Toward unique sensorimotor-language biomarkers of schizophrenia

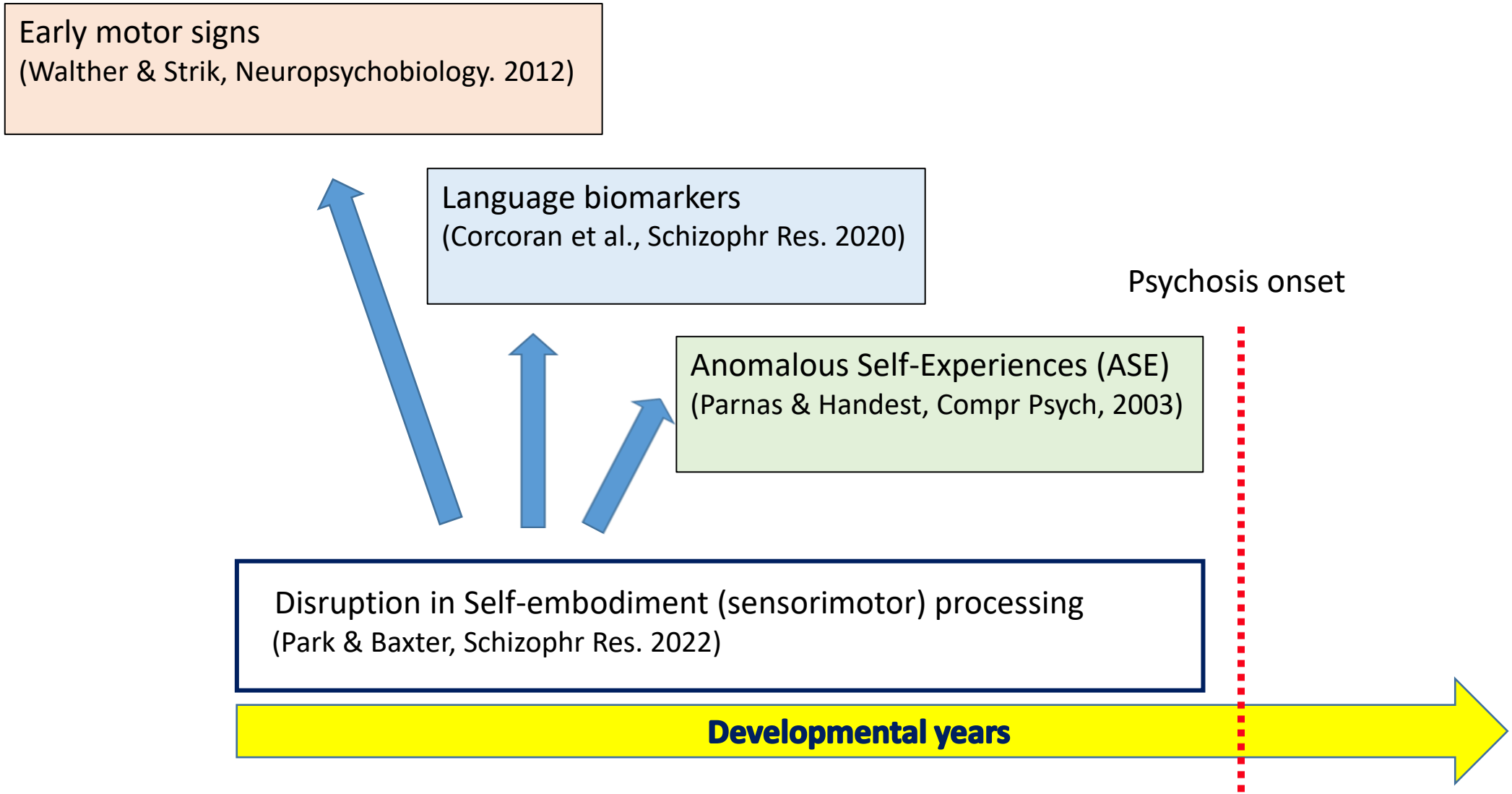
Discourse in Psychosis Satellite meeting

Pavia 08/IV/2024

Matteo Tonna, MD, PhD

Neurodevelopmental pathways to Psychosis

- An endophenotype is a quantitative biological trait that is reliable in reflecting the function of a discrete biological system and is reasonably heritable, and as such is more closely related to the root cause of the disease than the broad clinical phenotype.
  (Gottesman and Gould, 2003; Cannon and Keller, 2006; Meyer-Lindenberg and Weinberger, 2006; Tan et al., 2008).


Early motor signs
(Walther & Strik, Neuropsychobiology. 2012)
Language biomarkers
(Corcoran et al., Schizophr Res. 2020)
Psychosis onset
Anomalous Self-Experiences (ASE)
(Parnas & Handest, Compr Psych, 2003)
Disruption in Self-embodiment (sensorimotor) processing
(Park & Baxter, Schizophr Res. 2022)
Developmental years

Bodily self

(implicit consciousness of one's own body;
"first person perspective")

- weakening of the basic sense of the self
- disruption of implicit bodily functioning
- hyper-reflective distancing from others and worldly objects

Park & Baxter, Schizophr Res. 2022

Anomalous self-experiences (ASE)

- attenuated sense of self-presence
- blurred self-demarcation
- disturbance in the tacit fluidity of the field of awareness
- difficulty in grasping familiar meanings
- hyper-reflexivity; "ontological" concerns

Parnas & Handest, Compr Psych, 2003

Self-embodiment processes:

(agency, ownership, fixed boundaries)

- An integrated network of multisensory integration (visual, vestibular and proprioceptive), and constrained by the motor potentialities of our own body

Gallese & Ferri, Psychopathology, 2014; Tonna et al., Early Int Psych, 2022.

The bodily self is multisensorial, dynamic and relational in nature, within a network of self-others and wordly interactions

Ciaunica et al., 2021; Rochat & Striano, 2000

Multisensory integration

Animals' perceptual view of the world is an integrated and holistic one in which sensory cues are blended seamlessy into a singular perceptual Gestalt.
Multisensory integration is the process through which information from different senses is combined by the brain to influence our behaviors and shape our percpetions.

PRINCIPLES OF MULTISENSORY INTEGRATION

Space principle
stimuli detected within a specific spatial distance (cm) are integrated.

Time principle
stimuli detected within a specific temporal window (msec) are integrated.

Effectiveness principle
Stimuli singularly weakly effective obtained largest enhancement when combined

Stevenson et al., 2014

Multisensory integration - properties

- 1) Multisensory integration is present immediately after birth, but it takes a long time to be shaped in the adult form. Multisensory integration **development** depends on the nature of the sensory experiences acquired (De Klerk et al., 2021).

- 2) Multisensory integration show **plasticity** features (Powers et al., 2009; 2012).

Sensorimotor integration

Matching between expected and actual results in motor enactment (Salomon; Soc Cogn, 2017)

- Mirror system

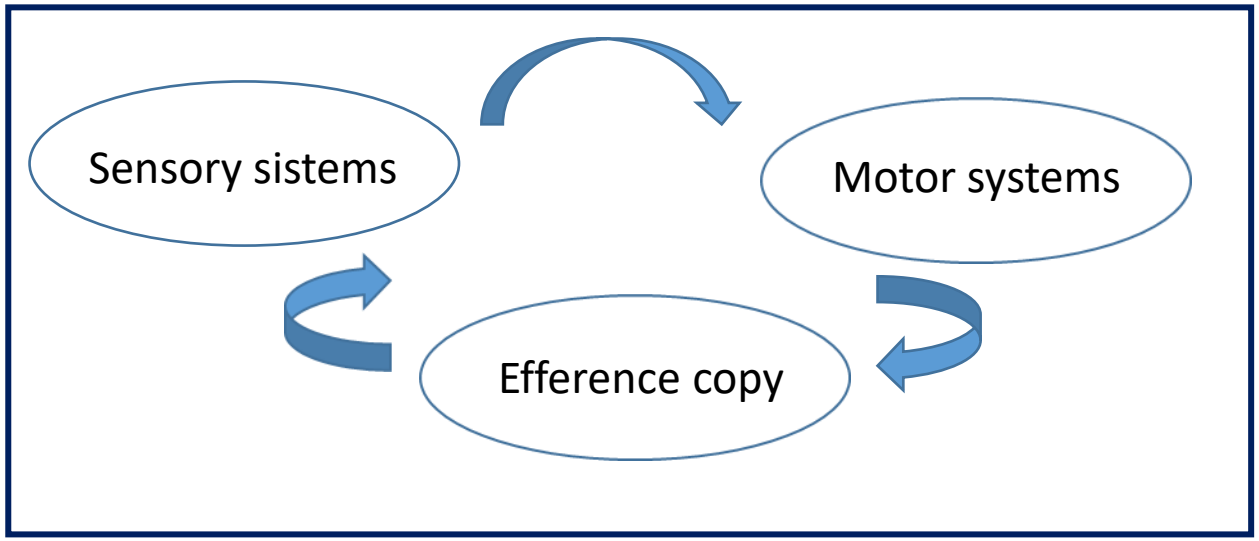
(Rizzolatti et al.; Cogn Brain Res,1996).

- «Corollary discharge (CD)»/ «efference copy» systems

(Sperry, von Hoist and Mittelstaedt, 1950)

- Comparator model (CM) of motor control

(Frith et al., 2000)



- CD links impairment of the sense of **agency** with motor **dyscoordination** in childhood (Poletti et al., Schizophr Bull, 2019).
- Strong association between childhood **dyspraxia, speech and language organization** and adult **schizophrenia outcome** (Schiffman et al., Development and Psychopathology, 2015).

