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Methodological challenges before translation from psychopathology to neuroscience: top-down or bottom-up models?

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There is delivered in this paper a conceptual background of a research program to re-validate psychopathological constructs by means of functional neuroimaging. The philosophical concepts employed are identity and supervenience theory of mind, and eliminative materialism. Our empirical research is then mapped on those theoretical frameworks. There are reported differential activations of clinical depression assessment scale between healthy controls and depressed patients on one hand and between depression and schizophrenia clinical populations of the other. Further there has been explored the possibility to discriminate the two nosological groups by means of machine learning experiment. Our bottom line message is that the complexity and inter-disciplinary nature of psychiatric diagnosis demands profound understanding of mind-brain interactions. This understanding calls for pluralist account concerning possible solutions of the psycho-physical problem and refraining from attempts to impose universal, monopolistic and paradigmatic decisions.

Keywords: psychopathology, neuroscience, validity operations, mind-brain problem, functional magnetic-resonance imaging (fMRI)

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1. CRITICAL REAPPRAISAL OF PSYCHIATRY AND MIND-BRAIN PROBLEM

The conceptual crisis in psychiatry remained a paramount problem in his research interests mainly because none of the existing explanatory models for mental disorders transcend to the desired level of consensus to define a sound medical discipline. In particular, there are still missing (Stoyanov and Di Nicola, 2017, 2018):

- Consensual theory of the person (as main object of normal psychology), besides some recent advances, yet quite complex to reach broader audience.
- Consensual theory of the mental disorder, beyond ordinary descriptive psychopathology.
- Consensual theory of change.

In particular, this state of crisis is rooted back in the mind-brain debate and the controversial forms of modern physicalism.

1.1 Psychophysical dilemma

One leading tacit position in current psychiatric explanations remained **Cartesian dualism** (Stoyanov, 2018), which underpins

most of the contemporary paradigms in psychotherapy. On the other hand, biological neuropsychiatry is looking into various forms of **monistic physicalism**, which provide conceptual grounds for biological treatment programs, such as psychopharmacology, ECT, rTMS, among others. The latter might be seen as reductive and non-reductive. Reductive physicalism has developed in the 20th century into several influential traditions relevant to psychiatry: eliminative materialism and identity theory of mind. Both of them assume supremacy of neurobiological models and tend to reduce psychological and psychopathological phenomena to events and processes in the brain.

Eliminative materialism is attributed to the works of Paul and Patricia Churchland and presumes that "folk psychology", will be dismissed (eliminated) by computational neuroscience (Stoyanov, 2018). Most of the biological interventions in psychiatry are also rooted back in eliminative materialism on the level of 'tacit knowledge'. Essentially this

means that we no longer need to articulate the subjective content (phenomenology) of psychopathological experiences since all of them are completely reducibly to biochemical entities. It is critical to stress here that this inference is taken *without residuum*, i.e. no further social, cultural or religious interference is assumed as being related on causal level to production of the phenomenon.

Another reductive paradigm, known as **identity** theory of mind (ITM) was derived from claims in the field of experimental arguments, namely the so-called "c-fiber' argument. This argument refers to the differential activation of the c- and a-delta-fibers of the pain perception system. The c-fibers provide slower transduction of the neural signal from the peripheral pain receptors to central areas as compared to a-delta-fibers, therefore are defined as substrate or immediate correlate of the emotional experience of pain (see Stoyanov, 2018 for details).

1.2 Objections at reductive physicalism

What actually matters to psychiatry (and in that sense to psychology as well) is what kind of objections might be delivered contra reductive physicalism in general and ITM in particular.

There are two main objections of relevance to mental disorders: the presence of qualia and multiple realizability.

Qualia is an argument which is pertinent to phenomenological psychopathology and refers to the qualitative dimension of human experience. For instance, if we accept it provisionally that all verbal acoustic hallucinations (VAH) are produced by one and the same brain mechanism (Hugdahl, 2017) then a reasonable query would be why they differ that much on inter-individual level in terms of their inter-subjective content?

Multiple realizability refers to the observed fact that there are multiple brain regions and networks in the brain implicated in the production of certain psychopathological phenomenon (like VAH) and the experimental data reported remain highly inconsistent. At the same time, other than VAH psychopathological manifestations (like delusions) converge on the same neural substrate as VAH.

There has been formulated a moderate form of

physicalism in response to the critical accounts on reductive physicalism, the **supervenience theory of mind (STM)** brought forward by Donald Davidson and Jaegwon Kim.

