

По списък публикации в реферирани издания (приравнени с монография)  
показател 4

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**4.1 Application of functional magnetic resonance imaging in psychiatric clinical evaluation: Controversies and avenues**

Sevdalina Kandilarova, Drozdstoy Stoyanov, Ivo D. Popivanov, Stefan Kostianev, J Eval Clin Pract. 2018 Aug;24(4):807-814. <https://doi.org/10.1111/jep.12906>

Rationale, aims, and objectives: In this study, we have attempted to replicate the findings of altered emotional processing in depressed patients compared with healthy controls by means of functional magnetic resonance imaging during passive viewing of positive, negative, and neutral pictures from the International Affective Pictures System.

Methods: Nineteen medicated depressed patients and 19 sex and age-matched healthy controls underwent functional magnetic resonance imaging during presentation of affective pictures in a block design. The differences between the blood oxygen level dependent signal elicited in the three conditions were compared. Within-group and between-group analyses were performed with stringent criteria for statistical inference ( $P < .05$  with family-wise error correction).

Results: In medicated depressed patients, positive pictures compared with neutral pictures activated predominantly the posterior cingulate cortex and precuneus, as well as occipital and middle temporal areas mainly on the left side, while in healthy controls, only the occipito-temporal areas demonstrated significant activation. The negative pictures elicited stronger activation of occipital and temporal regions in both groups and of inferior frontal gyrus only in control subjects. The difference between the groups did not reach statistical significance. Positive correlation was demonstrated between activation levels of clusters located in left precuneus/posterior cingulate cortex and left inferior/middle occipital gyrus and Montgomery-Asberg Depression Rating Scale scores in patients while viewing positive compared with neutral pictures.

Conclusions: Although the within-group analysis demonstrated significant activations in both groups with apparent discrepancies, the between-group analysis did not reach statistical significance under the stringent criteria for statistical inference. These results are further contextualized in the critical debate on the methodological issues of clinical evaluation in psychiatry, more specifically the validity and consistency of the applied methods and the limitations existing in the attempts to provide sound cross-disciplinary validation of the diagnostic tools by means of neuroscience.

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**4.2 Altered Resting State Effective Connectivity of Anterior Insula in Depression**

Sevdalina Kandilarova, Drozdstoy Stoyanov, Stefan Kostianev, Karsten Specht. Front Psychiatry. 2018 Mar 15;9:83. doi: 10.3389/fpsy.2018.00083. eCollection 2018.

Depression has been associated with changes in both functional and effective connectivity of large scale brain networks, including the default mode network, executive network, and salience network. However, studies of effective connectivity by means of spectral dynamic causal modeling (spDCM) are still rare and the interaction between the different resting state networks has not been investigated

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in detail. Thus, we aimed at exploring differences in effective connectivity among eight right hemisphere brain areas-anterior insula, inferior frontal gyrus, middle frontal gyrus (MFG), frontal eye field, anterior cingulate cortex, superior parietal lobe, amygdala, and hippocampus, between a group of healthy controls (N = 20) and medicated depressed patients (N = 20). We found that patients not only had significantly reduced strength of the connection from the anterior insula to the MFG (i.e., dorsolateral prefrontal cortex) but also a significant connection between the amygdala and the anterior insula. Moreover, depression severity correlated with connectivity of the hippocampal node. In conclusion, the results from this resting state spDCM study support and enrich previous data on the role of the right anterior insula in the pathophysiology of depression. Furthermore, our findings add to the growing evidence of an association between depression severity and disturbances of the hippocampal function in terms of impaired connectivity with other brain regions.

Keywords: anterior insula; brain networks; depression; dorsolateral prefrontal cortex; effective connectivity; hippocampus; resting state functional MRI; spectral dynamic causal modeling.

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### 4.3 Psychopathology Assessment Methods Revisited: On Translational Cross-Validation of Clinical Self-Evaluation Scale and fMRI

Drozdstoy Stoyanov, Sevdalina Kandilarova, Stefan Borgwardt, Rolf-Dieter Stieglitz, Kenneth Hugdahl, Stefan Kostianev. *Front Psychiatry*. 2018 Feb 8;9:21. doi: 10.3389/fpsy.2018.00021. eCollection 2018.

We present in this article a study design that combines clinical self-assessment scale, simultaneously administered with fMRI data acquisition. We have used a standard block-design with two different conditions. Each active block consisted of four text statements (items), alternating diagnostically specific (DS) blocks comprising items from von Zerssen depression scale and diagnostically neutral (DN) blocks with items from a questionnaire about general interests. All items were rated on four degree Likert scale, and patients provided responses with corresponding four buttons during the fMRI session. Our results demonstrated that in healthy controls, contrasting the two types of stimuli yielded no residual activations, e.g., the DS did not produce significantly different activations compared to the DN stimuli. Furthermore, the correlation analyses did not find a relationship between brain activations and the total score of the DS statements in this group. However, contrasting the DS stimuli to the DN stimuli in the patients produced significant residual activations in several brain regions: right pre- and postcentral gyrus (including right supramarginal gyrus), left middle frontal gyrus, triangular part of the left inferior frontal gyrus and middle temporal gyrus. The left precuneus demonstrated correlations with the patients' DS score. In the between-group comparisons, we found residual activations in the right pre- and postcentral gyrus, right supplementary motor area, medial segment of the right precentral gyrus, right superior parietal lobule, left middle frontal gyrus, left superior frontal gyrus, left occipital pole. Our results confirm the possibility of translational cross-validation of a clinical psychological test (von Zerssen's depression scale) and fMRI. At this stage, however, we can only confirm the sensitivity of the method (its ability to distinguish healthy controls from depressed patients), but we cannot conclude anything about its specificity (distinction from different psychopathology conditions).