A phylogenetic perspective

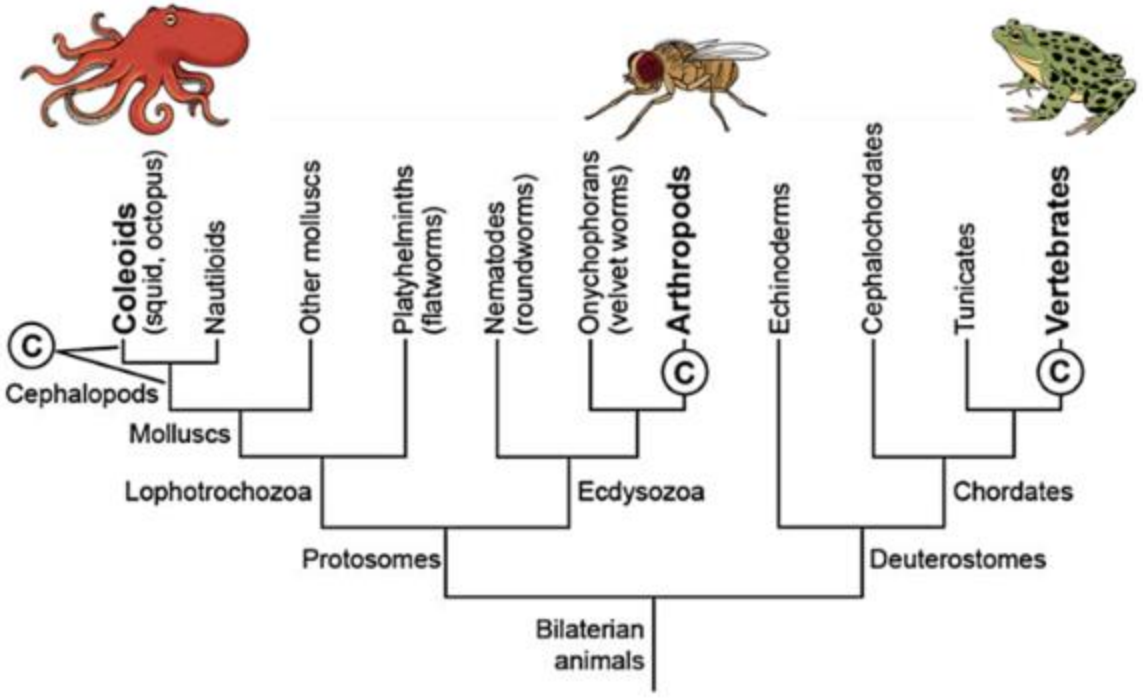
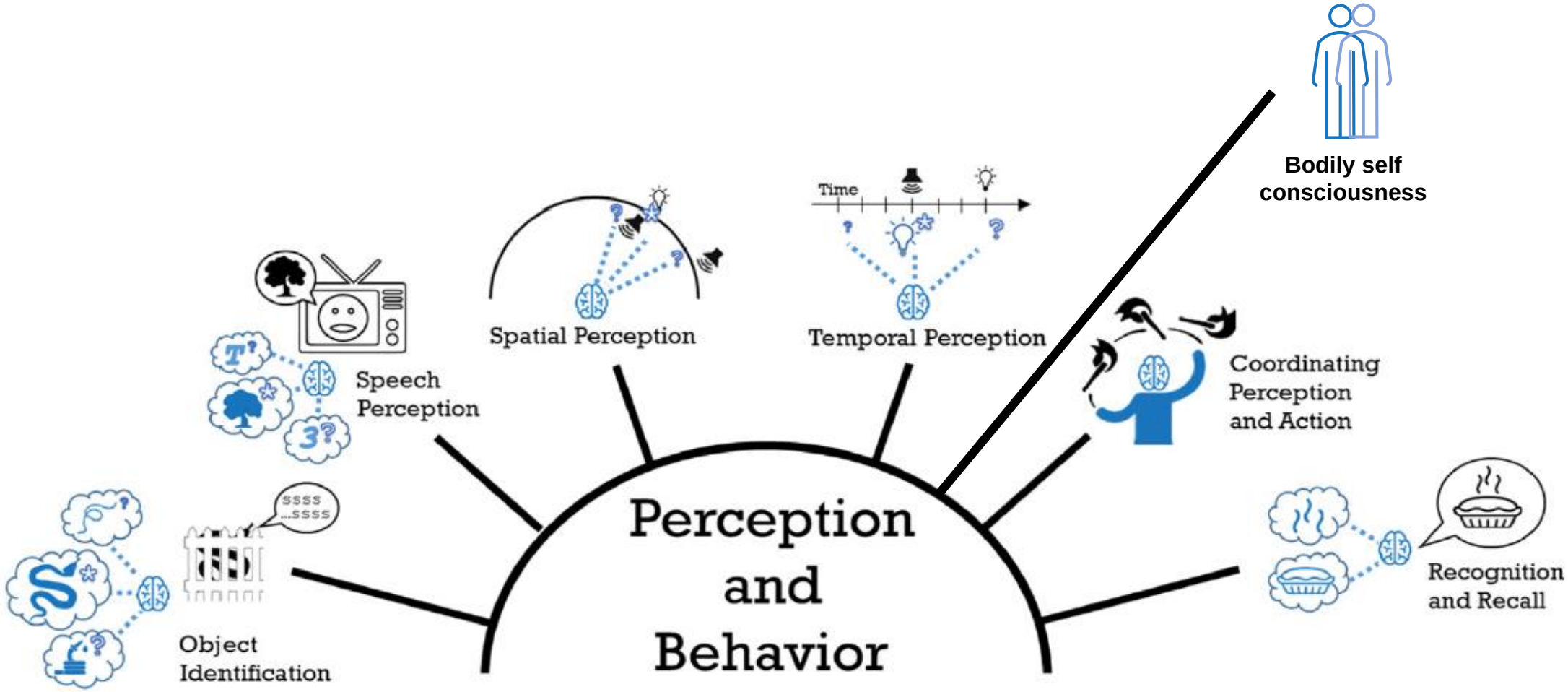


FIGURE 2 | A simplified phylogenetic tree of animal relationships showing that consciousness (©) emerged independently in three different lines of animals. At left, the two leaders extending from the © mean that we cannot tell whether the consciousness evolved in the first cephalopod mollusks or else in the coleoid ancestor of squid, octopus, and cuttlefish. Reproduced with the permission of the copyright holder Mount Sinai Health System.

Mallatt & Feinberg, Front Psychol, 2021

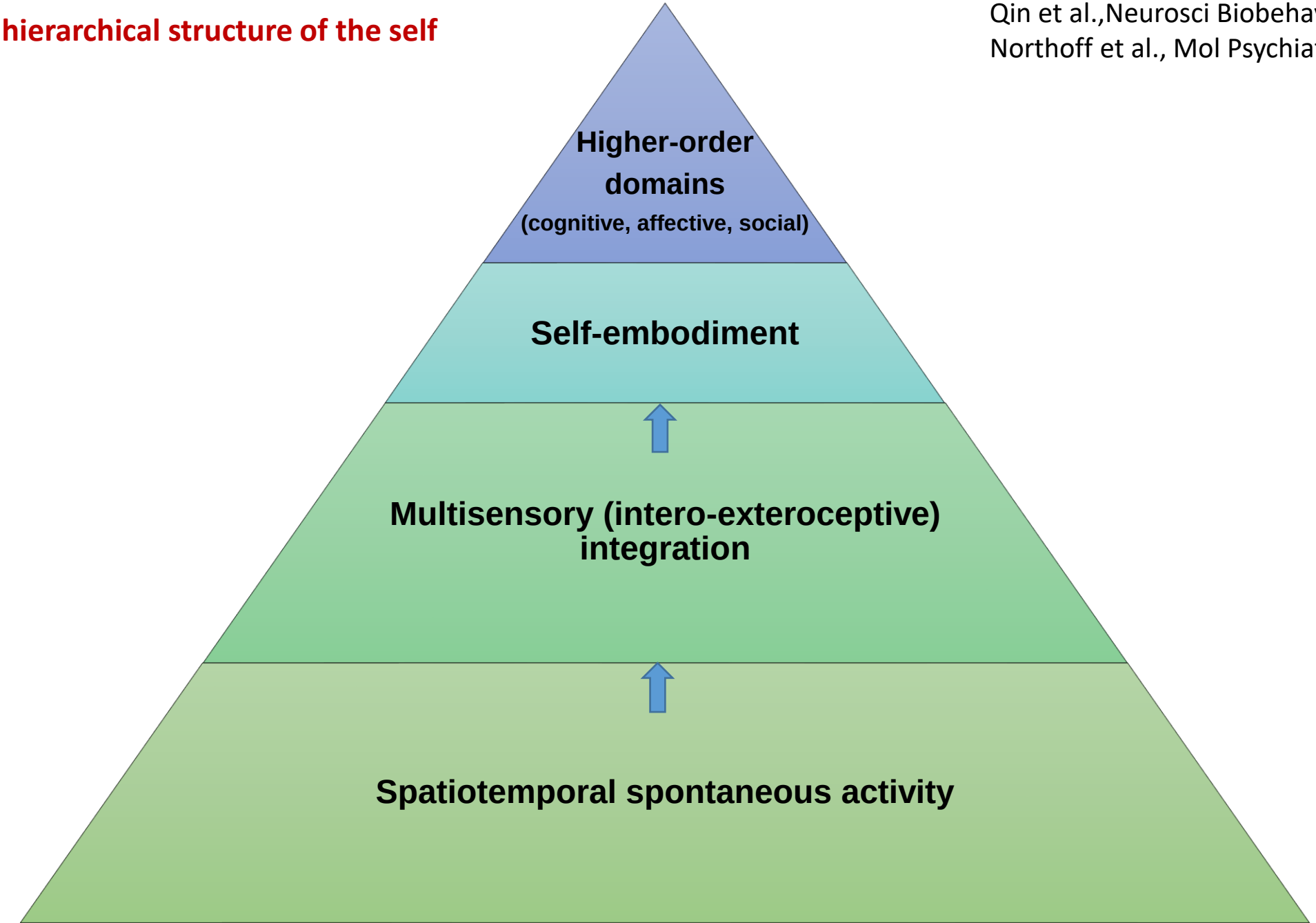
Multisensory integration is the scaffold for several higher level cognitive processes.