1.3 Non-reductive physicalism. Supervenience theory of mind

Supervenience theory (Kim, 1993, 2010) adopts the stance that any difference in physical properties (neural events or mechanisms) should cause differences in the mental world (states or traits dependent phenomena), but not *viceversa*. This means that any contrast measured by means of functional MRI between patients and healthy control group should be associated with a difference in the clinical manifestations (observations) respectively in the score on various rating scales. However not every difference in the clinical observation might be reduced to physical properties of the brain,

There are considered two forms of supervenience: global and local. Transferred to the field of psychiatry and psychology **global supervenience** may appear like this:

There are differences in patterns of brain activations in all patients with depression when compared to patients with schizophrenia or healthy controls.

This position appears to be false for many empirical and meta-empirical reasons as discussed elsewhere (Stoyanov, 2014, 2018), so we should rather adhere to the **local supervenience**. In our case it applies like this:

There are differences in the patterns of brain activations between the item responses on depression inventory as compared to diagnostically neutral items and to paranoid items in patients with presumed depressive disorder when compared to patients with schizophrenia and to healthy controls.

2. EMPIRICAL EVIDENCE

My initial claim was (Stoyanov, 2014) that the identity theory is the right solution to the mindbrain problem and that a proper fMRI protocol might capture an integral system of the mindand-brain (Stoyanov, 2009). In this perspective all mental phenomena may be reduced to brain signals without residuum. My original

protocol was to apply actually self-assessment psychological inventories simultaneously with the fMRI scan and by this approach to establish "perfect correlation", which is identity by definition (Boring, 1932). We have employed a rather atypical method in our study. The typical, or "mainstream" methods in psychiatric neuroimaging include emotionally valent visual stimuli from the International Affective Picture System, cognitive tasks (e.g. trial making test, go-no go test), behavioral stimuli (such as money incentive task) as well as resting state functional MRI.

Based on our collaborations with the University of Basel in Switzerland and the University of Bergen in Norway (Stoyanov et al., 2014; Stoyanov et al., 2018) we have implemented successfully an experimental protocol and paradigm for simultaneous administration of the Depression Scale of Von Zerssen and fMRI (Stoyanov et al., 2015). The rationale behind the selection of the method was to use essentially diagnostic items from a clinical scale in order to achieve trans-disciplinary validation of the clinical and neuroimaging measures (Aragona, 2017; Stoyanov et al., 2018). Those were initially designed in COGENT as event-related design, however it did not work properly due to heavy noise in the signal (Basel, February 2015). Then it was re-designed under E-Prime block matrix (Bergen, April 2015) in order to enhance the BOLD signal. The selected control items were derived from a diagnostically neutral interest scale ad hoc. Those were supposed to contrast the diagnostically significant depression items.

2.1 Top-down models. Sensitivity and specificity of the clinical scale

One direction of our empirical research program has been to validate the self-assessment measures as closely related to introspective psychopathology and thus more congruent with the underlying neurobiological processes. It is designed in top-down manner moving from the umbrella clinical observational diagnosis to the basic biological patterns behind the assessment scale. There have been reported evidence which reveals biological correlates of

state-independent (trait) measures. For example, most recently self-directedness as character trait in the psychobiological theory of personality has been demonstrated to be associated with anterior cingulate phosphocreatine and creatine levels established by means of magnetic-resonance spectroscopy (Squarcina et al., 2019). Our focus however was on establishment of inter-disciplinary correlation between psychopathology severity – as assessed by the clinical scale – and fMRI signal magnitude under current clinical states, thereby contributing to the concept of incremental validity (Zachar, 2012).

There were produced significant contrasts in the BOLD signal (activations) in the item responses of the patients when contrasting the diagnostically relevant Depression Scale (DS) and the neutral items from an interest scale by standard statistical operation, two-sample T-test (mainly in the central areas and medio-frontal cortex) (Stoyanov et al., 2017). Further, there were reported in the pilot sample differences in the between group analysis, as the depressed patients had increased activity of the medial frontal gyrus, anterior thalamus, parahippocampal gyrus and hippocampus when compared to healthy controls (Stoyanov et. al., 2017). Yet all those data refer to a self-assessment scale only and the results were uncorrected for multiple comparisons. When the observer based evaluation criteria (MADRS score>20) was applied, there were significant discrepancies and anomalies which caused a drop off of more than 50 patients from the project data reports. Many of the patients had reported item responses which resulted in a Depression Scale score corresponding to the diagnosis of depression; however, this was not confirmed by the MADRS interview score. The opposite phenomenon has been observed as well. Some patients reported relatively low (normal) score on depression scale and the psychiatrists evaluated the same patients on MADRS as moderately or mildly depressed. Finally, some of the healthy controls reported high depression scale with expected contrast activations in the brain regions of interest, but inconsistent with the MADRS assessment. In the full case-control sample, contrast activations in the middle frontal

