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Review

RAPIDLY TRADING DOWN DEPRESSION'S 3 PILLARS TO 5HT3-RECEPTORS THROUGH ECT OR PSILOCYBIN?

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SUMMARY

Depression astonishingly can be stopped instantly by electrotherapies or through some psychedelics like psilocybin. In explaining this, the traditional approaches to their antidepressant effects via "reset" models and orthosteric serotonin receptors has neglected the only serotonin channel 5HT3, which e.g. has emerged as being helpful for the neurotrophic translation for all anti-depressants and final synaptic effects. Psychedelics here are confronted with a panorama of also anti-depressant 5HT3-channels and a search for their part e.g. in the "3 pillars" reigning depression. Of these M1) mitochondria, parasitic organelles from a fusion between some proto-bacteria and archae, founding eukaryotes, also through 5HT3 in depression determine much of its somatic crises. Two further pillars, "pushback" and "shame-link", are clarified by the parasympathetic (PS-) conspiciously 5HT3-rich "nasal" pterygo-palatine ganglion (PPG): PPG-1.) Intramural "pushbacks" intoxicating brain's tissues, show up on MRI e.g. along branches of the peri-/subcallosal artery. The brain-draining circular chambers, by CIMURAF, are plausibly driven by the PPG (and other PS-ganglia) through their dense nitrergic grid, causing loose wrung areas creating hyperboloid stenoses where they delimit contracted sliding segments PPG-2.) Existential conflicts trigger last-resort attacks, whereby the subduing are stopped into submissive shame. This plausibly occurs via the antidromic "Suzuki-link" from preparatory attack-biting (V3) via the trigeminal ggl. V3-V2-crosstalk onto the PPG, which, blushing via PACAP, maybe via MCs opens the BBB causing foggy confusion. Mushrooms may have acquired psilocybin to similarly stop feeding moves of worms (C. elegans) via the >100 5HT3-like ion channels. While on MOD-1 serotonin elicits "dwelling", collective feeding on just one fungus, psilocin could on promote audacious "roaming" (protecting fungi) – channel LGC-50 learning from this. The biphasic and pervasive H_2S, being a dipole, might be flushed by ECT and on the 5HT3-receptors might get worms (and us) to move.

Key words: *depression – psilocin – pterygopalatine ganglion – 5HT3 – mitochondria – H_2S – mast cells*

Abbreviations: *T = Thought; A = Action; M = Mood; MC = mast cell; CSTCC = Cortico-striato-thalamo-cortical circuit; A = anterior; V = ventral; M = medial; L = lateral; P = Pre-; O = Orbito; FC = Frontal Cortex; VLPFC ⊃ IFG (⊃ BA44 & BA45) & LOFC ⊃ BA47. VMPFC ⊃ MOFC (⊃ BA11, BA12, BA14) & MFG (⊃ partial BA10) & ACC (⊃ BA32, BA25, BA24); MTC = Mitochondria; ECV = extracellular vesicle; ACT = Acceptance Commitment Therapy; SCZ = schizophrenia; FEP = 1st Episode Psychosis; DMT = N,N-DMT (ahayuasca); PCB = psylocybin; PSC = psilocin*

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Consider statehood as "biocracy in which the myriad of differentiated cells would be organized into functional organs all cooperating in a dynamic democracy in which any form of dictatorship would lead to degeneration and death"
Walter B. Cannon (N.Y.T. 1940)

Preliminary note

Among global urgencies "depression" (MDD) ranks high. Here we explore how targeting also cationic serotonin-3A channels (5HT3) e.g. with electro-flushable hydrogen sulfide on MDD's 3 "pillars" might help.

PSYCHEDELICS AND THALAMUS: ACTING ON A SUBCORTICAL TRIAD

5HT3 acts in mental and immune homeostasis (Arreola et al. 2015), mirroring the French triad of (abstract) "Thought" (T), "Action" (A: effort), and "Mood" (M: overall growth). Besides systemic crises (-M) of mitochondrial respiration (Karabatsiakis et al. 2014, 2024) two further "pillars" – toxic interstitial "pushback" (-T) and braking "shame" (-A) – pertain to the parasympathic (PS-), also cerebro-vascular pterygo-palatine ganglion (PPG). A typology (Chen et al. D 2023) of early lesions in MDD - of hippocampus (HC; -T), subgenual ACC (sgACC; -A), or up to the OFC (-M) also reflect triadic effects within the 3 medial "artery-encountering" CSTCCs (Cortico-Subcortico-Thalamo-Cortical Circuits), showing serotonin-receptors (5HT2A) on both ends (Barre et al. 2016). The thalamic effects may result from psychedelics (PSD; Preller et al. 2018) or from mast cells (MC) intruding (Trv.2018) at the paraventricular nucleus of the thalamus (PVT) now "seen" through 7T-MRI (Kark et al. 2021) - within the medial CSTCC through ACC (A~ "effort"). A 5HT2A-centric review (Doss et al. 2022) of subcortical effects of psychedelics (PSD) centers on the personal experience-building, massively connected thin claustrum beneath the insula, while considering a thalamic failure of segregation initiated by weak cortical 5HT2A-inputs. After PCB the thalamus among 10 CSTCCs (Gaddis et al. 2022) revealed less connected loops only when subjects reported purpose-/thought- and actionless equanimity or joy – not being asked other slight mixed states (Treviranus 2024). Maybe probands were preselected from the bipolar spectrum (Aaronson et al. 2023), PSDs thereby provoking such subcortical switches, as in the real world of bipolar persons (Della Crosse et al. 2022). A first study has discovered patterns of dysfunction

between thalamic territories with "resting state networks" (CSTCCs) across early psychotic phases and relatives (Kim et al. 2023).