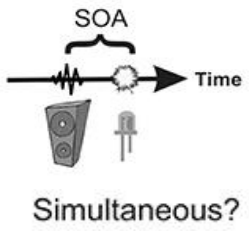
Stein et al., 2020; Blanke, 2012

The hierarchical structure of the self

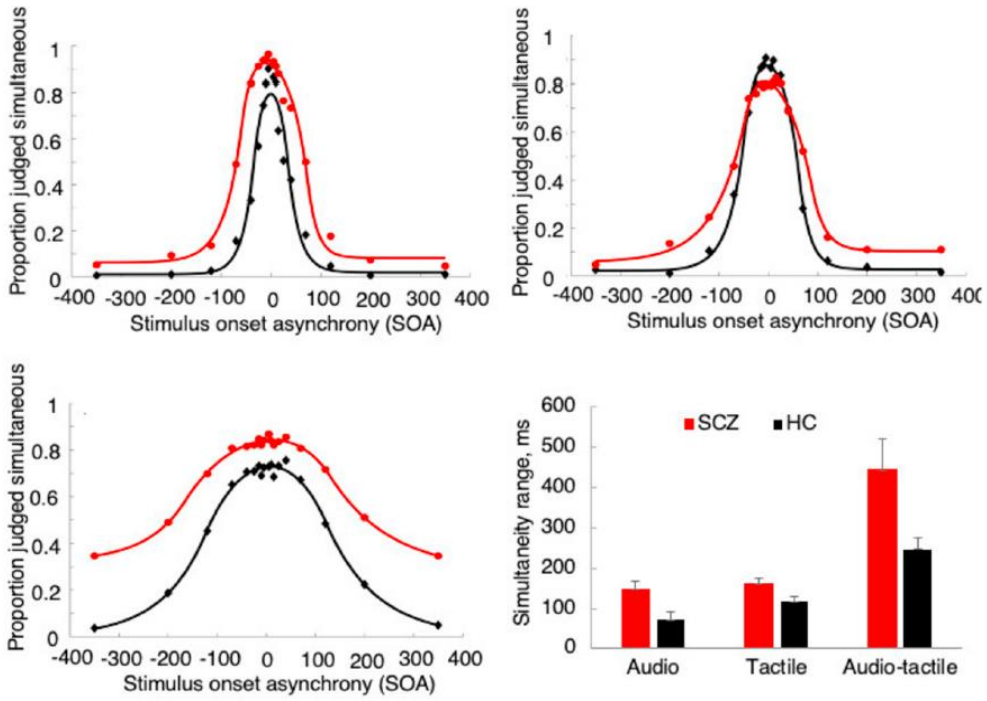
Qin et al.,Neurosci Biobehav Rev. 2020
Northoff et al., Mol Psychiatry. 2021



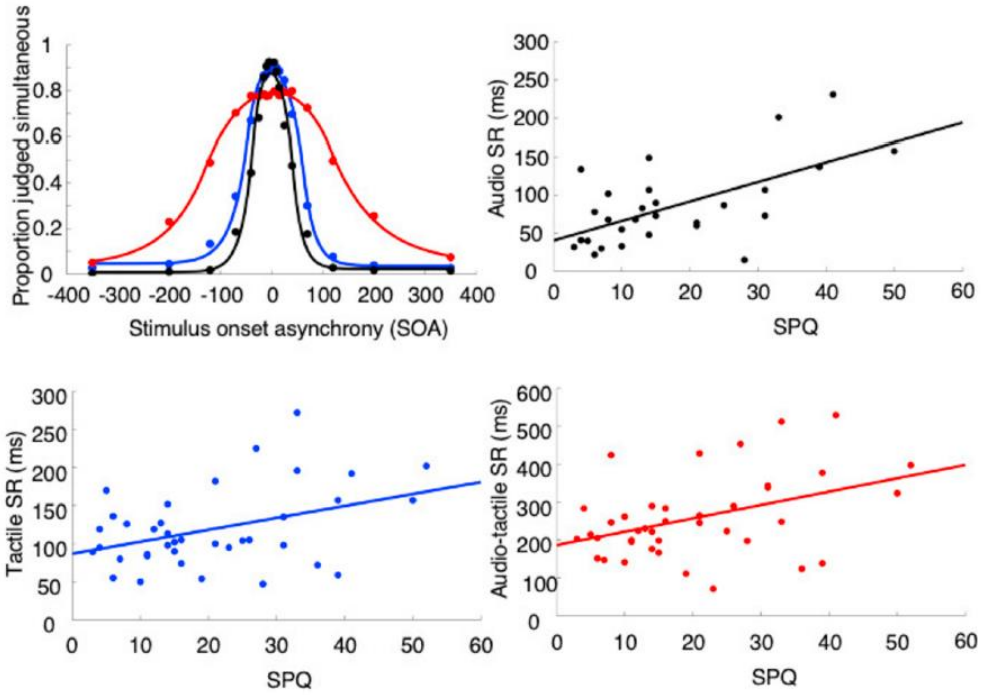
Multisensory integration – Time principle



Schizophrenia patients vs. healthy controls



High schizotypy vs low schizotypy



Di Cosmo et al., 2021

Neuropsychologia 147 (2020) 107579

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: http://www.elsevier.com/locate/neuropsychologia

Schizotypy and individual differences in peripersonal space plasticity

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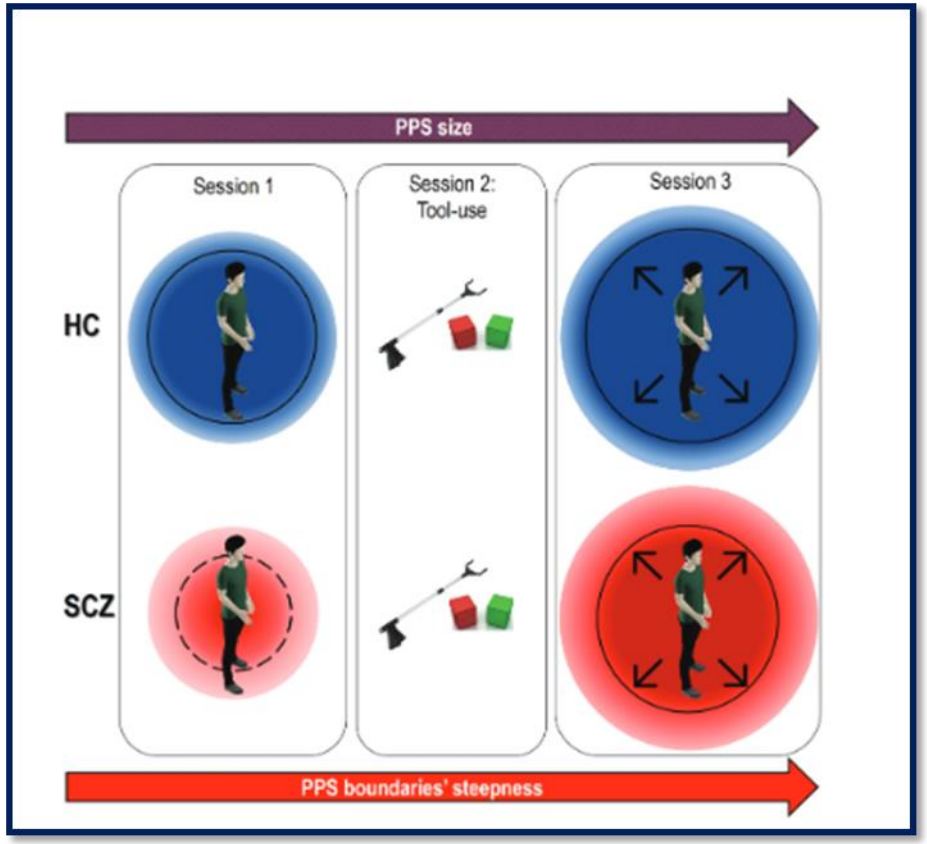
Multisensory integration – Space principle

PPS size varies across people, depending on different individual characteristics, including **schizotypy**.



Schizophrenia Bulletin
https://doi.org/10.1093/schbul/sbac067

Tool-use Extends Peripersonal Space Boundaries in Schizophrenic Patients

Francesca Ferroni[*,1,•], **Martina Ardizzi**[1,•], **Francesca Magnani**[1], **Francesca Ferri**[2], **Nunzio Langiulli**[1], **Francesca Rastelli**[1], **Valeria Lucarini**[3], **Francesca Giustozzi**[1], **Roberto Volpe**[1], **Carlo Marchesi**[1], **Matteo Tonna**[1,4], **and Vittorio Gallese**[1]

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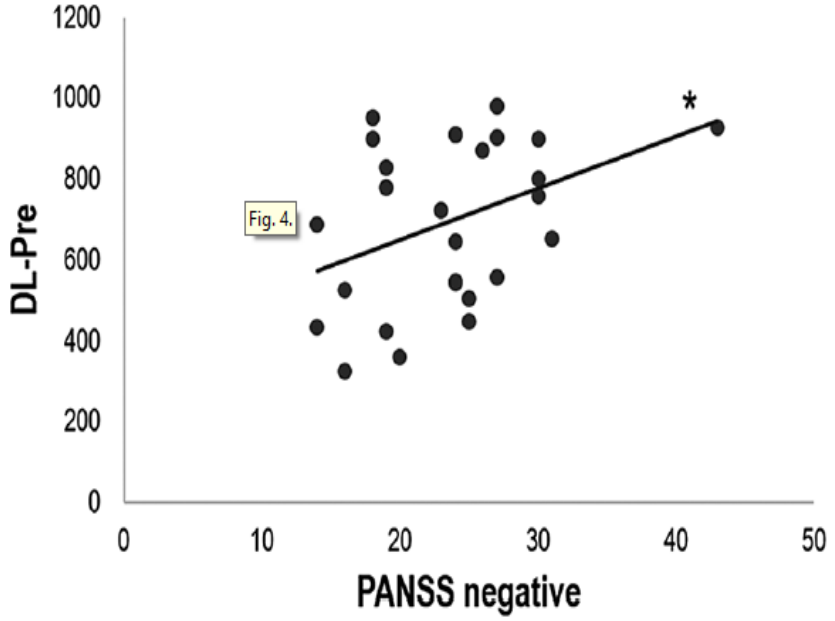
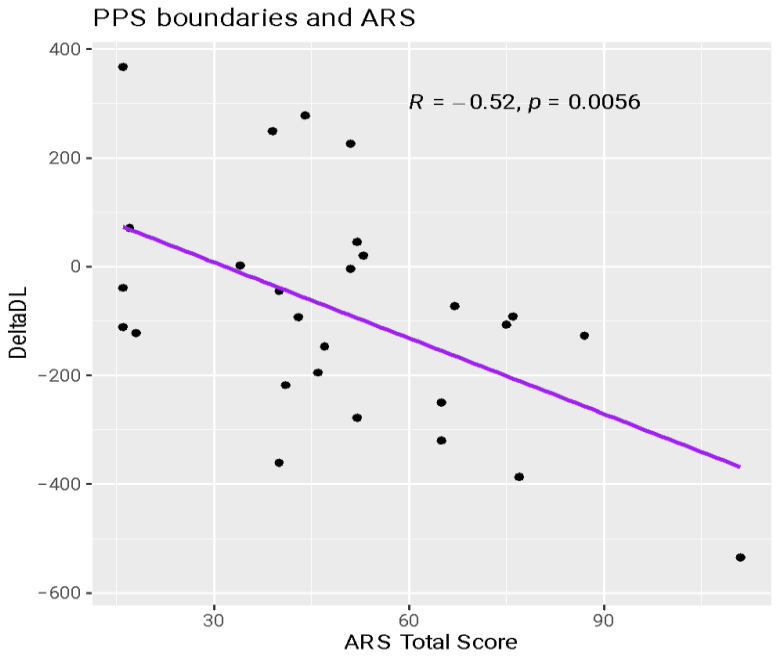


- **Narrow PPS** extent in SCZ.
- **Preserved PPS plasticity** in SCZ.
- **Weaker differentiation** from others
- **Sharper demarcation** of PPS boundaries after the action with the tool.