Keywords: depression; functional neuroimaging; neuroscience; psychopathology; translational medical research.

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### 4.4 Cross-Validation of Functional MRI and Paranoid-Depressive Scale: Results From Multivariate Analysis

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Drozdostoy Stoyanov, Sevdalina Kandilarova, Rositsa Paunova, Javier Barranco Garcia, Adeliya Latypova, Ferath Kherif. *Front Psychiatry*. 2019 Nov 25;10:869. doi: 10.3389/fpsyt.2019.00869. eCollection 2019.

**Introduction:** There exists over the past decades a constant debate driven by controversies in the validity of psychiatric diagnosis. This debate is grounded in queries about both the validity and evidence strength of clinical measures.

**Materials and Methods:** The objective of the study is to construct a bottom-up unsupervised machine learning approach, where the brain signatures identified by three principal components based on activations yielded from the three kinds of diagnostically relevant stimuli are used in order to produce cross-validation markers which may effectively predict the variance on the level of clinical populations and eventually delineate diagnostic and classification groups. The stimuli represent items from a paranoid-depressive self-evaluation scale, administered simultaneously with functional magnetic resonance imaging (fMRI).

**Results:** We have been able to separate the two investigated clinical entities - schizophrenia and recurrent depression by use of multivariate linear model and principal component analysis. Following the individual and group MLM, we identified the three brain patterns that summarized all the individual variabilities of the individual brain patterns.

**Discussion:** This is a confirmation of the possibility to achieve bottom-up classification of mental disorders, by use of the brain signatures relevant to clinical evaluation tests.

**Keywords:** classification; functional MRI; machine learning; psychopathology; validation.

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## **4.5 Cross-Validation of Paranoid-Depressive Scale and Functional MRI: New Paradigm for Neuroscience Informed Clinical Psychopathology**

Drozdostoy Stoyanov, Sevdalina Kandilarova, Zlatoslav Arabadzhiev, Rossitsa Paunova, André Schmidt, Stefan Borgwardt. *Front Psychiatry*. 2019 Sep 27;10:711. doi: 10.3389/fpsyt.2019.00711. eCollection 2019.

There is reported a study performed with a novel paradigm aiming at investigation of the translational validity of von Zerssen's paranoid-depression scale and its fMRI correlates in terms of focus on exploration of the results on the contrast between the Paranoid Specific (DP) blocks and the Depression Specific (DS) blocks. 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 which differ topologically from those found in patients with major depression (left middle cingulate and right superior temporal gyrus). The direct comparison between the groups, however, did not yield any residual activations after correction.

**Keywords:** depression; functional MRI; psychopathology; schizophrenia; validation.

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#### **4.6 Reduced grey matter volume in frontal and temporal areas in depression: contributions from voxel-based morphometry study**

Sevdalina Kandilarova, Drozdstoy Stoyanov, Nickolay Sirakov, Michael Maes, Karsten Specht. *Acta Neuropsychiatr.* 2019 Oct;31(5):252-257. doi: 10.1017/neu.2019.20.

**Objective:** The aim of the current study was to examine whether and to what extent mood disorders, comprising major depression and bipolar disorder, are accompanied by structural changes in the brain as measured using voxel-based morphometry (VBM).

**Methods:** We performed a VBM study using a 3T MRI system (GE Discovery 750w) in patients with mood disorders (n=50), namely, 39 with major depression and 11 with bipolar disorder compared to 42 age-, sex- and education-matched healthy controls.

**Results:** Our results show that depression was associated with significant decreases in grey matter (GM) volume of the regions located within the medial frontal and anterior cingulate cortex on the left side and middle frontal gyrus, medial orbital gyrus, inferior frontal gyrus (triangular and orbital parts) and middle temporal gyrus (extending to the superior temporal gyrus) on the right side. When the patient group was separated into bipolar disorder and major depression, the reductions remained significant only for patients with major depressive disorder.

**Conclusions:** Using VBM the present study was able to replicate decreases in GM volume restricted to frontal and temporal regions in patients with mood disorders, mainly major depression, compared with healthy controls.

**Keywords:** bipolar disorder; grey matter volume; major depressive disorder; structural MRI; voxel-based morphometry.

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#### **4.7 Functional MRI in Depression—Multivariate Analysis of Emotional Task**

Sevdalina Kandilarova, Drozdstoy Stoyanov, Magdalena Stoeva, Adeliya Latypova, Ferath Kherif. *Journal of Medical and Biological Engineering* (2020) 40:535–544 <https://doi.org/10.1007/s40846-020-00547-2>

**Rationale, Aims and Objectives:** The field of translational neuroscience suffers from an extremely low replication levels compared to other life science fields. The objective of the present study was to test the hypothesis that multivariate analysis of a classical emotional pictures paradigm would produce meaningful brain signatures with some power to discriminate depressed patients from healthy subjects.

**Methods:** Participants in the study were eighteen medicated depressed patients and eighteen sex and age matched healthy controls. Functional MRI paradigm with a visual presentation of emotional pictures (positive, negative and neutral) from the International Affective Pictures System was used. The multivariate linear method (MLM) was used to derive the specific brain signatures on an individual and on a group level. The predictive power of the brain signatures is tested by use of linear discriminant analysis.