LEARNING FROM HT3

Serotonin (5HT; Reddy et al. 2024) shapes health and e.g. migraine (MIG) and MDD (Viudez-Martínez et al. 2024). Its nerves permeate the brain, while >90% of 5HT are produced in the gut (Rust et al. 2023). A dozen 5-HT-receptors modulate often other signals via 2nd-messengers, but here we approach 5HT3 – the only 5HT-driven "pentameric Ligand-Gated Cation Channel" (pLGIC) moving Na+ and Ca++ in, and K+ out, being also influenced by gasotransmitter hydrogen sulfide (H2S) (Shimizu et al. 2023, Yamamoto et al. 2020, Teng et al. 2019). By slight structural changes its >200 ortho- and/or allosteric ligands, via two half-way configurations (Rodriguez Araujo et al. 2020), 5HT3 can become unpredictably psychoactive. Interestingly 5HT3 is very present at the largest extracranial and -visceral "pterygopalatine" ganglion (PPG), sidelining all the others (Ishida et al. 2019). Higher 5HT3 compensates for weak 5HTT-transport of 5HT (Mössner et al. 2004). 5HT3 soothes pain helping the spinal descending path (Heijmans et al. 2021) or provokes emesis, while modulating neuro-psychiatric and somatic conditions (Fakhfouri et al. 2019, Irving et al. 2021), after shaping prenatal cortex, cerebellum and uroneurology (Murthy et al. 2014, Oostland et al. 2013, Ritter et al. 2017). 5HT3 via reelin secreted by interneurons, regulates their migration and cortical or cerebellar pruning (Murthy et al. 2014, Oostland et al. 2013). Presynaptic 5HT3 is very present on primary sensory afferents or in helping other, fast excitating synaptic neurotransmitters, while postsynaptic 5-HT3 abound on GABAergic interneurons - hereby inhibiting release of ACh and DA or boosting 5HT, with paroxetine (Dremencov et al. 2006). While they are homeostatic in cortical mini-columns, 5HT3 in the HC slow learning, unless setrons are given (Stäubli & Xu 1995). Antagonists calm 5-HT3-driven dopamine (DA) hyperactivity, social fears, withdrawal crises and aversive behavior (Costall et al. 1990). Figure 1 offers a "tunneling" synthesis of antagonists and agonists at 5HT3 and mentions pLGICs of worms. Small ape brains (Jones et al. 1002) show dense 5HT3 in the lower medulla and forebrain. Humans use 5HT3 in the HC, "thrilling" nucl. accumbens, "emotion-triggering" amygdala (AMY), "memorizing" entorhinal cortex, and vagal nerve. 5HT3 (Arreola et al. 2015) is used by many immunocytes like MCs (but not eosinophils), platelets, and within lymph nodes and tonsils. 5HT3 favors inflammatory cytokines, while OLZ diminishes 5HT3 on blood mononuclears (Shariati et al. 2009). Besides many valuable insights into "transformative" psychedelic facets and long-term effects (Vollenweider & Preller 2020), these have not yet delivered on a strong direct link with immediate antidepressant responses (Adep-R) 5HT3 has yet to be mentioned in comprehensive reviews of the manifold PSDs (Zamberlan et al. 2018, Holze et al. 2024). Many substituted tryptamines like DMT e.g., themselves variants of tryptophan, constitute one of their six major psychedelic classes (Tittarelli et al. 2015).

DEPUZZLING RESISTANCE: PSYCHEDELICS, 5HT3, MITOCHONDRIA, SIGNALING TRAINS, AND H2S

The Adep-R of PCB amounts to an effect size of > 2.2, often combined with rapidity and a switch-like complete longevity (Gukasyan et al. 2022), only halved in MDD-persisters (TR-MDD; Aaronson ST, van der Vaart et al. 2024), and of 0.7 against mere symptoms (Galvão-Coelho et al. 2024). The real problem seems to be resistance, and not onset and delay, since the individual Adep-R triggered by drugs or placebo occurs very homogenously before and after two weeks (Stassen & et al. 2007). A large consensus also in research sustains a double postulate for PSDs: 1.) the psychedelic psycho-correlational effects (Vollenweider & Preller 2020, Daws et al. 2022) are pivotal to the often long-term Adep-R and thus 2.) also for the Adep-like effects justify once more a focus on 5HT2A (serotonin-2A-receptors; Madsen et al. 2019), known from SSRIs. This lacked support from a few animal trials, but now game-changing neurotrophic insights have emerged. The anchoring of the highly relevant receptor TRKB (installed only after neuronal activation) among the membrane's lipid-rafts, attracting 5HT3, favors the binding of key neurotrophic BDNF to it, jointly realizing a pivotal step (Casarotto et al. 2021, Enkavi et al. 2024, Eisensamer et al. 2005). This is improved by all Adeps in proportion to their inhibition of 5HT3 (KET, FLX, TCA, DMI, CLZ, also E2 – but not by MTZ, CBZ, MCL, RISP) or cholesterol (Nothdurfter et al. 2010). Then the formed BDNF-TRKB-complex from the synapse needs to arrive at the nucleus for to insert the neurotrophic programs. It's here where the inflammatory resistance occurs, when at the synapse the tubular "signaling train" to the nucleus (endosome) can't be boarded because the complex lacks his recycling-tag, this ubiquination being impeded by too much IL-1b (or Abeta) (Carlos et al. 2017). Inflammations usually start with IL-1b, which at a picogram level disturbs distant cells (O'Neill et al. 2013). All 5-HT-receptors favor the final transcription of BDNF and its receptor TRKB - except 5-HT3 itself (Marin 2020): its job being to travel. In mitochondria (MTC) of neurons 5HT3 is usually colocalized with P2X2 (a prurinergic pLGICs for ATP) which it needs to travel at 1mm/s in vesicles on microtubules to the synapses to influence transmitter releases or to reach surfaces (Emerit et al. 2016) – quitting when an agonist is bound (Ilegems et al. 2004).