- Weaker **PPS boundaries** (DL-Pre) at higher negative symptoms (**PANSS neg**).
- Disturbances in the intersubjective domain (**ARS scores**).

- **Increased self-others demarcation** (DeltaDL) and higher **ARS** scores in **EOS**.

(Lucarini et al., Early Interv Psych, Under Review).

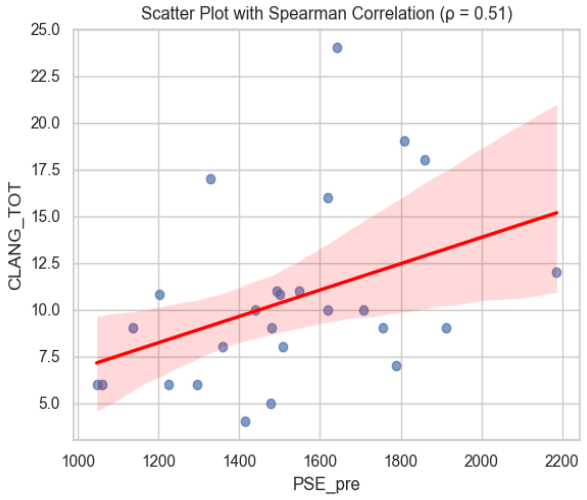


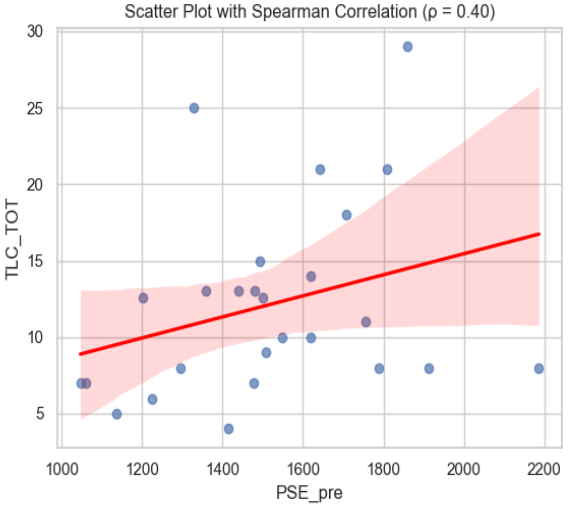
Language and sensorimotor integration

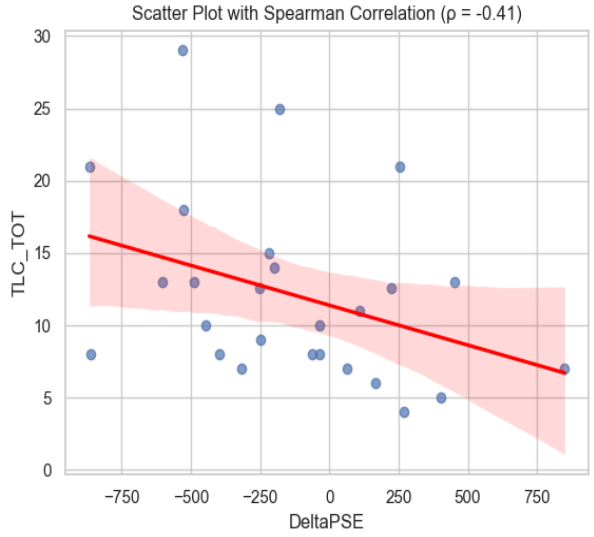
- The more **restricted basal PPS size**, the more language processes impaired (**TLC and CLANG total scores**).

- **Lesser PPS plasticity**, more severe language deficits (**TLC total score; CLANG and TLC productivity**).

Magnani et al., Psychol Studies, Under Review







Language and sensorimotor integration

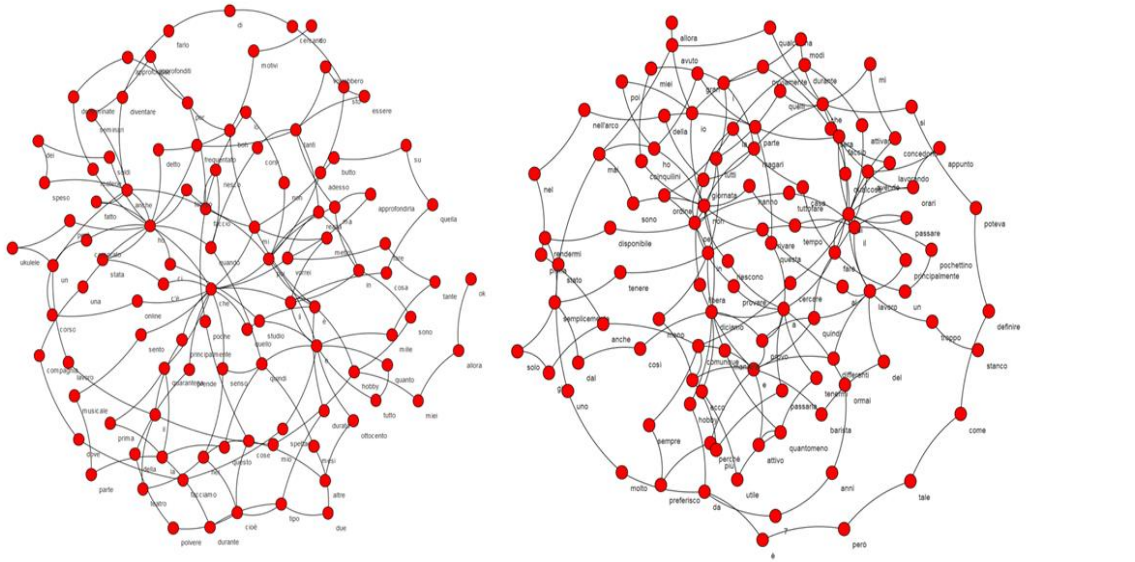


Figure 1 - Two graphs from one-minute of speech extraction in two healthy controls

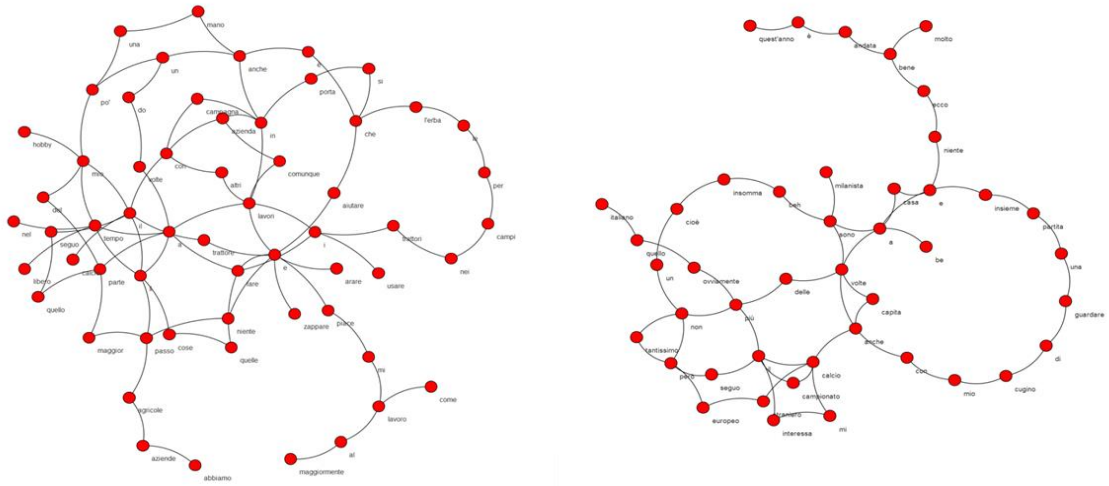
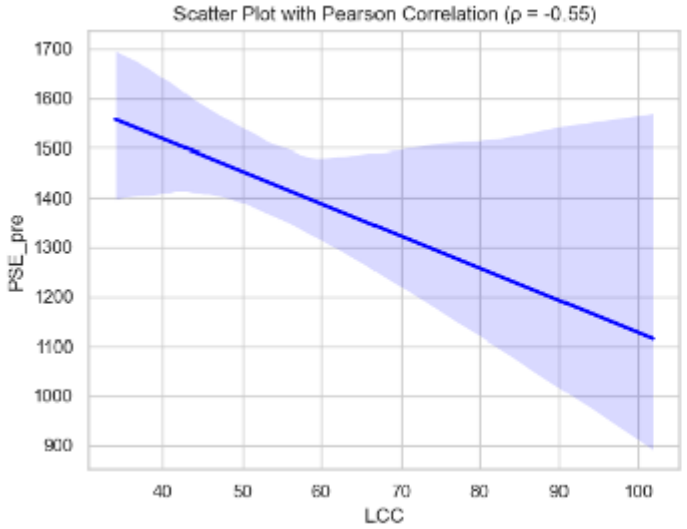
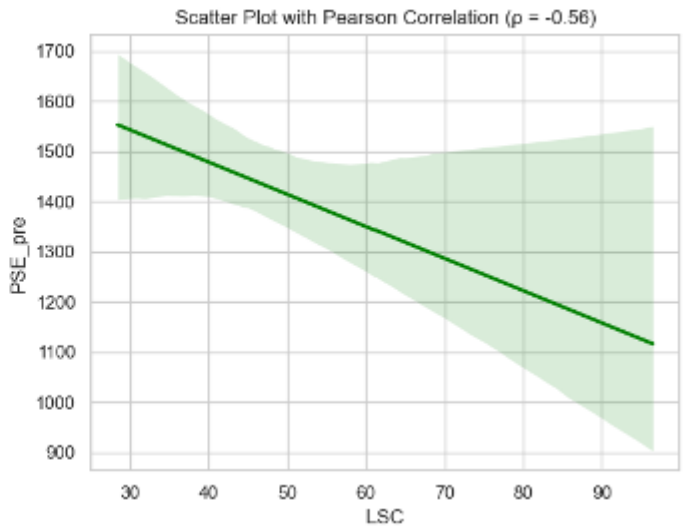