gyrus (MFG) between patients and healthy control group were immediately associated with clinically significant differences in the score of Depression Scale of Von Zerssen in further study with correction for multiple comparisons duly applied to the results (Stoyanov et. al., 2018). In other words, difference in the von Zerssen DS item responses (score) is associated with contrast measured in the underlying brain processes with fMRI.

In this perspective, the remaining question is whether there is still any room left for ITM here?

The provisional answer is "maybe", under specific conditions and in particular reference to the self-evaluation measures.

(i) The first condition in order to maintain identity thesis here is that the determined differences in the mental states (normal and depressed) and the differences in the correlated brain activations should present not only at the level of statistical aggregates but *on individual level without any inter-individual variability*, which is not the case.

(ii) Another condition would be to investigate further necessary, replicable, and specific differences in comparison to other constructs employed in clinical psychopathology, e.g paranoia. In order to achieve the latter we performed another investigation, including the items from the Von Zerssen Paranoid Scale (DP) to investigate the contrasts with the Depression Scale (DS). In the next section of this paper I shall present the approach that our group has adopted in order to meet the latter challenge.

The direct comparison of the DP > DS contrast between the two clinical populations produced multiple clusters of activation with significance level < 0.001 which did not survive above the 0.05 p-level after FWE (family wise error, a type of multiple comparisons correction). On the same inter-group level and prior to inclusion of gender as co-variate there was localized a cluster in right angular gyrus, with peak activation significance level p = 0.036, consistent with our findings on group level. This cluster was above the level of significance after inclusion of gender as co-variate, which demonstrates the critical role of gender confound in such study design. On the group level (one sample t-test) the schizophrenic patients demonstrated residual activations in several clusters encompassing medial parietal and limbic structures (posterior cingulum and precuneus), as well as temporal and subcortical regions (for details see Table 1). The depressed patients, on the other hand, showed only two clusters with peak activations in middle cingulate and in superior temporal gyrus (Table 1). An illustration of these results is given in Figure 1.

Patients with schizophrenia demonstrated significant activations in a number of regions (right angular gyrus, left posterior cingulate and precuneus, right transverse temporal gyrus) during responses to paranoia versus depression items (DP > DS contrast) which differ topologically from those found in patients with major depression (left middle cingulate and right superior temporal gyrus).

That falsification (*trial-and-error*) brought our group away from reductive physicalism as we needed a more liberal cognitive framework in order to interpret the results and this is how we came to the supervenience theory of mind (STM).

Anatomical localization	Cluster size (voxels)	Peak MNI coordinates			p-value (FWE)
		x	у	z	(FVVE)
Schizophrenic patients					
Right angular gyrus, SMG	128	28	-46	36	0.004
Left posterior cingulus and precuneus	575	-6	-30	28	0.02
Right transverse temporal gyrus and anterior insula	3756	28	8	-10	0.05
Right caudate, thalamus	76	20	-12	22	0.05
Depressed patients					
Left middle cingulate gyrus	212	-8	-16	48	0.007
Right superior temporal gyrus	1243	42	-42	20	0.02

Table 1 (From Stoyanov et al., 2019a)

2.2 Bottom-up models: unsupervised machine learning in identifying brain signatures of disease

The advances of computational neuroscience, inspired by eliminative materialism have facilitated ground-breaking research programs with far more sophisticated, high-technological data processing facilities, which are practically designed to accumulate data from many basic disciplines in order to reconstruct a computational *bottom-up* model from the brain dysfunctions to mental disorders.

In this more ambitious agenda, there is embedded a claim that besides the clinical assessment tool (PD scale in our case), entire groups of psychiatric diagnostic entities (nosological groups) may be cross-validated and differentiated based on the brain signatures of disease.