Antagonists:	Pubmed PMID	Effects & Consequences	Agonists:	Effects & Consequences	Pubmed PMID
5-HT	37179732	↓MDD via Exercising	5-HT	↑Parasympathic (vesical)	3607365
Psilocin	38238974	↓cluster headache number	Dopamine	↑K+-inflow	14556235
Menthol	23965380	↓(np)	5-HT, mCPBG	↓PAIN [lHb μOp→5HT3DRN]	28626482
Clozapine MetS	23527073	↓ mitochondria; ↑ MetSyn	5-HT, mCPBG	↑PAIN acu. Chr. spinal (rat)	22289689
Clozapine (cp)	15024394	↓(cp) Na^+-Ca^{++}-entry	5-HT, mCPBG	↑PAIN acute local paw (rat)	22289689
HydroCortisone	21190655	↓(al); ↑intermediate states	5-HT	↑PAIN Neonatal (x 5HT7)	34257402
Risperdidone	15024394	((↓))	5-HT	↑PPG parasymp- Neurons	3607365
FGA, Hal, Lmp	15024394	↓(np) Ca^{++}-entry	5-HT	↑[Dopamine:(↑)5HT3]	10728877
TCA	14647397	↓(np); ↓ MDD	5-HT	↑ **REM-sleep**	11532385
Mirtazapine	36707180	↓(cp;desensitizes); ↓ MDD	5-HT CGE-INs	↑early neuronal migration	25409778
Escitalopram	31680773	↓ MDD	2-methyl-5-HT	↑ spinal [GABA-A density]	34678470
Bupropion	31871303	↓5HT3A/3B heteromer	2-methyl-5-HT	↓ spinal pain	11454930
(OH-)-Bupropion	27671323	(↓?)↓(np); ↓ MDD	2-methyl-5-HT	↑ T-cell active, proliferate	10496177
5HT3→ IGF-1→	37179732	↑HC neurogenesis	5HT3A	↓5HT2CdPAG▶↓Fear	34547341
RG3487	24317442	↑↘ DA, ACh (Cortex, HC)	via SSRI (FVX)	↓ seizures	25590967
Memantine	11403963	↓(np) (if add to ↓ MDD)	DRN→5HT3→VTA	▶↘DA, ↑REWARD	30699344
Cannabinoides:	36439263	(not via CB1, CB2)	5-HT	(5HT3 & CCK-1) ▶↓feed	16269356
- Cannabidiol	20160007	↓(al)	5-HT	(5HT3 & CCK-4) ▶↑ACTH	9397424
- D9-THC	12381672	↓(al)	5HT3-var. lab.	Binding▶priming▶opening	32946769
Capsaicin	*32982728*	↓(al)	Dopamine	(↑)5HT3	10728877
Setrons	31243157	↓ ↑ neuro-psychiatry	Tryptamin	(↑)(o) single bursts	
Setrons	7855223	↓REWARD heroin	5OHKynurenamin	((↑)) gut ileum	3572806
Odansetron	26979154	↑ [Fluoxetine ▶↓ MDD]	Varenicline	(↑) 5HT3, nausea; ↓? F17	17157884
Granisetron	19942458	↑ PTZ-seizures	Tianeptine	↓ visceral PAIN	22348811
Estrogen 17β	29956631	E2 ▶↑5HT▶↓seizure	Paracetamol	↓PAIN Dorsal Horn balance	34135207
Testosteron	12510009	↓	Ethanol, 3CL-EtOH	↑[Dopamine→(↑)5HT3]	10728877
DHEA→Estrogen	12510009	E2 ▶↓(a)	Ethanol	↑[5HT3▶↘GABA(HC: CA1)]	33275959
MDL-7222	31133812	↓MCmening▶PAINmigraine	Gabapentin	↓Neuropathy (lesion)	16150546
CSP-2503	15777774	↓anxiety; mainly (↑5HT1)	5,7DMCoumarin	↓ Neuropathy (vincristine)	37920212
Minocycline	35426093	↓PTZ-seizure			
Progesteron	12510009	(↓) MDD, Anxiety	High-Fat-Diet	↓[2-Me-5HT [↓ MDD]	26979154
5-HTP-FLX	1386914	↑ Prolactin	High-Fat-Diet	↓[Fluoxetine: ↓ MDD]	26979154
DHEAS	19420298	↑↘Glutamate Cortex	High-Fat-Diet	↓[ForcedSwim: ↑ MDD]	26979154
Y-25130	12479948	↓REWARD cocain			
Lamotrigine	28280410	↓ seizures	5-Chloroindole	↑(o&al-transmb) needs 5HT	27677804
MDL72222	23792143	↓REWARD MMDA	Terpenes	↑(al) burst series (=0 MOD1)	26456648
LChain1.MAP1	18063656	↓(d) 5HT3 via Cytoskeleton	Pregnenolone	↑5HT3 x σ1 x GABA-A →	11303034
Y25130	20010428	↓ colon cancer cell line	Phenylbiguanide	↓vagal cardiac HR control	36622083
Co-/Lidocaine	7682657	↓ Na^+ influx	Bisphenol-A	↓E-cadherin, ↑mitosis	34743013
MOD-1 Pipera-zine Musci-mol	35952761	↓ C.legans locomotion (dwelling)	MOD-1 C. elegans 5-HT	↓ dwelling-feed programme	37607537
				↑ MOD1▶disgust-roaming	23023001
				↑ C. elegans locomotion	35952761
LGC-50			LGC-50 Tryp	↑ learn aversive roaming	37192620
Psilocybin PSC	?	? MOD-1 ? LGC-50	*Psilocybin PSC*	? MOD-1 ? LGC-50	Trv. 2023

Headings: Antagonists inhibit & Agonists increase ion movements. Effects point to observed changes. PMID by Pubmed: the code retrieves the paper in Pubmed at https://pubmed.ncbi.nlm.nih.gov/.

Abbreviations: (al) – allosteric; (d) - desensitization; (o) – orthosteric; (cp) – competitive; (np) – non-competitive; Tryp – Tryptamine; m-CPBG:1-(m-chlorophenyl)-biguanide; SGA: 2nd Generation Antipsychotics; 5-HTP 5-OH -tryptophan → 5HT: serotonin; SSRI: FLX Fluoxetine; FVX: Fluvoxamine; CCK: cholecystokinin; lHB: lateral Habenula; DRN: Dorsal Raphe nucl.; CGE-IN: reelin-interneurons from Caudal Ganglionic Eminence (for cortico-genesis); ↑ :increase; ↓ : decrease; ↘ : release; ▶: consequence

Figure 1. Effects and consequences of 5HT3-channel modulation: an approximative, tunneling overview