Figure 2 - Two graphs from one-minute of speech extraction in two schizophrenia patients





Lower global level of connectedness
correlate with **narrow basal PPS size**

Magnani et al., in preparation

Speech Prosody as a Bridge Between Psychopathology and Linguistics: The Case of the Schizophrenia Spectrum

Valeria Lucarini[1], Martine Grice[2], Francesco Cangemi[2], Juliane T. Zimmermann[3], Carlo Marchesi[1], Kai Vogeley[3,4] and Matteo Tonna[5]*

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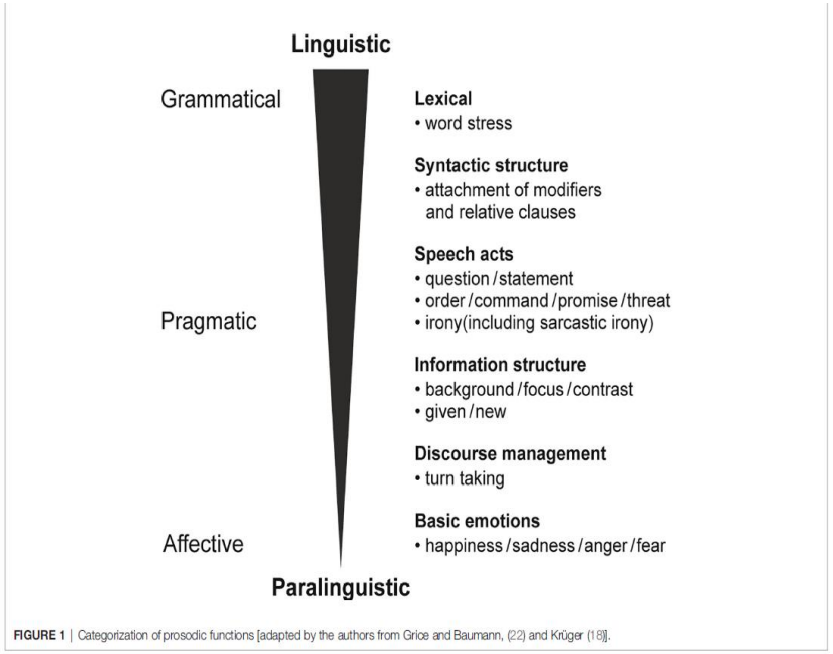
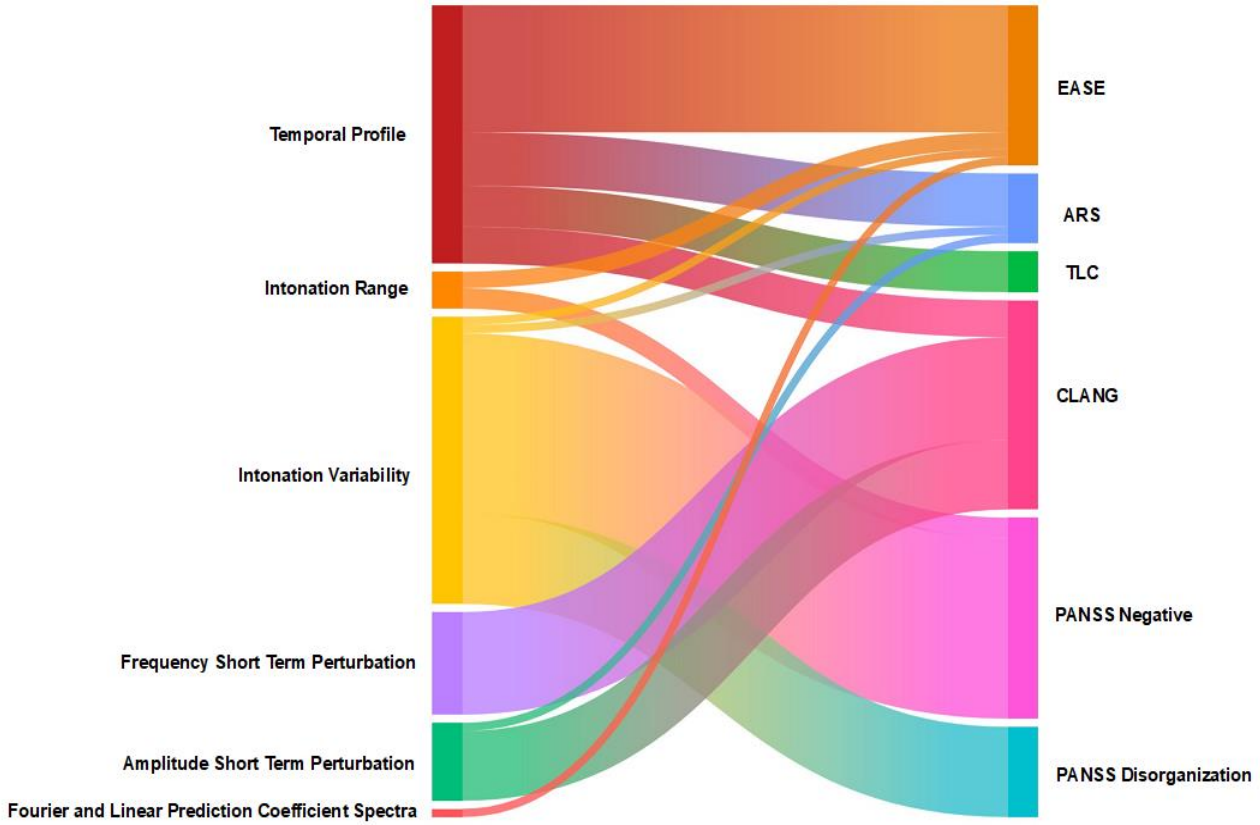


FIGURE 1 | Categorization of prosodic functions [adapted by the authors from Grice and Baumann, (22) and Krüger (18)].

Specific impairment in prosodic expression of both **pragmatic functions** and **emotions**.



Significant correlations between acoustic data domains (on the left) and psychopathological dimensions (on the right).

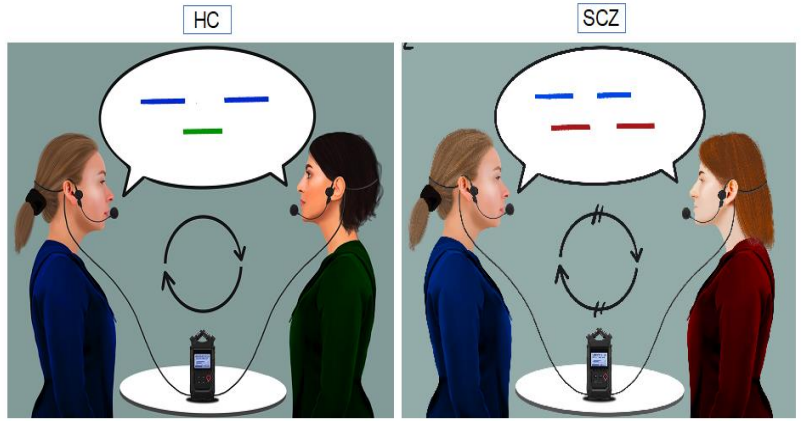
Lucarini et al., In preparation

European Archives of Psychiatry and Clinical Neuroscience (2022) 272:997–1005
https://doi.org/10.1007/s00406-021-01329-w

ORIGINAL PAPER

Conversational metrics, psychopathological dimensions and self-disturbances in patients with schizophrenia

Valeria Lucarini[1] · Francesco Cangemi[2] · Benyamin Daniel Daniel[1] · Jacopo Lucchese[3] · Francesca Paraboschi[1] · Chiara Cattani[4] · Carlo Marchesi[1,3] · Martine Grice[2] · Kai Vogeley[5,6] · Matteo Tonna[1,3]

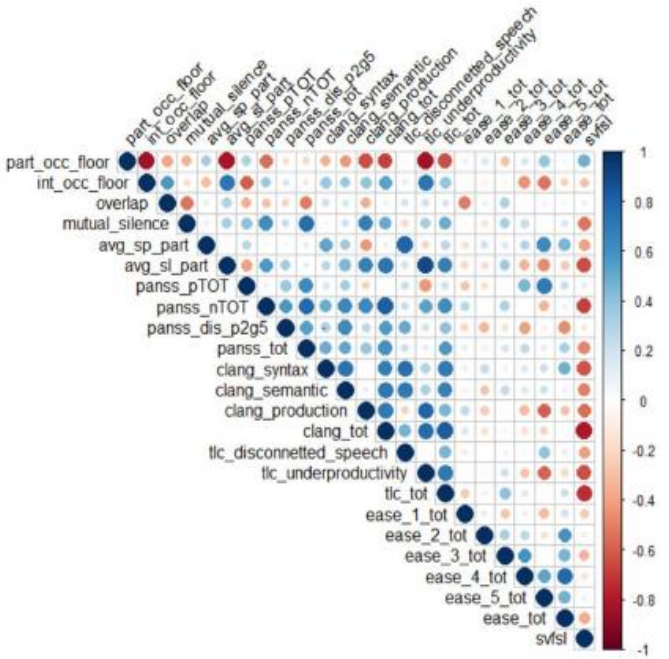


- More **fragmented** dialogues, together with increased levels of **overlaps** and **mutual silence**.
- Conversational data were associated with **negative symptoms** and **social functioning**, but not with positive or disorganization symptoms.

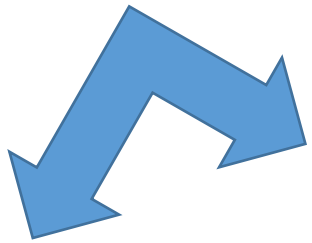
- A significant positive correlation was found between **"pause duration"** and the EASE item **"Spatialization of thought"**.