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Results: Following the individual and group MLM, the three brain patterns that summarized all the individual variabilities of the individual brain patterns were produced. The discriminant analysis yielded accuracy levels for the three brain signatures ranging from 67 to 98%.

Conclusion: The present study demonstrated that the multivariate linear method resulted in meaningful brain signatures with significant potential for distinction between healthy and depressed subjects. Such findings will fuel the emerging paradigm shift from more conventional statistical analysis to the probably more appropriate for the field of functional neuroimaging machine learning techniques.

Keywords: Functional magnetic resonance imaging · Multivariate analysis · Depression · Affective pictures · Clinical diagnosis

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### **4.8 Multivariate Analysis of Structural and Functional Neuroimaging Can Inform Psychiatric Differential Diagnosis**

Drozdstoy Stoyanov, Sevdalina Kandilarova, Katrin Aryutova, Rositsa Paunova, Anna Todeva-Radneva, Adeliya Latypova and Ferath Kherif. *Diagnostics* 2021, 11(1), 19; <https://doi.org/10.3390/diagnostics11010019>

Traditional psychiatric diagnosis has been overly reliant on either self-reported measures (introspection) or clinical rating scales (interviews). This produced the so-called explanatory gap with the bio-medical disciplines, such as neuroscience, which are supposed to deliver biological explanations of disease. In that context the neuro-biological and clinical assessment in psychiatry remained discrepant and incommensurable under conventional statistical frameworks. The emerging field of translational neuroimaging attempted to bridge the explanatory gap by means of simultaneous application of clinical assessment tools and functional magnetic resonance imaging, which also turned out to be problematic when analyzed with standard statistical methods. In order to overcome this problem our group designed a novel machine learning technique, multivariate linear method (MLM) which can capture convergent data from voxel-based morphometry, functional resting state and task-related neuroimaging and the relevant clinical measures. In this paper we report results from convergent cross-validation of biological signatures of disease in a sample of patients with schizophrenia as compared to depression. Our model provides evidence that the combination of the neuroimaging and clinical data in MLM analysis can inform the differential diagnosis in terms of incremental validity.

Keywords: multivariate linear method; validation; diagnosis; discriminative; signatures of disease; schizophrenia; depression

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### **4.9 Diagnostic Task Specific Activations in Functional MRI and Aberrant Connectivity of Insula with Middle Frontal Gyrus Can Inform the Differential Diagnosis of Psychosis**

Drozdstoy Stoyanov, Katrin Aryutova, Sevdalina Kandilarova, Rositsa Paunova, Zlatoslav Arabadzhiev, Anna Todeva-Radneva, Stefan Kostianev, Stefan Borgwardt. *Diagnostics (Basel)*. 2021 Jan 8;11(1):95. doi: 10.3390/diagnostics11010095.

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We constructed a novel design integrating the administration of a clinical self-assessment scale with simultaneous acquisition of functional Magnetic Resonance Imaging (fMRI), aiming at cross-validation between psychopathology evaluation and neuroimaging techniques. We hypothesized that areas demonstrating differential activation in two groups of patients (the first group exhibiting paranoid delusions in the context of paranoid schizophrenia-SCH-and second group with a depressive episode in the context of major depressive disorder or bipolar disorder-DEP) will have distinct connectivity patterns and structural differences. Fifty-one patients with SCH (n = 25) or DEP (n = 26) were scanned with three different MRI sequences: a structural and two functional sequences-resting-state and task-related fMRI (the stimuli represent items from a paranoid-depressive self-evaluation scale). While no significant differences were found in gray matter volumes, we were able to discriminate between the two clinical entities by identifying two significant clusters of activations in the SCH group-the left Precuneus (PreCu) extending to the left Posterior Cingulate Cortex (PCC) and the right Angular Gyrus (AG). Additionally, the effective connectivity of the middle frontal gyrus (MFG), a part of the Dorsolateral Prefrontal Cortex (DLPFC) to the Anterior Insula (AI), demonstrated a significant difference between the two groups with inhibitory connection demonstrated only in SCH. The observed activations of PreCu, PCC, and AG (involved in the Default Mode Network DMN) might be indirect evidence of the inhibitory connection from the DLPFC to AI, interfering with the balancing function of the insula as the dynamic switch in the DMN. The findings of our current study might suggest that the connectivity from DLPFC to the anterior insula can be interpreted as evidence for the presence of an aberrant network that leads to behavioral abnormalities, the manifestation of which depends on the direction of influence. The reduced effective connectivity from the AI to the DLPFC is manifested as depressive symptoms, and the inhibitory effect from the DLPFC to the AI is reflected in the paranoid symptoms of schizophrenia.

Keywords: brain networks; connectivity; default mode network; depression; frontal cortex; insula; neuroimaging; neuropsychiatric disorders; precuneus; schizophrenia; translational neuroscience.