LEARNING FROM CORTICAL MIGRAINE: FROM BAD IL-1B TO AMBIVALENT DIPOLE H2S AND MAST CELLS

This resistance among many cytokines in MDD correlated only with steroid-resistant auto-immunogenic IL-17A (Nothdurfter et al. 2021), which mobilizes immunocytes secreting IL-1b. By actually not being a dipole, IL-1b may not be the very signal flushed away with electricity (ECT, NIBS; Treviranus 2019). But the gasotransmitter hydrogen sulfide (H_2S), might take on that bridging role: by being in 85% a dipole as HS-. The feared H_2S eco-toxin, at low doses nevertheless is very healthy, while becoming noxious at higher doses: H_2S relation to electrotherapies is presently unknown. Mice by H_2S were prevented from suffering MDD-like behavior as expected, after LPS (instead of chronic mild stress) triggered NLRP3-inflammasomes to release IL-1b, while causing relevant cell deaths of astrocytes in HC (Bao et al. 2024). But H_2S increases "neurogenic inflammation" via TRPV1 or TRPA1, while also stabilizing MCs (Koroleva et al. 2020, Rodrigues et al. 2017, Samama et al. 1988) - also via their own H_2S and similar SO2 (Zhang et al. 2020). H_2S (and NO) are prime modulators of arteriolar (and arterial) tone (Dongó et al. 2020). MIG by common fatigue and arousal recalls the comorbid bipolar spectrum (Karsan et al. 2021, Duan et al. 2021), also through the powerful downstream agent IL-1b showing in MIG its peaks stemming from "Cortical Spreading Depolarization" (CSD; Aristide Leão 1944). CSD is a functional parallel upstream constriction of nerves and arteries (with a 2nd hyperemic phase) slowly wandering over cortical gyr, brought about by pericytes stimulated with (endothelin) ET-1 (Dreier 2002) - strongly increased by chymase from MCs (Houde et al. 2013) – acting on receptors upregulated by cytokines and growth factors (Ahnstedt et al. 2012). Recently in mice CSD, optogenetics triggered just cortical neurons (Böhm et al. 2020), inducing a proportional rapid peak of IL-1b (10th min to 4th h), potentiated by repetition. Such a rapid release of IL-1b in CSD (via ambient ATP) was not due to neuronal P2X7/Panx1-channels, slowly inducing inflammation (and more IL-1b) via inflammasome NRLP3. Instead, an ignition of CSD was required, which allowed NMDAR-receptors to react to K+ via L-type Ca2+-channels (LVGCC; Takizawa et al. 2023), their gene CACNAC1 being well known in psychiatry (Harrison et al. 2020). LVGCC-blockers in fact shorten CSD (Menyhárt et al. 2024), while calming MCs and harming their defenses against MTC-caused cell death after IgE (Suzuki et al. 2009). At least P2X7-mediated degranulation of MCs triggering pain in MIG is prevented by H_2S, also via decreasing extracellular ATP (Koroleva et al. 2020). MCs could well start or amplify CSD – after being stirred at their MRGPRX2 with PACAP (Sbei et al. 2023) or SP – or by IgE. While being painfully transmitted to the TG-system via PACAP, such inflammation in MIG spreads also into the skull marrow through meningeal channels (Dalkara et al. 2024, Chen PY et al. 2023) - or might even stem from there. MCs after a plausible descent onto the meninges (and further) along the adventitia of the dense calvario-meningeal vessels (Cai et al. 2019), using E-cadherin as AML-cells do (Yao et al. 2018, Pastwińska et al. 2020), as the very first trigger could well spill tryptase from their vesicles, thus transiently dissolving dendritic cytoskeletons as seen in CSD (Medic et al. 2010, Kirov et al. 2020). Such cortical irritations recall auras in MIG or effects of PSDs: like long-term flash-backs (Müller et al. 2022), hallucinations (Orsolini et al. 2017, van den Berg et al. 2022), visual snow (Puledda et al. 2020), experiential pseudo-seizures, near-death and locked-in states or dreaming (Sanz et al. 2018), and FND-conversion disorders (Gonsalvez et al. 2021). Next to the TG-ganglion and dura also some cervical root input, e.g. from the lymphatics, or adventitial vertebral artery input, could disturb the trigeminal and the PPG-feeding salivatory brainstem (SNS). Thus the dura (and pia) through the versatile mast cells would somehow map the defense situation of the body. The contralateral TG-V3-neurons e.g., from the thalamus reach beyond migraine into the visual system (Noseda 2011).

THE PTERYGOPALATINE GANGLION: WHAT ELSE? PUSHBACK!

The PPG's 70.000 cells are excited along the facial cholinergic nerves from SSN, and their postsynaptic 2 x 4000 grid-like nitrergic nerves (Taktakishvili et al. 2010) project via the cavernous sinus to most cerebral arteries (De Oliveira et al. 1993). By relaxing primarily contracted smooth muscles (VSMC), the PPG seems to coordinate the serial histological rings (Albargothy et al. 2018), or cylindrical chambers of "Cerebral IntraMUral Reverse Arterial Flow" (CIMURAF; Treviranus 2019) draining brain's tissue proper, while, when it fails, toxic "pushbacks" occur. In rodents branches of the internal and external carotid and maybe the distal basilary artery (BA) are dilated by the otic ggl., and some internal carotid (and cavernous sinus-) mini-ganglia (CMG) reach out to the circle of Willis and branches (Roloff et al. 2016). Nitrergic dilation at the BA of pigs through local axo-axonal nicotinic inputs may even occur from the sympathicus (Si et al. 2011). The PS-influences on the posterior circulation (Roloff et al. 2016) received little attention, even in stroke (Tamayo et al. 2021). All this recalls Meynert's bipolar manically dilated or depressed arteries (Theodor Meynert 1884), only considered by