Relationship between the natural fluidity of conversation and of the natural unraveling of thoughts.

Fig. 2 Correlations among conversation variables, symptom dimensions, language and thought disorders, self-disturbances and global functioning in the study sample. The figure is a graphic representation of a correlation matrix among the study variables. The colors of the spots represent the direction of the correlation (blue for positive, red for negative) and the dimension of the correlation magnitude (the biggest the spot, the highest the correlation coefficient)

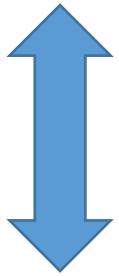


- Association between **postural** (impaired sway area), and **gait cycle** patterns and **subjective bodily** experiences (loss of bodily integrity, cohesion and demarcation).
(Tonna et al., Early Int Psych, 2022)



Self-disembodiment

Motor symptoms



- Correlation between "pause duration" and "EASE-Spatialization of thought"
(Lucarini et al., Eur Arch Psych Cl Neurosci, 2021)
- Association between acoustic pattern, ASE and ARS
(Lucarini et al., In preparation)

Language impairment

- Impaired **integration of abstract speech-gesture** Combinations (Straube et al., Schizophr Bull, 2014)
- **Receptive and expressive language** in EOS (Nicolson et al., Am J Psych, 2000)
- **Receptive language** in at-risk individuals (Blanchard et al., Schizophr Res, 2010)
- Narrower PPS size and underproductivity (Magnani et al., Psychol Studies, Under Review)

Developmental years

An evolutionary explanation of motor-language intertwining

Schizophrenia Bulletin
https://doi.org/10.1093/schbul/sbac146

Disembodiment and Language in Schizophrenia: An Integrated Psychopathological and Evolutionary Perspective

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Sch: severe neurodevelopmental disorder with a notably stable 1% prevalence, regardless of epochs and cultures.

Uniquely human condition, being absent in other close species, like great apes.

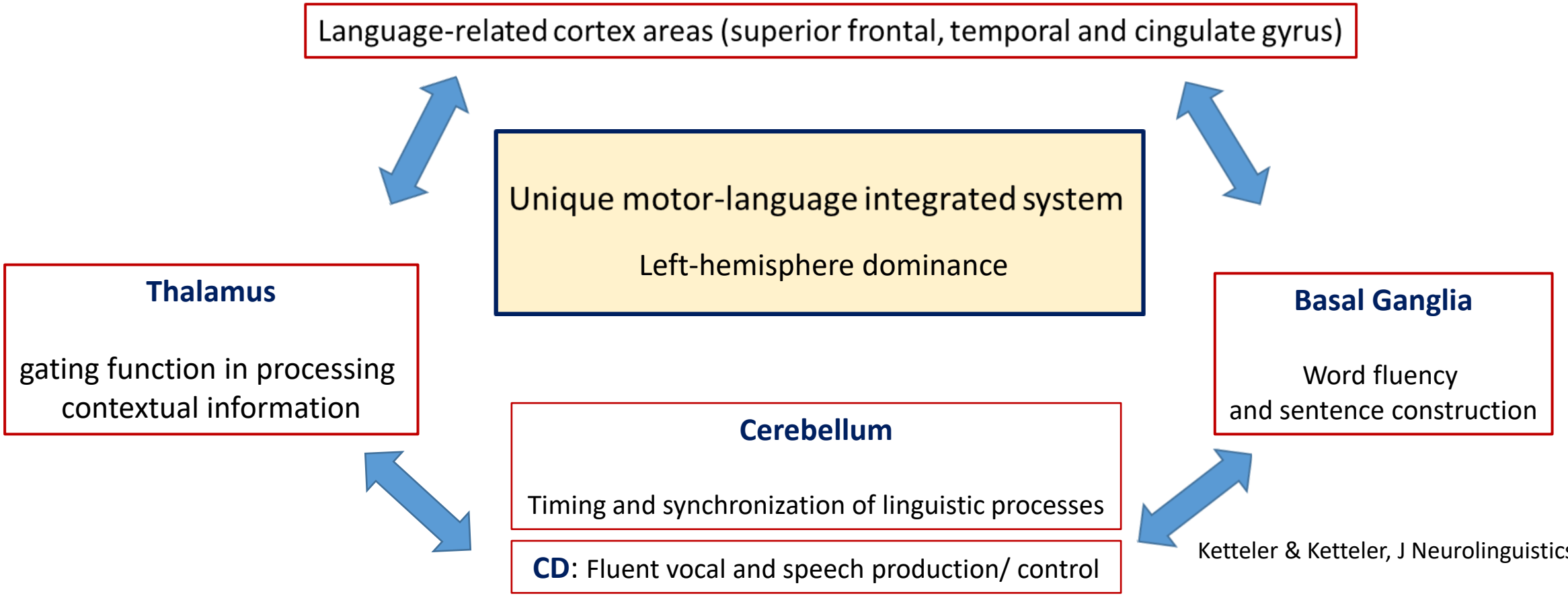
Recent selection for specifically human traits.

Brain-language coevolution

"Novel, widespread neuronal rearrangement, which entailed new patterns of brain rhythmicity, long-distance connections among distributed neurons, and a global remodelling of brain development and function"

Murphy & Benítez-Burraco, Neurosci Biobehav Rev. 2017

“Neural reuse” of sensorimotor connectivity for language



Ketteler & Ketteler, J Neurolinguistics. 2010

Sensorimotor flexibility:

1) Context dependence: specific functional configurations are the result of specific bio-cultural inputs.

2) intrinsic neural dynamicity: novel functions emerge from the mutual plastic modulation between the nodes of the same network.

Anderson, Behav Brain Sci. 2010

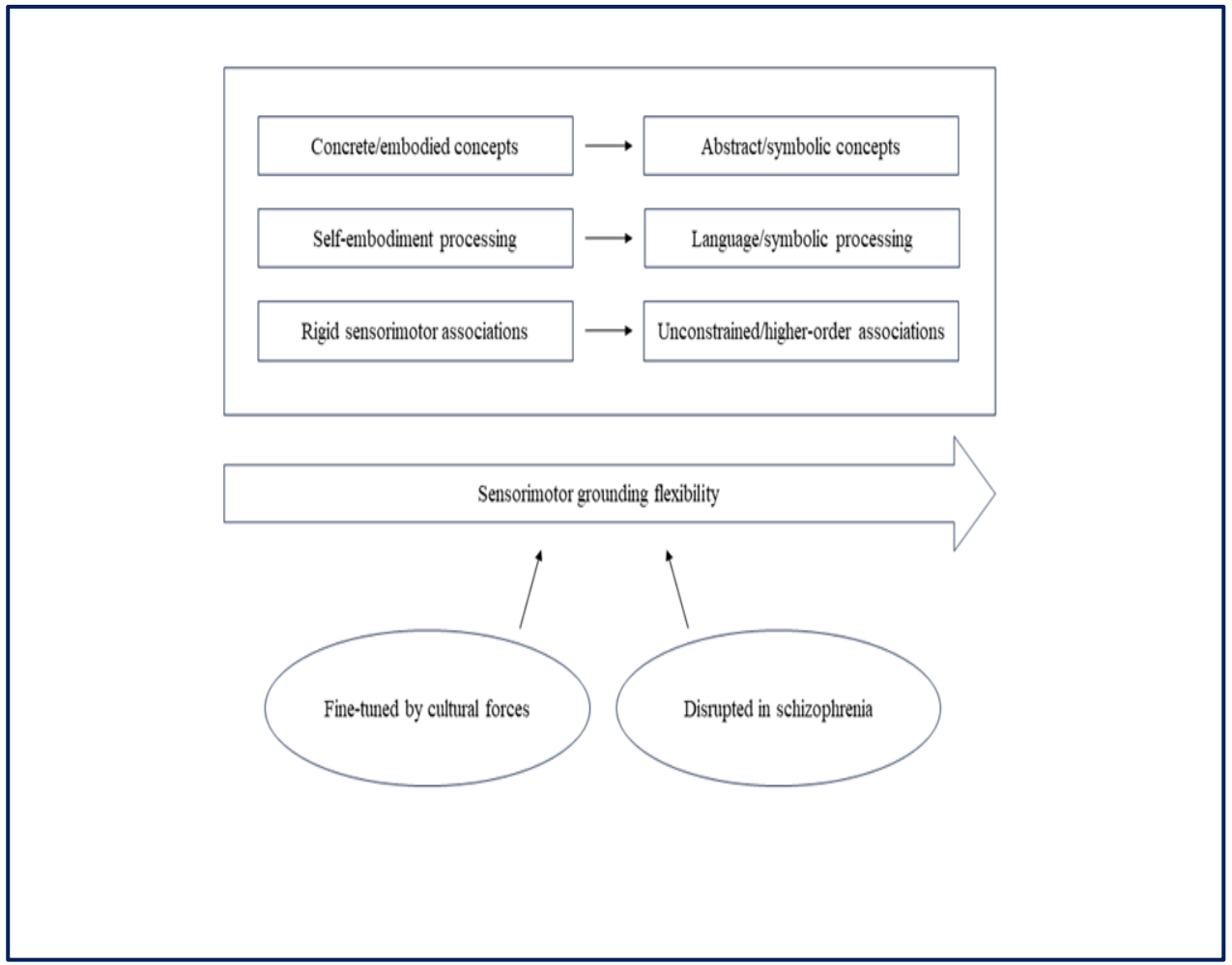


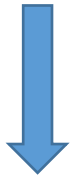
Figure: Sensorimotor grounding from embodiment to symbolic processing