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### **4.10 Structural brain correlates in major depression, anxiety disorders and post-traumatic stress disorder: A voxel-based morphometry meta-analysis**

Maria Serra-Blasco, Joaquim Radua, Carles Soriano-Mas, Alba Gómez-Benlloch, Daniel Porta-Casteràs, Marta Carulla-Roig, Anton Albajes-Eizagirre, Danilo Arnone, Paul Klauser, Eric J Canales-Rodríguez, Kevin Hilbert, Toby Wise, Yuqui Cheng, Sevdalina Kandilarova, David Mataix-Cols, Eduard Vieta, Esther Via, Narcís Cardoner. Review *Neurosci Biobehav Rev* 2021 Oct; 129:269-281. doi: 10.1016/j.neubiorev.2021.07.002. Epub 2021 Jul 10.

The high comorbidity of Major Depressive Disorder (MDD), Anxiety Disorders (ANX), and Posttraumatic Stress Disorder (PTSD) has hindered the study of their structural neural correlates. The authors analyzed specific and common grey matter volume (GMV) characteristics by comparing them with healthy controls (HC). The meta-analysis of voxel-based morphometry (VBM) studies showed unique GMV diminutions for each disorder ( $p < 0.05$ , corrected) and less robust smaller GMV across diagnostics ( $p < 0.01$ , uncorrected). Pairwise comparison between the disorders showed GMV differences in MDD versus ANX and in ANX versus PTSD. These results endorse the hypothesis that unique clinical features characterizing MDD, ANX, and PTSD are also reflected by disorder specific GMV correlates.

Keywords: Anxiety disorders; Comorbidities; Gray matter volume; Major depressive disorder; Meta-analysis; Neuropsychiatry; Posttraumatic stress disorder; Structural neuroimaging.

### **7.1 Differential Aberrant Connectivity of Precuneus and Anterior Insula May Underpin the Diagnosis of Schizophrenia and Mood Disorders**

Aryutova K, Paunova R, Kandilarova S, Maes M, Stoyanova K, Stoyanov D. World J Psychiatr 2021; In press

**BACKGROUND.** Over the past decade, resting-state functional magnetic resonance imaging (rs-fMRI) has concentrated on brain networks such as the default mode network (DMN), the salience network (SN), and the central executive network (CEN), allowing for a better understanding of cognitive deficits observed in mental disorders, as well as other characteristic psychopathological phenomena such as thought and behavior disorganization.

**AIM.** To investigate differential patterns of effective connectivity across distributed brain networks involved in schizophrenia (SCH) and mood disorders.

**METHODS.** The sample is comprised of 58 patients with either paranoid syndrome in the context of SCH (n = 26) or depressive syndrome (Ds) (n = 32), in the context of major depressive disorder or Bipolar disorder. The methods used include rs-fMRI and subsequent dynamic causal modeling to determine the direction and strength of connections to and from various nodes in the DMN, SN, and CEN.

**RESULTS.** A significant excitatory connection from the dorsal anterior cingulate cortex to the anterior insula (aI) was observed in the SCH patient group, whereas inhibitory connections from the precuneus to the ventro-lateral prefrontal cortex and from the aI to the Pc were observed in the Ds group.

**CONCLUSION.** The results delineate specific patterns associated with SCH and Ds and can further contribute to a better explanation of the underlying mechanisms of these disorders as well as to inform differential diagnosis and precise treatment targeting.

**Key Words:** Schizophrenia; Major depressive disorder; Bipolar disorder; Resting-state Fmri; effective connectivity; Precuneus; Insula; Default mode network; Salience network

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### **7.2 Anterior insula (dis) connectivity across major psychiatric disorders**

Kandilarova S. In: Contemporary Neuropsychiatry: Implications from Cognitive Neuroscience. Ed. Stoyanov D. Cambridge Scholar Publishing. In press

The insular cortex is involved in consciousness and plays a role in a variety of functions linked to compassion, empathy, taste, perception, motor control, self-awareness, cognitive functioning, interpersonal experience, and awareness. The anterior part of the insula (AI) is mediating the dynamic interactions between large-scale brain networks engaged in externally oriented attention and self-cognition, and as part of the salience network (SN) is supporting the bottom-up identification of salient events, the shifting between other large-scale networks to promote access to attention and working memory, and the adjustment of the autonomic response to salient stimuli. Since most of these insula-related functions are impaired in psychiatric disorders, it is not surprising that findings of structural, functional and connectivity abnormalities have been reported in a variety of patient groups. In this chapter we present the most recent findings concerning the common and distinct AI connectivity disturbances in schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD). In conclusion, an explanatory model is described in which the abnormality of the SN results in either predominance of externalizing mental representations leading to psychotic

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symptoms in SCZ or an overrepresented internalizing leading to self-defeating depressive symptoms in mood disorders. Moreover, the inability of the SN to adequately perform its main function of a dynamic switch between the DMN and the CEN produces the well-known cognitive symptoms in both patient groups.

Key words: Anterior insula, connectivity, schizophrenia, bipolar disorder, major depressive disorder.

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### **7.3 Effective Connectivity Between the Orbitofrontal Cortex and the Precuneus Differentiates Major Psychiatric Disorders: Results from a Transdiagnostic Spectral DCM Study**

Kandilarova S, Stoyanov D, Aryutova K, Paunova R, Mantarkov M, Mitrev I, Todeva-Radneva A, Specht K. *CNS Neurol Disord Drug Targets*. 2021. doi:10.2174/1871527320666210917142815.

**Background & objective:** We have previously identified aberrant connectivity of the left precuneus, ventrolateral prefrontal cortex, anterior cingulate cortex, and anterior insula in patients with either a paranoid (schizophrenia), or a depressive syndrome (both unipolar and bipolar). In the current study, we attempted to replicate and expand these findings by including a healthy control sample and separating the patients in a depressive episode into two groups: unipolar and bipolar depression. We hypothesized that the connections between those major nodes of the resting state networks would demonstrate different patterns in the three patient groups compared to the healthy subjects.