geriatric psychiatry in atherosclerosis - triggered by MCs via foam cells (Shi et al. 2015). The vasodilating PS along the facial nerve since 100 years is targeted coarsely or closely on the outside of the PPG (Borsody & Sacristan 2016), to successfully treat excruciating headaches (Baker et al. 2021), also helped by PCB (Schindler et al. 2024, Madsen et al. 2024). Stimulation here increases CBF, opens or stabilizes the BBB (Lim et al. 2023), or even relieves vasospasm in rabbits if its neurons are sufficiently dense (Kara et al. 2024). MCs regulate the BBB mostly from its outside, and freely enter brain tissue (Zhuang et al. 1996), releasing vesicles asking for drainage. Yet the PPG might be a neglected candidate for two further "vascular" roles: "shame" by releasing MCs (see below) and "pushback". According to the "Cerebral Intra-MUral Reverse Arterial Flow"-framework (Treviranus 2020) the PPG seems to steer an astonishing machinery within the walls of human's only "dilatable" cerebral arteries, hereby draining brain's interstitium upstream (while offering compliance against incoming pulses, also conveying adventitial cells advancing counter-current through autocrinicity). The long and straight – and thus CIMURAF-optimizing - peri- and sub-callosal arteries and their orthogonal branches (Neurangio 2024, Mincă et al. 2022) are where to look for the predictable consequences of "pushback". A congestion from undrained intramural interstitial fluid will plausibly increase interstitial heat, inter-axonal extracellular water with toxic solutes, and dry out axons, offering less compliance against pulsatile inflow, and conveyance to autocrine immune cells, like mast cells (MCs), along long straight arterial conduits, loosing MCs into tissues in curves. In MRI pushback might show up as neuronally unopposed indentations of RCVS or periarterial "worms ending up in blebs" (Fig. 5 in Treviranus 2022) - telling suicidal severity in TRD (Vandeloo et al. 2023). Pushbacks will disturb the local BBB and its companion cells including MCs, and even downstream arterioles, thus intoxicating the CNS and finally relaxing the arterial wall easing supply. Many among the serotonergic PSDs (Holez et al. 2024) can be presumed to normalize CIMURAF – opening the "knot" – at the PPG because of their quick and lasting effect, and for some cues from early fMRI (Carhart-Harris et al. 2017) hidden behind, at times dubious, RSN-correlations (Stoliker et al. 2024, Pagani et al. 2024). PSDs in fact activate the anterior and posterior cingulate cortex (ACC; PCC), and PSC within 10 min also the retrosplenial cortex in rats eliciting via EGR1 widespread protein production (Liu et al. 2023). A normal CIMURAF-drainage along the straight callosal arteries would drain rostrally and towards the rear, emptying into outside lymphatics. An inverted peristalsis instead would lead to a pushback peak at the half-way center, congestive sequelae spreading less towards both ends, where branches take off to the mPFC and the posterior cingulate cortex, two areas dense with 5HT2A. Their rostral parts e.g. feed the dmPFC, building social trust, an area as crucial for MDD as sgACC (Pizzagalli et al. 2022). In "low-trusters" social trust areas (dmPFC, dlPFC, precuneus) are as thinned out as in MDD (Fermin et al. 2022), while in the mPFC PTSD-like states in rats seem compensated by more 5HT3 (Mohammadi-Farani et al. 2021). Instead under verbal fluency testing in naïve MDD local blood-O2 (by NIRS) was boosted less in the R dlPFC (correlating with severity) and not at all in TRD-cases in the midline dmPFC and L dlPFC (Sun et al. 2023). Yet "depressive perfusions" from proxymal PPG dysfunction remain muddlesome, while ECT heals even cerebellar fluctuations (Chen X et al. 2023). PCB-induced felt changes instead go hand in hand with recovered connectivities and serum-PSC (Olsen et al. 2023). The first volunteer test with PCB showed that 30% of the VAS-graded effects were attributable to less supply to the ACC, 15% to that to PCC, sparing the middle third (Carhart-Harris et al. 2012) of the pericallosal supply (Siegel et al. 2024), as if recovery from "pushback" had boosted local over interactive processing at the less attained ends, while arterial branches at the most "pushed" by and inverted CIMURAF-peristalsis in the middle third had just recovered their muscular functions restoring their bloated diameters. In 7 healthy persons again PCB markedly disrupted correlations also in the PVT, but again sparing the "middle third". At the HC the acute and residual desynchronization seemed limited to the arch of the PCA, sparing the (less accessible to MCs) arteriole-distributing parallel arch (Xu et al. 2021). Whilst these interpretations may be bold, they show, that "plumbing" is still "psychiatric". That PCB (Carhart-Harris et al. 2012) had attenuated arterial supply not only to the posterior cingulate cortex (PCC) within the "DMN", but also to the main spot of damage in MDD, the subgenual cingular cortex (sgACC; Drevets et al. 2008), came as a lasting "surprise" (Nutt 2019). Both PCC and sgACC – at the extremes of the pericallosal artery - increased their common lockstep after PCB-therapy for TRD. The changes of perfusion were so highly circumscribed to the left AMY correlated (0.59) with less depression (Carhart-Harris et al. 2017), that also an interrupted intrusion of MCs via the anterior choroidal artery seems possible. rTMS (acting downstream of PPG) makes resting states at the precunei and right sgACC less predictable (Tan et al. 2024). Remission of MDD furthermore, following high U/S-tissue-pulsatility (Desmidt et al. 2022), rescues arteries from insufficient arterial wall compliance, which by CIMURAF is normally provided via the pulses` encounters with the oncoming serial rigid sliding chambers, which fails in ME/CSF (Treviranus 2021). Bipolar depression (BDD) with atrophic MDD-typical sgACC suffers worse outcomes (Alexander et al. 2021), meriting a "combined BDD/MDD" hypothesis.

SHAME: FAILING PPG FROM CHRONIC PSYCHOSOCIAL STRESS?

