and Mtb-meningeal psychoses could signify bipolarity (Rahim & Ghazali 2016), while valproate helps (Nieto-Patlan 2019) against intracellular mycobacteria (Rao 2018), yet weakening defense (Zhu 2019).

Mtb mows lifes on a global scale, but *after* 2 months only 1-in-10 infected progress from just immunoreactive (1-in-4 humans)-"latent infection" (LTBI) to initial reactive and cutaneous, and eventually *after* 9(-24) months to "active" disease. Since *before* bacteriology a- or pre-symptomatic "latent" inapparent – miliary or lymph-node or tonsillar – infections were observed post-mortem e. g. after *sudden death*. Thereafter mere (today less sampled, than molecularly understood) long-dormant colonization was subsumed under "latency", and finally - with the sadly imperfect tests - mega-"latency" presently includes 1-in-4 humans (!) merely testing positive. While reinfection is the (uncommon) rule (Behr 2021), late reactivation *can* even produce father-son transmission (Lillebaek 2002, Behr 2018). Nevertheless, not so rare "sleepers" remain complex immuno-subverters (Mariotti 2013, Gengenbacher & Kaufmann 2012). Mtb enters shielding alveolar macrophages and then their phagosomes - feeding on the latter´ lipids and Fe-Mn-Ca-Zn-cations), thus hibernating and resisting drugs and genetically anticipated host responses like MCs extracellular traps (Campillo-Navarro 2018), for decades surrounded by induced hypoxic granulomas, until only forcedly disseminating through drilled pores (Zondervan 2018) - especially in susceptible hosts (Researchgate: "MSMD" project 2022). A spectrum spanning from inert, non-replicating «dormant», via latent, yet immuno-active (Mariotti 2013), to active or deadly stealth Mtb-meningitis is reflected in NK-cells (Choreño-Parra 2021, Seddon JA & Thwaites 2019). Neither the latter nor scrofula, usually from reactivated Mtb, are referred to cranial sources (Mathiasen 2019). Luckily MLVs (see 1.3) might easily explain how meningeal intracellular mycobacteria could reach cervical lymphatic nodes (by bypassing ethmoïd (Rotter 2020) and ocular stops) causing scrofula through draining lymph and CFS.

Vignette: *V#3fS1992 seen for bouts of severe anergia and wheals since college, now was treated with standard non-CNS regime for Tbc-scrofula - not considering that a Mtb-related (Arumugam 2016) post-partal atypical eclampsia with PRES (Masai 2019), which is usually MC- and not placenta-driven (Mitani 2002, Broekhuizen 2021, Szewczyk 2012), had occurred a decade beforehand - even after the meninges were suspect on MRI. Her toddler son being severely hyperactive, the possibility of Mtb-subverted meningeal MCs was submitted for consideration, and answered with an ongoing professional ban procedure.*

While tuberculomas rarely interfere with pregnancy (Ahmadi 2011) the origin of the common cervical lymph node changes in Tbc remains unsolved.

What to learn from "Mendelian Susceptibility e. g. to (atypical) Mycobacterial Disorders"

Mendelian susceptibility to diseases caused by intra-macrophagic pathogens, such as BCG, non-/tuberculous mycobacteria, or salmonella (MSMD; OMIM #209950) denotes mutations (1:50´000 births; www.lovd.nl/IL12RB1) concerning crucial innate pathways through the IL12/23/INF-γ-axis, in 79% of IFN-γ´s receptors, yet rarely the ligand. These allow weakly virulent, environmental (or «BCG»-) atypical mycobacteria – or *similarly* non-gut salmonella or *intra*-macrophagic (and -mastocytic) bacteria, fungi, and parasites to cause particular maladies (Kerner 2020) like multifocal SBO (Tsumura 2020).

MSMD informs a much larger range of especially familiar disorders e. g. from autoimmune (Suárez 2017) failures «around» the macrophage-activator IFN-γ stemming mostly from NK-cells and T lymphocytes.

EMERGING THERAPIES AND CAVEATS: THE EXAMPLE OF CIPROFLOXACIN

In an emerging field much cannot be confidently treated, and antibiotic choices (Kourbeti 2015) illustrate such rational meandering: e. g. long-term microbiome-preserving (Kourbeti 2010) high-dose ciprofloxacin (preferring macrophages) is a microglial soother (Zusso 2019) - like rifampicin (Wang 2013), by inhibiting (artery-dissolving; den Dekker 2013) TRL4. Yet besides mitochondrial damage (Salimiaghdam 2022) MC-activation (like from phenothiazines; Hou 2019) occurs exclusively via (non-memorizing) MRGPRX2-variants (Ogasawara & Noguchi 2021) - with "rare & severe" side-effects (CNS, eye, aneurysms), restrained by nutraceuticals (Ogasawara & Noguchi 2021) or micro-dosing (Çelebioğlu 2021). Blessedly clarithromycin emerges as MRGPRX2-blocker overcoming – in *tandem* with ciprofloxacin – M. chelonae (Zahid 1994) even within cells, helped by GABAA-ergics (Kim 2018). Such "wicked" problems (Conley 2018) call for case-specific jointly arguing expertise.

CONCLUSIONS AND OUTLOOK

Longstanding subacute diseases of the brain's wrappings e. g. extending from the ORL-domains emerge through MRI-imaging and "tangible" interdisciplinary medical psychiatry in the neglected (para-)infectious realm of psycho-neuro-endocrino-immunology. The persistently "successful" mycobacteria or the spectrum of 22q11.2 DS teach us much about our weaknesses. Medical psychiatry of MCs hereby actually understands often morally offensive "early life stress" (Duque-Wilckens 2022).

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