**Method:** Resting-state functional MRI was performed on a sample of 101 participants, of which 26 patients with schizophrenia (current psychotic episodes), 24 subjects with bipolar disorder (BD), 33 with major depressive disorder (MDD) (both BD and MDD patients were in a current depressive episode), and 21 healthy controls. Spectral Dynamic Causal Modeling was used to calculate the coupling values between eight regions of interest, including the anterior precuneus (PRC), anterior hippocampus, anterior insula, angular gyrus, lateral orbitofrontal cortex (OFC), middle frontal gyrus, planum temporale, and anterior thalamus.

**Results & conclusion:** We identified disturbed effective connectivity from the left lateral orbitofrontal cortex to the left anterior precuneus that differed significantly between unipolar depression, where the influence was inhibitory, and bipolar depression, where the effect was excitatory. A logistic regression analysis correctly classified 75% of patients with unipolar and bipolar depression based solely on the coupling values of this connection. In addition, patients with schizophrenia demonstrated negative effective connectivity from the anterior PRC to the lateral OFC, which distinguished them from healthy controls and patients with major depression. Future studies with unmedicated patients will be needed to establish the replicability of our findings.

**Keywords:** Effective connectivity; bipolar disorder; major depression; orbitofrontal cortex; precuneus; resting state MRI; schizophrenia; spectral Dynamic Causal Modeling; transdiagnostic.

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### **7.4 Clinical Use of Neurophysiological Biomarkers and Self-Assessment Scales to Predict and Monitor Treatment Response for Psychotic and Affective disorders**

Katrin Aryutova, Drozdostoy St Stoyanov, Sevdalina Kandilarova, Anna Todeva-Radneva, Stefan S Kostianev. *Curr Pharm Des*. 2021 Apr 6. doi: 10.2174/1381612827666210406151447.

Psychoses and affective disorders are severe mental illnesses with a considerable negative effect on an individual and global scale. They are among the most damaging and socially significant diseases, which contribute to permanent disabilities for the patients. The aim of this review is to analyse the capacity of neuroscientific methods as tools to reform psychiatry into a biologically valid medical

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discipline. Furthermore, it will focus on the application of the translational approach towards the diagnostic and therapeutic processes, as well as monitoring of treatment response by using valid biomarkers and psychometric instruments. By combining translational neuroscience with the latest psychopharmacology advances clinicians might be able to provide better quality of precision and individualized medical care for their patients. We visualise a reality in which neuroimaging methods will modify standard clinical evaluation of neuropsychiatric disorders, leading to a biologically valid diagnosis, monitoring and treatment in everyday clinical practice.

Keywords: depression; evidence-based psychiatry; neurophysiological biomarkers.; psychopharmacology; schizophrenia; translational neuroscience; treatment response.

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### **7.5 Implications from translational cross-validation of clinical assessment tools for diagnosis and treatment in psychiatry**

Katrin Aryutova, Rositsa Paunova, Sevdalina Kandilarova, Anna Todeva-Radneva, Drozdstoy Stoyanov. Review World J Psychiatry. 2021 May 19;11(5):169-180. doi: 10.5498/wjp.v11.i5.169.

Traditional therapeutic methods in psychiatry, such as psychopharmacology and psychotherapy help many people suffering from mental disorders, but in the long-term prove to be effective in a relatively small proportion of those affected. Therapeutically, resistant forms of mental disorders such as schizophrenia, major depressive disorder, and bipolar disorder lead to persistent distress and dysfunction in personal, social, and professional aspects. In an effort to address these problems, the translational approach in neuroscience has initiated the inclusion of novel or modified unconventional diagnostic and therapeutic techniques with promising results. For instance, neuroimaging data sets from multiple modalities provide insight into the nature of pathophysiological mechanisms such as disruptions of connectivity, integration, and segregation of neural networks, focusing on the treatment of mental disorders through instrumental biomedical methods such as electro-convulsive therapy (ECT), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and deep brain stimulation (DBS). These methodologies have yielded promising results that have yet to be understood and improved to enhance the prognosis of the severe and persistent psychotic and affective disorders. The current review is focused on the translational approach in the management of schizophrenia and mood disorders, as well as the adaptation of new transdisciplinary diagnostic tools such as neuroimaging with concurrently administered psychopathological questionnaires and integration of the results into the therapeutic framework using various advanced instrumental biomedical tools such as ECT, TMS, tDCS and DBS.

Keywords: Affective disorders; Deep brain stimulation; Electro-convulsive therapy; Evidence-based psychiatry; Psychopharmacology; Schizophrenia; Transcranial direct current stimulation; Transcranial magnetic stimulation; Translational neuroscience.