This crude explanation of shame by the direct "Suzuki-link" between the TG- and the PS-system (PPG) plausibly connects biting inhibition with the shame-reaction. It favors a definition of shame as a rapid brake of, by definition, murderous, last-resort attacks triggered by vital threats, or such felt as vital, elicited by a judgement of inferiority in battle - in often even innocuous relational contexts with conspecifics. This own concept was derived from teachings of Intensive short term dynamic psychotherapy (ISTDP) by Habib Davanloo (1927-2024; Wikipedia 2024). Hereby quite murderous individual attack programs, which are half-unconsciously installed by vitally threatening trauma, but also by innocuous childhood experiences of ruptured bonding (thereafter triggered in sense-less transference contexts) surface through astonishingly uniform sessions providing focused, but carefully modulated therapeutic comprehensive collisions with sighing, wringing and freezing fear and various redirection activities, like diverting gaze or rationalizations, which finally trigger sudden and lasting liberations from one of several episodes of "neurotic" cornering, which may amount to severe depressive states. Davanloo and followers were not interested in the "Suzuki-link", and would only use the term "guilt" - only slowly being separated from shame (Dearing et al. 2005). The psychological overmolding of shame- and guilt-reactions occurring mainly through adjunctive, threatening versus encouraging, social evaluations of the "social-self" during the life-cycle – i.e. through socially shaped self-asserting expectancies (risking thought-less fear and depression) versus cognitive (also worrisome) approaches to defeats (Zhu et al. 2019) - is usually considered more as a contrast between generalized (shame) versus specific impeachment (guilt), while the lack versus incitement of problem-solving cognition receives less attention (Stewart et al. 2023). Shame is often misidentified, as it lacks a facial expression - besides blushing ignited via PACAP from the PPG. Not just submissive, but also overmolded chronic shame requires evaluations of self- and other representations respecting to group values and thus higher cognition. Shame seems to be the only negative emotion harming the health of the shunned (Sedighimornani et al. 2018). This could explain why even the not just fantasizing BDSM-practicing (at times humiliated) mostly female submissives seem less neurotic, in better mental shape, despite being less agreeable (Wismeijer et al. 2013) or narcissistic: BDSM-culture insists on safety, rarely becomes serious as in very common choking (Hou et al. 2023), and thus is just about having "social play" fun by inflicting and sensing commonly aversive stimuli probing the limits of play. Within the adult forensic world true sadism, boredom and violence, psychopathy concern different "dark" minorities with little overlap. Social play (SPL) as modulated in rats since 1980 was pivotal to Jaak Panksepp's "Affective Neuroscience", reflecting ecological "discomfort" or "comfort" in most vertebrates (Cromwell et al. 2022). He also tested "PLAY" as pro-social therapy reducing negative affect like anger. While moderate prepubertal stress will increases SPL, high stressors decrease SPL, whereby high-players show vicious attacks and MTC-activation at the AMY. Unsupportive companions and lack of SPL ruin young rats` dopaminergic systems (Parvopassu et al. 2021). Only male rats need play for adult adequacy (Achterberg & Vanderschuren 2023). Shame (to me) is a submissive response to threat, embarrassment a response to unsettled ranking, and guilt a cognitive remediating response – and influential in FND-seizures (Myers et al. 2021). Shame, but not guilt, predicts neuroticism (r=0.45), its more intra- und less extraversion being "uniquely" associated with worry and social fear (Muris et al. 2018). Chronic shame subverts aggressive self-affirmation and quality of daily life. Liberation from depression and shame can instead be relieved by revealing attack programs in intensive short dynamic psychotherapy by Habib Davanloo (Kakarinos & Koutsomitros 2019) - who only used the term (specific) "guilt". A more tragic method of neurotic relief yet seems to be conscious, often hidden, aggressivity (Potegal & Nordman 2023), practiced by fascists e.g., who "see everything through the lense of (…) dominance and submissiveness." (Reich & Lofthouse 2024), while realizing, that (originally neurotic last resort triggered) aggression against conspecifics can be understood and controlled. Violence can be legitimated through group or societal norms and abandoned via societal hope and self-compassion (https://apps.who.int/violence-info/). The "masculine" overcoming of fear by rage as in hunting (Elbert et al. 2010) usually yet doesn't amount to enjoyed "dark" sadism (Lobbestael et al. 2024). Looking for a connection between the nearby forensic lab's brainstem casomorphine and SIDS (Pasi et al. 1992, Coquerel et al. 2021) I realized that the PPG possibly could open the BBB and thus also provide a plausible biology of neurotic biting-inhibiting "shame" as an elicitor of the innate response to social defeat stress (Biltz et al. 2022). Clenching, migraine, cerebral vessels, and the temporal pole (synthesizing data on single conspecifics; Balgova et al. 2022) interact somehow in inflamed dysfunctions (Zaproudina et al. 2018). Intranasal lidocaine somehow relieves sensitized migraine pain, but not brainstem central nociceptor allodynia (Yarnitzky et al. 2003). Maybe it's primarily more about trigeminal ganglion irritation from cervical nerve roots, than the PPG-feeding salivatory brainstem, but then the PPG modulates this. But slowly a connection between the biting V3-root and a

neurogenically inflaming pathway into the PPG appeared. In 1989 Suzuki established an "axon reflex"-like connection outside the brainstem (Suzuki et al. 1989). Potentially inflammatory V2-TG pain-sensory nerves (SP, CGRP) as fine baskets encircled the principal PS-ganglionic neurons (VIP, muscarinic; Beckers et al. 1991) of the PPG – heading as adjunctive vasodilators to the anterior cerebral vessels. Since the intra-trigeminal V3-to-V2 cross-talk (Messlinger et al. 2020) was not known of, and increases of CBF were not convincing, this became soon forgotten. The scope of 5HT3 on top of TRPV1-channels in these sensory TG-afferents is not understood, since facial pain sensitivity via 5HT3 is only increased in neurogenic inflammation, and not - as it is in the periphery – in normal sensation (Kaur et al. 2021). Within the wall of leptomeningeal arteries granular type II-MCs commonly contact PS-nerves (Dimitriadou et al. 1987), each, and not the endothelium, storing half of local 5HT, whereby MCs when stimulated with ACh (or compound 48/80) release their 5HT (Reynier-Rebuffel et al. 1992). The PPG, uses PACAP, but not CGRP, while being unique in using a "purposeless" M2-muscarinic path to inflame the BBB at small arteries (Margas et al. 2009). Importantly this activity could stimulated MCs on both of their mAChR and nAChR (Nazarov & Pronina 2012) to open the BBB especially via histamine (Yue et al. 2023) from thus disinhibited MCs. Also, dural and cerebral efferent PS-fibres (VIP, NO) from PPG (using PACAP, but not CGRP), and otic ggl., can tell unmyelinated TG-fibres via mAChR and nAChR to cause (via CGRP, SP) pain and extravasation in small dural arteries (Delépine & Aubineau 1997). Yet CGRP in MIG failed to cause extravasation or the biphasic vascular reaction under CSD (Schain et al. 2019), albeit slow (or rapid) PPG-stimulation in cluster headache (CH) favors (or calms) CH-attacks (Schytz et al. 2013). Large arterial feeders to the meninges in MIG are involved in neurogenic inflammation (Levy D et al. 2019) and should not be basically different from other cerebral arteries. The comprehensive obnubilation during acute shame thus becomes a likely result of the "Suzuki-link".

LEARNING FROM MUSHROOMS, LIGAND-GATED CATION CHANNELS, AND WORMS

Since orthosteric ligands on 5-HT3 by minimal structural differences intriguingly achieve their effects on the entire range from superagonist to full agonist, partial agonist, and complete antagonist (Alix et al. 2016), by actually causing degrees of twisting of the extracellular domain, which result in skewing of the distribution from pre-activated to open-like states (Felt et al. 2024), opening of various pLGCCs in fact requires, the membrane`s lipid rafts aiding, a sequence (or a simultaneous flip) of 3-4 closed preopen-states of 1-2 sec at binding sites – determining efficacy – before full opening (Corradi & Bouzat 2014). The psychedelic "receptorome" (Ray 2010) originally didn't yet include the unique 5HT3-channels. While 5HT3 activates the PPG, the effect of PSC on conformational changes of 5HT3 has not been reported in man, nor those on >100 pLGCs (Hernando et al. 2023) of worms. The model worm C. elegans (see: http://www.wormbook.org/) has helped with many bottom-up explorations. Its CNS is ring-shaped and surrounded by 4 glial cells with processes sensing the oral area (Singhvi & Shaham 2019), allowing to imagine a homology with the PPG of the ORL-area.