This was achieved in the same sample by means of a rather different

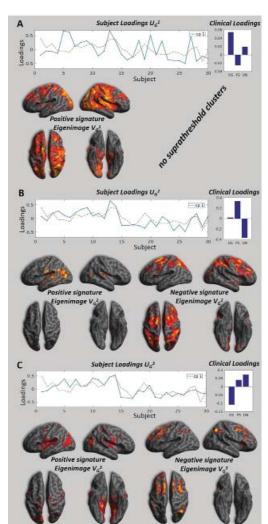


Figure 2 (From Stoyanov et al., 2019b)

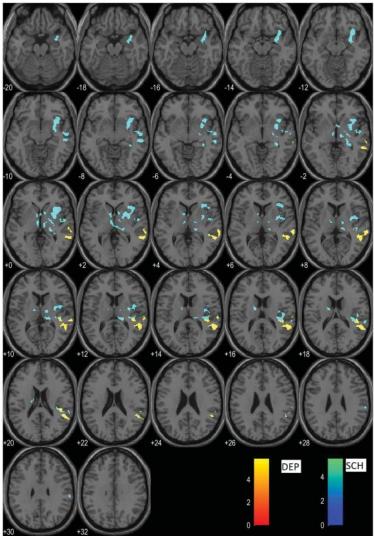


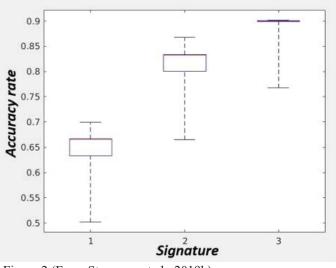
Figure 1 (From Stoyanov et al., 2019a)

processing and data analysis with the goal to deliver a model able to discriminate diseases' complex transdisciplinary signature integrating psychopathological and neuro-biological measures.

Our purpose was to explore whether or not there exist divergent brain patterns of schizophrenia and major depression corresponding to relevant (paranoid and depressive) item responses on the PD-S by Von Zerssen. The semi-unsupervised multivariate machine learning (multivariate linear model in particular) and principle component analysis produced brain activation patterns behind the item responses which reached the power to discriminate the diagnostic groups of major depression from schizophrenia estimated at up to 90 % accuracy.

This study is an exemplar cross-validation of nosological units in psychiatry by identifying brain signatures corresponding to clinical diagnostic scale item responses registered simultaneously with functional MRI (Stoyanov et al., 2019b).

These results of course are produced under many limitations and demand further replications.



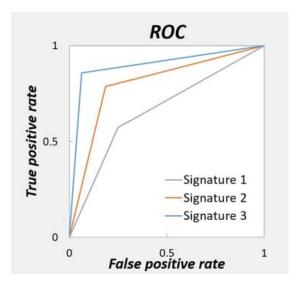


Figure 2 (From Stoyanov et al., 2019b)

CONCLUSION

In this paper we have summarized three major stances of physicalism as potential cognitive frameworks to fit and interpret the results from an attempt to translate and cross-validate data from psychopathology and functional neuroimaging in psychopathology.

One was the more conservative type identity theory of mind, which can frame the identification of normal and abnormal mental states in general as illustrated with the sensitivity study. In this modus correlations between the clinical scale and the BOLD signal distinguish on inter-group level the mental health from mental disorder.

The other was the more liberal supervenience theory, which encompasses the possibility to cross-validate diagnostic measurements (scales) that are presumably meant to differentiate actual pathological mental states one from another. In that case the correlation is established only on within-group level with the clinical scale score corresponding to functional MRI signal magnitude. It is assumed here that mental disorders are continuum of mental states without specific borders between them to be detected on inter-group level.

Last but not least is the radical eliminative materialism, which underpins the effort to distinguish nosological diagnoses in psychiatry in bottom-up fashion based on the biological signatures of disease, where the functional MRI signal, together with the clinical assessment scale comprise principle components in machine learning experiment.

My current claim as based on the above empirical evidence is that so far the intrasubjective (introspective) evaluation embodied in self-evaluation instruments and fMRI measures as proxy variables might be approached with local supervenience theory. This implies the perspective for translational cross-validation of clinical constructs and respective state-dependent scales with functional MRI, however without any claim at ontological reduction and with limited implementation for validation of diagnostic entities on nosological level.

Specificity of the assessment scale in terms of functional neuroimaging correlates is different from specificity on the level of nosological diagnosis.

The inter-subjective evaluation (observer-based interviews) can only supervene in terms of global supervenience on physical (neurobiological) properties. This is entailed from the complex irreducibility of the *reflexive* and intuitive space of inter-subjectivity.

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