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### **7.6 The Translational Potential of Non-coding RNAs and Multimodal MRI Data Sets as Diagnostic and Differential Diagnostic Biomarkers for Mood Disorders**

Anna Todeva-Radneva, Katrin Aryutova, Sevdalina Kandilarova, Rositsa Paunova, Drozdstoy Stoyanov. Current Topics in Medicinal Chemistry, Volume 21 , Issue 11 , 2021; DOI : 10.2174/1568026621666210521144534

Major Depressive Disorder (MDD) and Bipolar Disorder (BD) have a high prevalence and detrimental socio-economic consequences for the patients and the community. Furthermore, the depressive symptomatology of both disorders is essentially identical, thus rendering the clinical differential diagnosis between the two significantly more difficult considering the concomitant lack

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of objective biomarkers. Mood disorders are multifactorial disorders the pathophysiology of which includes genetic, epigenetic, neurobiological, neuroimmunological, structural and functional brain alterations, etc. Aberrant genetic variants as well as changed differential expression of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have been implicated in the pathophysiology of MDD and BD. MiRNAs as well as lncRNAs have regulatory and modulating functions on protein-coding gene expression thus influencing the remodeling of the architecture, neurotransmission, immunomodulation, etc. in the Central Nervous System (CNS) which are essential in the development of psychiatric disorders including MDD and BD.

Moreover, both shared and distinct structural, connectivity, task-related and metabolic features have been observed via functional magnetic resonance imaging and magnetic resonance spectroscopy, suggesting the possibility of a dimensional continuum between the two disorders instead of a categorical differentiation. Aberrant connectivity within and between the Default Mode Network, the Salience Network, Executive Network, etc. as well as dysfunctional emotion, cognitive and executive processing have been associated with mood disorders.

Therefore, the aim of this review is to explore a more multidimensional framework in the scientific research of mood disorders, including epigenetic and neuroimaging data in order to shape an outline for their translational capacity in clinical practice.

Keywords: Major Depressive Disorder, Bipolar Disorder, Functional magnetic resonance imaging, Magnetic resonance spectroscopy, Non-coding RNAs, Biomarker, Connectivity.

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### **7.7 T134. THE ROLE OF THE DEFAULT MODE NETWORK IN SCHIZOPHRENIA AND AUDITORY VERBAL HALLUCINATIONS – AN INVESTIGATION OF DYNAMIC FMRI RESTING STATE CONNECTIVITY**

Sarah Weber, Erik Johnsen, Rune Kroken, Else-Marie Løberg, Sevdalina Kandilarova, Drozdstoy Stoyanov, Kristiina Kompus, Kenneth Hugdahl. *Schizophrenia Bulletin*, Volume 46, Issue Supplement\_1, April 2020, Pages S281–S282, <https://doi.org/10.1093/schbul/sbaa029.694>

Background: There is a wealth of evidence showing aberrant functional connectivity (FC) in schizophrenia but with considerable variability in findings across studies. Dynamic FC is an extension of traditional static FC, in that such analyses allow for explorations of temporal changes in connectivity. Thereby they also provide more detailed information on connectivity abnormalities in psychiatric disorders such as schizophrenia.

Methods: The current study investigated dynamic FC in a sample of 80 schizophrenia patients and 80 matched healthy control subjects. Furthermore, relationships with auditory verbal hallucinations (AVH), a core symptom of schizophrenia, were explored. Two measures of AVH were used, one measure of current AVH severity assessed on the day of scanning, and one trait-measure where AVH were assessed repeatedly over the course of one year.

Results: Compared to healthy controls, schizophrenia patients showed increased dwell times in states with high connectivity within the default mode network (DMN). Current AVH severity did not show a significant relationship with dynamic FC. However, the trait-measure of AVH proneness over one year showed a significant relationship with dynamic FC. Patients with high AVH proneness spent less time in connectivity states characterized by strong anti-correlation between the DMN and task-positive networks.

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Discussion: The results provide further evidence for a DMN dysfunction in schizophrenia, which could be linked to thought disturbances in relation to an increased internal focus of cognitive processing. The effects of AVH proneness on dynamic FC support theoretical models of AVH which have proposed an instability of the DMN and impaired cognitive control in AVH patients. The results also point to AVH proneness as a potential marker for identifying distinct subgroups of schizophrenia patients.

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### 7.8 M140. WHAT HAPPENS IN THE BRAIN A FEW SECONDS BEFORE THE ONSET AND OFFSET OF AN HALLUCINATORY EPISODE?

Alexander Craven, Lars Ersland, Drozdstoy Stoyanov, Sevdalina Kandilarova, Iris Sommer, Erik Johnsen, Kenneth Hugdahl. *Schizophrenia Bulletin*, Volume 46, Issue Supplement\_1, April 2020, Pages S188–S189, <https://doi.org/10.1093/schbul/sbaa030.452>

Background: Auditory verbal hallucinations (AVH), the sense of “hearing voices” in the absence of a corresponding auditory source, are a major symptom in schizophrenia. Hemodynamic and electrophysiology studies have shown aberrant activation in fronto-temporal speech and language areas (Curcic-Blake et al., 2017 for review) – indicating neurobiological mediators relating to onset and duration of AVH episodes. However, unanswered is the question of specific neuronal precursors to the spontaneous cessation of an AVH episode. We therefore studied what happens in the brain a few seconds before both the onset and offset of an AVH episode.

Methods: Structural and functional MRI data were collected from 44 patients diagnosed with a schizophrenia spectrum disorder, at three sites (University of Bergen, Norway, n=12; Medical University of Plovdiv, Bulgaria, n=13; Utrecht University Medical Center, Netherlands, n=19, total 25m, 19f, age 37.9+/-13.2 years). Symptom severity was assessed with the PANSS; mean total (+/-SD) 64.9+/-16.9; P3 hallucinatory behaviour 4.6+/-1.1. Additional assessments (not reported), scanner hardware and particulars of the MR acquisition varied between sites.