Several fungal branches acquired PCB (Kosentka et al. 2013) likely not to kill worms, as N,N-DMT from Ayahuasca (DMT) does (Meyer 2017, Meyer & Slot 2023), but rather to "shame" the locomotion of worms, their main feeding adversaries, into simple "dwelling" as 5HT does on pentameric channel MOD-1. This results in collective feeding at just one place – whereby one sacrificed spot might save others. Less basic models in foraging mirror "dwelling" vs. "roaming" by defining anxious "social" dwelling vs. audacious "solitary" roaming (Dwyer 2018). While e.g. MOD-1, just in the now, disgusted from smelling bad bacteria, enhances "roaming", it is allosterically inhibited by Adep mianserin (Venkatachalam et al. 2016, Savin et al. 2000); but being an exclusive Cl-channel, it may behave very differently from 5HT3. LGC-50 instead mediates learning from such disgusting smells (Morud et al. 2021). While the effects of PSC are unknown, 5HT activates 5HT3 at the PPG and sustains "dwelling" of worms via MOD-1, which plausibly results in feeding on mushrooms (Treviranus 2023). Yet hereby on mushrooms one sacrificed spot might save others as an inverse model (Dwyer 2018) defines: anxious dwelling vs. audacious roaming. Maybe 5HT, exciting 5HT3 also on the "shaming" PPG – an analogue movement-stopping network – on LGC-50, would cause "social dwelling", while PSC (or several SGAs antagonizing 5HT3; Rammes et al. 2004) in worms would energize "solitary roaming" causing wounds to more fungi. Serum from TRD-responders or PSC therefore might activate worms. Still worms' olfaction is key to the systemic stress response (Dishart et al. 2024), which via "non-autonomous" vesicles shed by 5HT-neurons calls for protein recycling by UPR in organelles (EPR, MTC) - or else via DA-neurons for lipid store depletion in the whole worm (Higuchi-Sanabria et al. 2020). Clinical research on such by nature double-edged processes has just started (van Ziel et al. 2020). Circulating "non-autonomous" signals (molecules, vesicles) move centerstage. MTC sense many stress-signals, persue strategies and exchange own signals with peers: via microtubes or even in distant cells via mitokines (Picard &

McEwen 20218, Merry et al. 2020). Senescence seems accelerated after early life stress, as mirrored by slowed restitution of telomere length (TL) after cell division by telomerase reverse transcriptase (TERT) – e.g. in immune cells (Liu et al. 2024). While 20% of TL were explained by the leading steroid DHEA (De Punder et al. 2024), this possibly reflects a parallel downsizing of a sulfur-pool of DHEA-S and resilience-factor H_2S (Moustafa 2021), since DHEA/DHEA-S is constant (Zumoff et al. 1980). The PPG can be conceived as pivotal to neurosis when a submissive shame after inter-conspecific trauma has become notched, while biologists can rarely calculate out the traits inherited from many perpetrators. Nevertheless, the transfer of oncological concepts and technology now help to tackle ELStress-problems: extra-cellular compensatory factors determine disease, i.e. MDD, beyond the "autonomy" of the cell while defending the organism's "longevity" by trespassing various barriers.

LEARNING FROM MITOCHONDRIA

Mitochondria (MTCs) stem from a finally fusing genetically balanced cooperation of protobacteria with hosting archae, enabling plants, fungi, and animals to be through energetics, synthesis e.g. of nucleotides, and also epigenetic signaling (Yadav et al. 2022). Most metabotropic 5HT-receptors seem to increase biogenesis of MTCs, and thus the very costly cerebral cell maintenance, by providing, after oxidant injury, the energetic ATP-currency rather through the SIRT1-PGC-1α axis. This axis is crucial for healing of often systemic (and comorbid) mood disorders (Khan et al. 2023) and correlates with anxiogenic stress in PFC (Zhao et al. 2023). Setrons decrease 5HT3, SIRT1 and various cell injuries (Mirshafa et al. 2024). Thus DOI, the amphetaminic PSD and 5-HT2A-marker, augments intracellular ATP in renal (via SIRT1) and cortical cells (Rasbach et al. 2009). At the inner membrane of MTC (mIM) 5HT3A resides (Rao et al. 2023) in natural and transfected cells, being shuttled from other organelles, or released outside. Its 5HT3-type E-companion (known from the gut's mucosa) serves as glue to the membrane. MTC via its respiration chain provide ATP for the proton pump flow (PPF). This also drives the mitochondrial Ca2+ uniporter (MCU), sourcing Ca2+ fluxes for signaling and e.g. activation of cell death pathways. On the inner membrane of MTC (Mimb) one also found 5HT4 (Wang et al. 2016), and only cells of mice lacking them both deteriorated by losing ATP. Independently from PPF and hypoxia 5HT on 5HT4 reduced Ca2+ uptake at MCU, while 5HT3 in normoxia stayed quiet. Ischemia activates the MCU by inserting a toxic amount of Ca2+ into MTC and then the cytosol. Only in hypoxia 5HT3 further noxiously increased Ca2+ by 1/3. Flexibility of MTC respiration (RCR) was improved by 5HT3, lowered by 5HT4 and drugs targeting both 5HT3 and 5HT4 emerged as welcome: to stabilize Ca2+-fluxes (🡻5HT3 and 🡹5HT4), and antagonists to prevent small molecules (provoking swelling or apoptosis) to enter at the mPTP-pore through the Mimb at early reperfusion. Also by GWAS MTCs dominant L-type-VG-Ca2+-channel has been suspected of broadly disturbing MTC and mental health (Khan et al. 2023). Psychotropics – yet not lithium – target complex I, boosted by mania, and IV (de Sousa et al. 2015), but antidepressants which also promote the PPF in MTCs (versus hindering Adep-s) double manic switches. These latter nevertheless, and possibly hereby, heal many depressions, which are often due to obstruction or overload of MCTs (like stresses of life, glucocorticoids, fat, pollution, which act in various tissues and ways). But pre-existing genetic hinderance may put some bipolar patients at depressive risk (Gardea-Resendez et al. 2023). The essential fission-fusion-cycles and deployments of MTCs to needy areas of cells required early cooperation with cytoskeleton's myosin-motors, microtubulin and actin anchors (Yadav et al. 2022). As to plausible PSD-effects, especially also against fatigue (Fissler et al. 2023), motility of MTCs follows 5HT1A-activity, while 5HT2A-neurons after PSD recruit astrocytes rich in MCT, known to be infused via nanotubes into other cells, or spreading e.g. via Extra-Cellular Vesicles (ECV) as «momioma» (Valenti et al. 2021), as can be pictured (Guan et al. 2022). In MDD MTC-proteins in neuronal plasma ECVs recovered after SRI-response, except complex I-6 (ETC) and PGC-1α (master of biogenesis), while in FEP-psychosis ATP-synthesis was only down in astrocytic (not in neuronal) plasma ECVs (Goetzl et al. 2021, 2023).