Developmental pathways to symbolic language

- **Abstraction of semantic processing:**

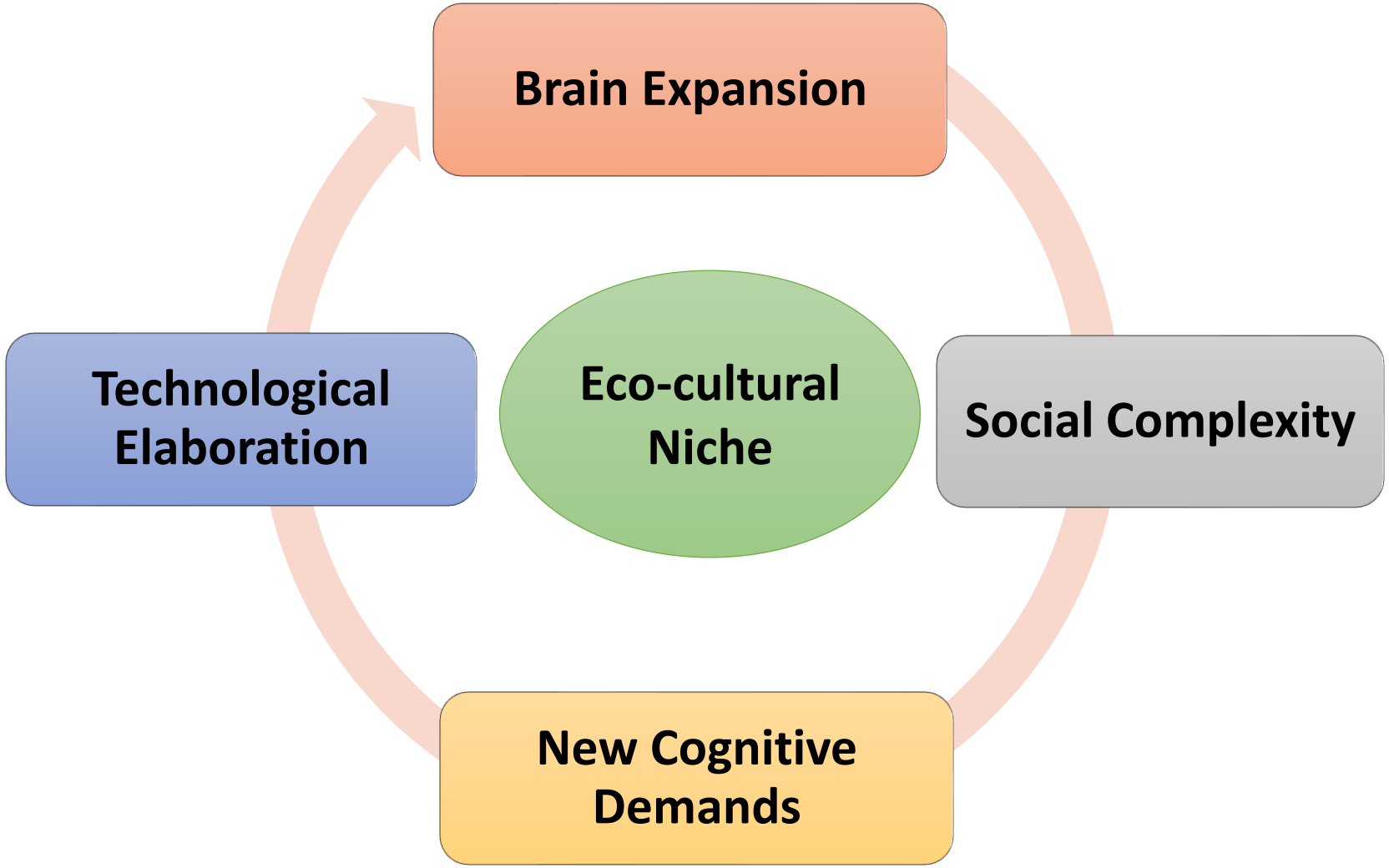
While retaining a link to sensorimotor circuits, it requires the involvement of additional "convergent" zones, in which higher-order conjunctions and correlations are captured and neurally stored.

- From strong neuro-chemical constraints to non-canonical association networks, primarily connected with each other rather than strictly constrained by sensorimotor systems



- Concepts are gradually freed from rigid sensorimotor constraints in favor of looser connections, whose degree of neural "relaxation" is shaped by socio-cultural context

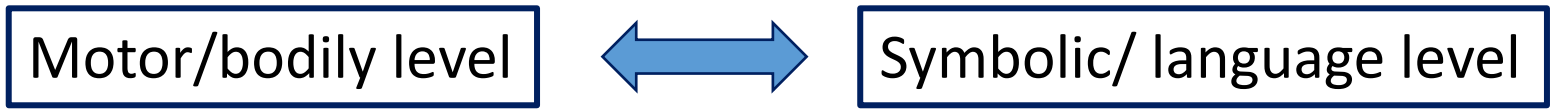
Buckner & Krienen, Trends Cogn Sci. 2013
Mazzuca et al., Brain Sci. 2021



Tonna et al., Schizophr Bull, 2023

- Complex developmental (pre- and perinatal, psychosocial, bio-cultural) mechanisms, acting on fine-tuning processes of neural circuitry, contribute calibrating, or alternatively decompensating such an integrated sensorimotor and language system into a full-blown psychosis.

Murray et al., Schizophr Bull, 2017



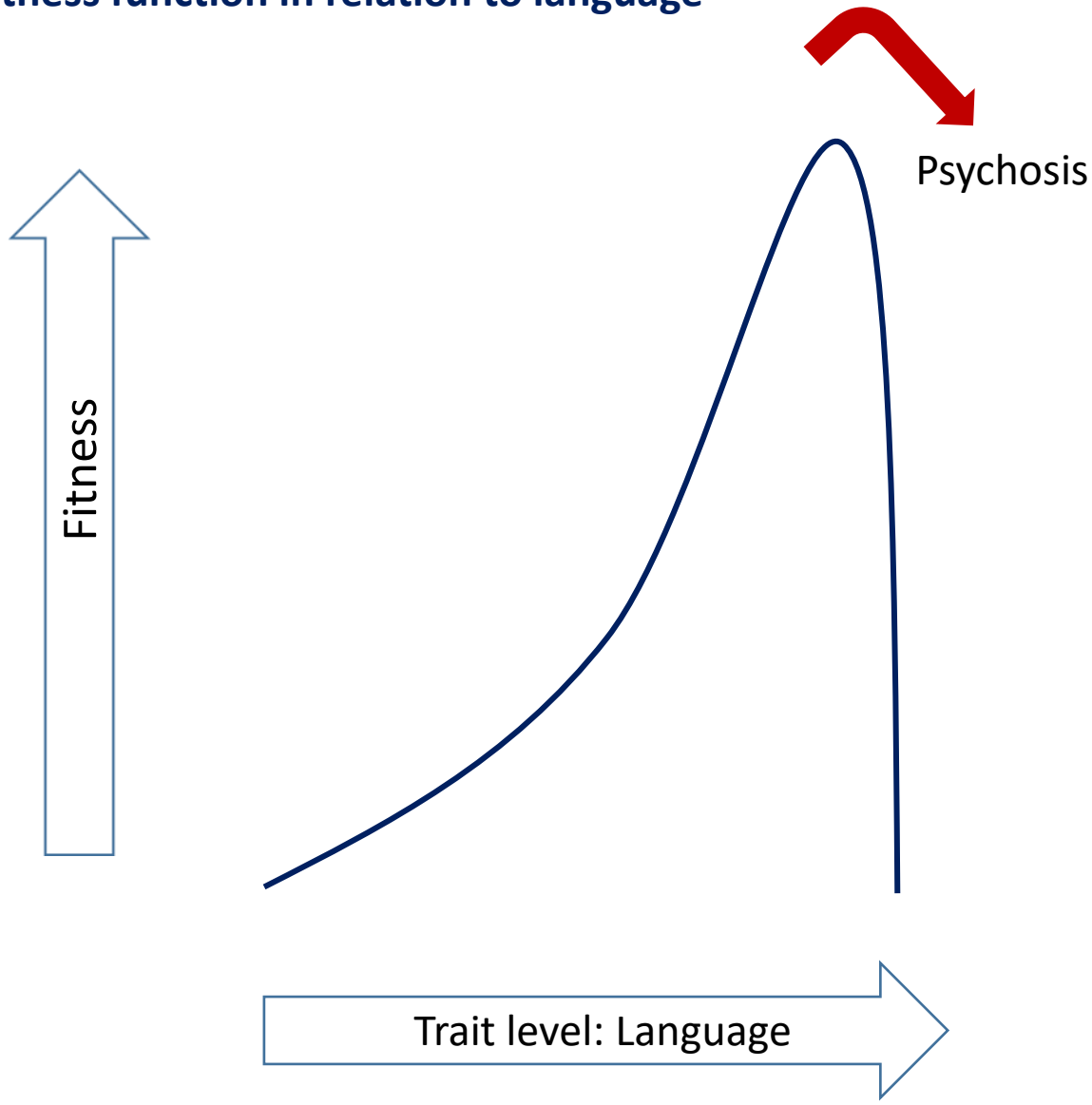
Failure of integrative processes:

Chaslin's «discordance» (1912)