Functional data were collected with a “symptom-capture” paradigm (Sommer et al., 2008), where subjects were instructed to press a button when a hallucinatory episode began, and another when the episode ended. Functional data were processed using an FSL FEAT pipeline, with additional filtering using the ICA\_AROMA method. Data were then subjected to statistical analysis, contrasting hallucinatory with non-hallucinatory periods; higher-level analysis allowed comparison with findings from previous meta-analyses (Kompus et al. 2011, Jardri et al., 2011).

A number of regions of interest were selected based on an initial PCA, in addition to regions nominated in the meta-analyses. For each region, for each start- and end-of-hallucination event, a time-course was extracted for the interval t=-10 to +15sec with respect to button-press onset. Time-courses were aligned and group-averaged (rejecting outliers iteratively) to yield a model time-course for start- and end- hallucinatory events in each region. Permutation analysis (n=5000) was performed to identify differential effects between start and end events.

Results: Functional block-analysis revealed several clusters of activation, including among others the left fronto-temporal language areas (superior temporal gyrus and Broca’s area). Similar patterns were present on a per-site basis. Time-course analysis demonstrated a differential effect in the left paracingulate sulcus, characterized by a significant dip in activation ( $\Delta=-158\text{iu}$ ,  $p=0.021$ ) at the end-of-hallucination events, in contrast to a significant peak ( $\Delta=35\text{iu}$ ,  $p=0.0142$ ) at the start-of-hallucination events. This activity preceded the motor response for the same events.

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Discussion: Clusters identified in the block-analysis at group-level were consistent with findings from meta-analyses; this attests to the validity of the source data and initial processing. The novel finding of anticipatory neuronal activity in the paracingulate region, differentiated between onset and offset of AVH- events, complements recent findings of reduced functional connectivity (Alonso-Solís et al., 2015) and morphological differences (Garrison et al., 2019) in the same region. This suggests that the paracingulate region may be crucial in both the initiation and the cessation of an AVH-episode and speaks to a kind of regulatory role for the region. This may in turn point to differential action of excitatory and inhibitory transmitters at a lower level of explanation.

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### **7.9 Transdisciplinary Validation of Clinical Psychological Scales and Functional MRI**

Anna Todeva-Radneva, Rossitsa Paunova, Denitsa Simeonova, Sevdalina Kandilarova & Drozdstoy Stoyanov. SAGE Research Methods Cases: Medicine and Health; 2020. DOI: <https://dx.doi.org/10.4135/9781529744286>

This case study illustrates our endeavor in expanding the new field of psychiatric neuroimaging by transdisciplinary cross-validation of clinical psychological scales and functional magnetic resonance imaging (fMRI). This further aims at closing the explanatory gap between psychiatry and neuroscience. This gap is reflected by the theoretical and methodological crisis in psychiatry, which fundamentally lies within the unresolved mind-brain problem and its contemporary interpretation as indicated in the Identity Theory of Mind and the Supervenience Theory of Mind.

We have tried to delineate the process of designing and refining an innovative nonconventional fMRI paradigm in the pursuit of implementing translational cross-validation between clinical and neuroimaging methods. Furthermore, we explain the necessity of using multiple creative statistical tools when analyzing compound and unique data sets to obtain reliable and valid results. In addition, we have shared our experience in facing and overcoming a number of unpredicted practical challenges during the implementation of our research project which we hope would be helpful to anyone aspiring to explore the field of neuroscientific research.

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### **7.10 Dynamic Functional Connectivity Patterns in Schizophrenia and the Relationship With Hallucinations**

Sarah Weber, Erik Johnsen, Rune A Kroken, Else-Marie Løberg, Sevdalina Kandilarova, Drozdstoy Stoyanov, Kristiina Kompus, Kenneth Hugdahl. *Front Psychiatry*. 2020 Mar 31;11:227. doi: 10.3389/fpsyt.2020.00227. eCollection 2020.

There is a wealth of evidence showing aberrant functional connectivity (FC) in schizophrenia but with considerable variability in findings across studies. Dynamic FC is an extension of traditional static FC, in that such analyses allow for explorations of temporal changes in connectivity. Thereby they also provide more detailed information on connectivity abnormalities in psychiatric disorders such as schizophrenia. The current study investigated dynamic FC in a sample of 80 schizophrenia patients and 80 matched healthy control subjects, replicating previous findings of aberrant dwell times in specific FC states, and further supporting a role for default mode network (DMN) dysfunction. Furthermore, relationships with hallucinations, a core symptom of schizophrenia, were explored. Two measures of hallucinations were used, one measure of current hallucination severity assessed on the day of scanning, and one trait-measure where hallucinations were assessed repeatedly over the course

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of 1 year. Current hallucination severity did not show a significant relationship with dynamic FC. However, the trait-measure of hallucination proneness over 1 year showed a significant relationship with dynamic FC. Patients with high hallucination proneness spent less time in connectivity states characterized by strong anti-correlation between the DMN and task-positive networks. The findings support theoretical models of hallucinations which have proposed an instability of the DMN and impaired cognitive control in patients with hallucinations. Furthermore, the results point to hallucination proneness as a potential marker for identifying distinct subgroups of schizophrenia patients.

Keywords: auditory verbal hallucinations; default mode network; fMRI; neuroimaging; psychosis; schizophrenia.