LEARNING FROM MAST CELLS IN THE PARAVENTRICULAR THALAMIC NUCLEUS?

MCs are hyper-complex stealth cells, which besides reproduction and activation of lymph nodes seem as mighty as replaceable (Norrby 2024). Furthermore, many MCs are strongly activated by toxins from Gram-(+)-bacteria, which compounds MCs` roles - also after subversion by pathogens (Jiménez et al. 2021; Table 1 in Treviranus 2020). MCs reside at barriers, in the meninges, and adjacent to arteries, which they dilate with their NO, VIP, VEGF, and TNFa, while their tryptase excites or (via C4) perforates neurons. Interestingly MCs, which lack 5HT7, signal via 5HT onto 5HT7 of all other immune cells (Quintero-Villegas & Valdés-Ferrer 2019), as if these were taking the MCs` commands. Among these, strongly MDD-associated (Maes et al. 2024) compensatory Treg-cells (Msallam et al. 2023) and special

B-cells seem activated. Now e.g. PSC-microdosing (Kiilerich et al. 2023) resulted in more resilient and less compulsive rats, while increasing their 5HT7 and synapses specifically in the PVT of the 1st CSTCC. The rat's compulsions being a more habitual appropriative mode with little thought, an inhibition of the PVT itself, and / of a local population of connective MCs by PSC seems likely, because MCs have been proven to be essential for a cognitive "sign-tracker"-temperament of rats exploring circumstances of feeding, rather than to eat (Fitzpatrick & Morrow 2017). This had been suggested to the lab based on the MDD-driven switch of the human "uncertainty-oriented" (R. M. Sorrentino 2012) sign-trackers, attracted by 4D-modeling, into the opposite intuitive, but certainty-driven mode. I had proposed a vertebro-basilar adventitial intrusion of "depressiogenic" MCs from the lymphatics along the thalamogeniculate artery (Treviranus 2017). M. Maes hesitated (personal communication, WFSBP 2015) to consider MCs in PNEI, but now (Maes et al. 2024) picked up the baton (Theoharides & Cochrane 2004, Theoharides et al. 2016). While the medial habenula need MCs for parenting (Zhuang et al. 1997), ketamine calms anti-reward (Taraku et al. 2024) at the nearby lateral habenula (Zhang et al. 2022), which are both pivotal for MDD: they bridge the basal forebrain with mid- and hindbrain by transforming insular decisions into willingness to act (Khalighinejad et al. 2021). Since ontogeny MCs are close to larger cerebral arteries, where >90% reside on the brain side of the BBB (Khalil et al. 2007). MCs plausibly use the adventitial pathway along calvario-meningeal vessels (Yao et al. 2018), e. g. after maturation from myeloid progenitors inside the skull, and from the leptomeninges into the brain (Lambracht-Hall et al. 1990). CSD also seems to relate to this (Treviranus 2023). In fact, the tryptase, which connective type MCs` vesicles liberate, not only harms the cytoskeleton of oligodendrocytes (Medic et al. 2010), but likely also that of axonal dendrites transiently de-structured by CSD (Kirov et al. 2020). Similarly, they might intrude along the carotid or thalamic arteries` adventitias (Treviranus 2017). As to painful states, MCs are triggered by neuropeptide SP from nearby nerves (with which they interact). This escalates neurogenic inflammation again with SP. By the CIMURAF-model intramurally sliding contracted chambers through radial shutters might flush MCs` autocrine signals, like SP, away, influencing their countercurrent intrusions and inflaming actions (Treviranus 2019). MCs through their high signaling complexity are strongly related to MIG, (pseudo-)allergic immune disorders, metabolism, bipolar disorder (Treviranus 2017, Fitzpatrick & Morrow 2017), in mastocytosis to unipolar MDD and generally to stress-sensitive neurogenic bodily inflammations (Oh et al. 2024, Theoharides et al. 2005, Sousa-Valente et al. 2018). Not least because of their role in regulating MCs (Xu et al. 2020) neuropeptides will likely explain also psychiatric conundrums (Theoharides1990, Horowitz et al. 2023). Peptidergic neurons combine fast release e.g. of glutamate via synaptic vesicles with delayed release of large dense-core vesicles (LDCV) spilling often several among >100 neuromodulators (neuropeptides and classical monoamines like DA) onto their post-synaptic receptors realizing broad mental states. Not fast glutamate but LDCV, releasing experimentally silenced neuropeptides, were shown to elicit aversive experiences to the murine amygdala (AMY) and even an inverse feed-back within the pontine fear circuit (Kim et al. 2024). The area between pons and cerebellum seems statistically pivotal to the overall p- and d-factors for psychiatric and connected somatic disorders (Stevanovic et al. 2024, Romer et al. 2018), and possibly because MCs could "fly off the adventitial track" at the syphons of two nearby cerebellar arteries - causing, like maybe at the subgenual curve in MDD (Drevets et al. 2008), another neural massacre (Figure 3 in Treviranus 2023). Arterial endothelium and VS-muscle cells exhibit c-kit, which guarantees NO-signaling and prevents atherosclerosis (Song et al. 2019), but c-kit can induce BBB transcytosis in whole arterioles (Shang et al. 2024) - via (forgotten) MCs, which have an ongoing strict dependence on c-kit signaling for their growth and long-term survival (Brown et al. 2018), while other hematopoietic cells quickly wean. On the meninges some MCs show c-kit, yet apparently none within the brain, where astrocytic processes carry c-kit (Shanas et al. 1998). The roles of the c-kit-receptor and its ligand SCF on MCs, who are uniquely dependent on them, and other e.g. arterial cells remains even more enigmatic as via its cofactor RasGRP4 (Stevens et al. 2005) c-kit may be a downstream target of lithium via DAG. Its ligand stem cell factor (SCF) is vital for the MCs proliferation, differentiation, and maturation.

CONCLUSION

Psychiatric neuroscience tackling basic problems merits attention and inputs from clinicians being a source of hope that progress in human affairs can be accelerated.

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