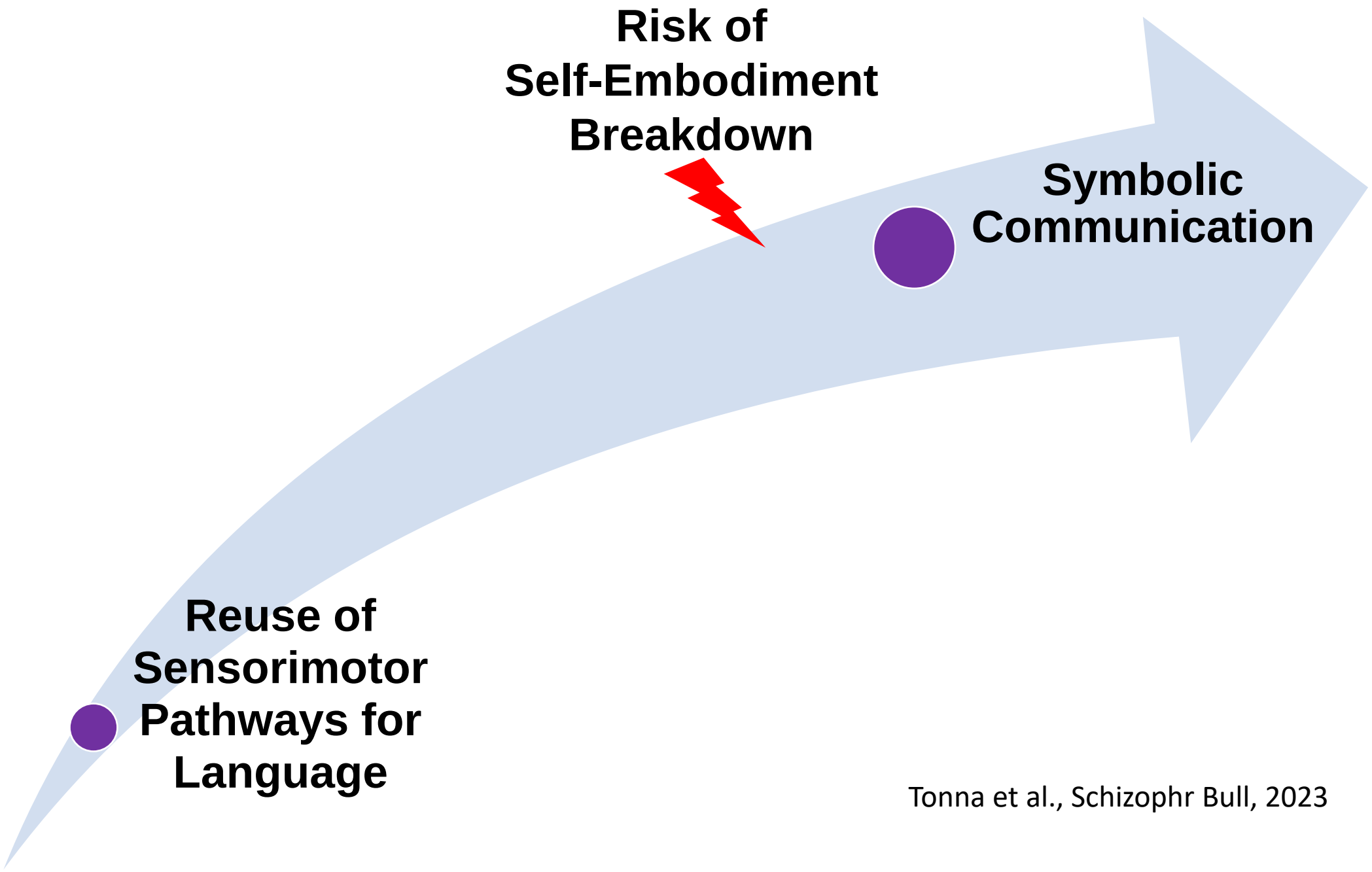
Bleuler's splitting («spaltung») (1911)

Meehl's «schizotaxia» (1962)

Cliff-edged fitness function in relation to language



Adapted from: Nesse, Behav Brain Sci. 2004



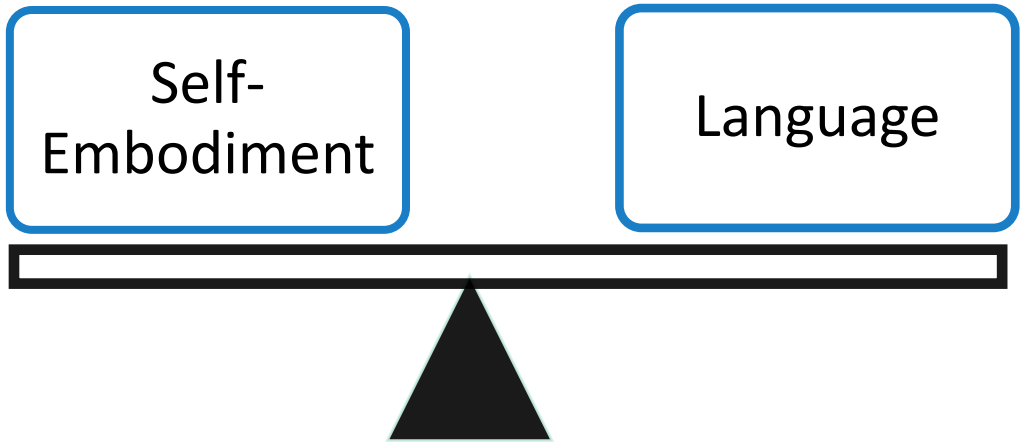
Tonna et al., Schizophr Bull, 2023

Evolutionary “tradeoff”

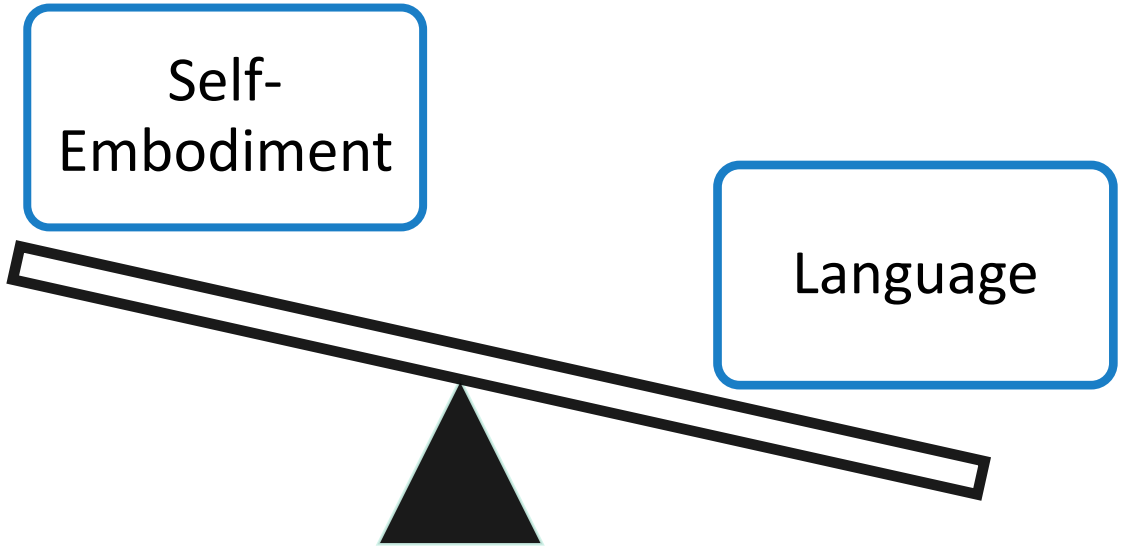
Stearns and Medzhitov, Evolutionary Medicine, 2015

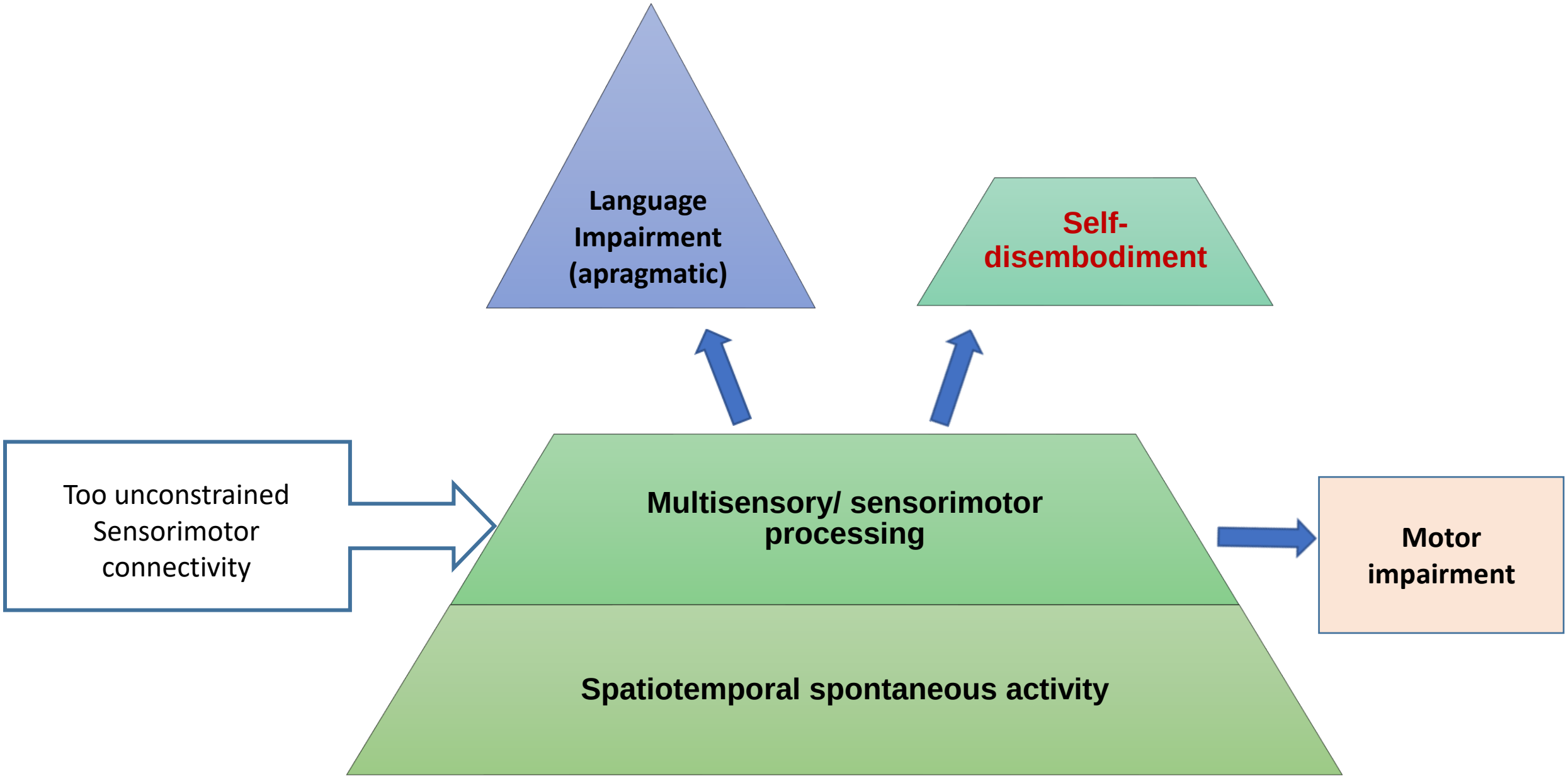
self-embodiment vs language processing

Healthy Individuals



Patients with schizophrenia




Language Impairment (apragmatic)
Self-disembodiment
Too unconstrained Sensorimotor connectivity
Multisensory/ sensorimotor processing
Motor impairment
Spatiotemporal spontaneous activity

Conclusions

- Evolutionary and neurodevelopmental framework:

- A) Integrated **“self-motor-language”** biomarkers of psychotic vulnerability alongside and before the first symptoms, lying on **a disrupted sensorimotor integration**.

- B) Focus on developmental determinants that impact on sensorimotor balance and potential adaptive responses (e.g., OCD)

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Thanks for your attention

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