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### **7.11 The Value of Neuroimaging Techniques in the Translation and Transdiagnostic Validation of Psychiatric Diagnoses - Selective Review**

Anna Todeva-Radneva, Rositsa Paunova, Sevdalina Kandilarova, Drozdostoy St Stoyanov. Review Curr Top Med Chem. 2020;20(7):540-553. doi: 10.2174/1568026620666200131095328.

Psychiatric diagnosis has long been perceived as more of an art than a science since its foundations lie within the observation, and the self-report of the patients themselves and objective diagnostic biomarkers are lacking. Furthermore, the diagnostic tools in use not only stray away from the conventional medical framework but also remain invalidated with evidence-based concepts. However, neuroscience, as a source of valid objective knowledge has initiated the process of a paradigm shift underlined by the main concept of psychiatric disorders being "brain disorders". It is also a bridge closing the explanatory gap among the different fields of medicine via the translation of the knowledge within a multidisciplinary framework. The contemporary neuroimaging methods, such as fMRI provide researchers with an entirely new set of tools to reform the current status quo by creating an opportunity to define and validate objective biomarkers that can be translated into clinical practice. Combining multiple neuroimaging techniques with the knowledge of the role of genetic factors, neurochemical imbalance and neuroinflammatory processes in the etiopathophysiology of psychiatric disorders is a step towards a comprehensive biological explanation of psychiatric disorders and a final differentiation of psychiatry as a well-founded medical science. In addition, the neuroscientific knowledge gained thus far suggests a necessity for directional change to exploring multidisciplinary concepts, such as multiple causality and dimensionality of psychiatric symptoms and disorders. A concomitant viewpoint transition of the notion of validity in psychiatry with a focus on an integrative validity approach may facilitate the building of a collaborative bridge above the wall existing between the scientific fields analyzing the mind and those studying the brain.

Keywords: Biomarkers; Neuroimaging; Psychiatry; Trans-diagnostic validation; Translation; fMRI.

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### **7.12 Structural neuroimaging in depression: results from voxel based morphometry study**

D. Stoyanov, S. Kandilarova, N. Sirakov, K. Specht. European psychiatry 56, s161-s162. doi:10.26226/morressier.5c642beb9ae8fb00131cf1f7

Background and aims: Voxel Based Morphometry (VBM) is a new promising technique that compare different patients' brains on a voxel-by-voxel basis after deformation fields have been used to

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spatially normalize the images. The method is used to detect differences in the density of the brain tissue, and present the results quantitatively. The aim of our study is to present our experience in the field of VBM of grey matter reduction in patients with depressive disorders.

Methods: For the present study we recruited fifty adult subjects complying with the DSM-IV-TR criteria for depressive episode of major depressive disorder/bipolar disorder and forty-two age and sex matched healthy controls. High resolution structural scans were obtained from all participants on a 3T MRI system. MRI data were analysed using the SPM 12 software running on MATLAB R2017 for Windows and the CAT 12 toolbox implemented in SPM.

Results: We performed two sample t-test on the grey matter images with a total intracranial volume as co-variable. The level of significance was set to  $p > 0.05$  false discovery rate corrected and an extent threshold of 36 voxels per cluster. The contrast between controls and patients yielded significant differences in clusters encompassing left medial frontal (MFC) and anterior cingulate cortex (ACC) as well as right frontal and temporal regions. The reverse contrast exploration did not produce any surviving significant clusters.

Conclusions: There has been confirmed significant reduction of grey matter volume in specific regions in patients with depressive disorder when compared to healthy controls.

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### **7.13 Translational validity of PASAT and the effect of fatigue and mood in patients with relapsing remitting MS: A functional MRI study.**

Dessislava Iancheva, Anastasiya G. Trenova, Kiril Terziyski, Sevdalina Kandilarova, Stefka Mantarova. *J Eval Clin Pract.* 2018 Aug;24(4):832-838. doi: 10.1111/jep.12913. Epub 2018 Apr 3.

Rationale, aims, and objectives: Paced Auditory Serial Addition Test (PASAT) is used for assessment of information processing speed, attention, and working memory, which are the most frequently affected cognitive domains in multiple sclerosis (MS) patients, and may be significantly affected by fatigue. However, the effect of fatigue and mood on the PASAT performance in MS patients translationally validated by fMRI has not been studied yet. The aim of this study is to investigate the translational validity of the PASAT, using fMRI during a paced visual serial addition test (PVSAT) paradigm in patients with relapsing remitting MS (RRMS) and to assess the impact of fatigue and mood on test performance.

Methods: Fourteen patients with RRMS in remission and 14 healthy controls, matched by sex, age, and educational status, were enrolled in the study. The subjects underwent a standard neurological examination, neuropsychological evaluation with the PASAT 3', fMRI scanning with a PVSAT paradigm, and Beck Depression Inventory. All patients were assessed by the Modified Fatigue Impact Scale.

Results: Paced Auditory Serial Addition Test score was lower in patients ( $41.4 \pm 15.5$  vs  $51.6 \pm 7.5$ ,  $P = .035$ ). A moderate negative correlation ( $P = -0.563$ ,  $P = 0.036$ ) was found between PASAT and MIFS scores. The fMRI scanning showed significant activations in several clusters that differed between patients and controls. The patient group presented wider cluster activation; Brodmann area (BA) 6—bilaterally; left BA7, 8, and 9; and right BA40, while controls presented with activations in left BA6 and BA44. Significant negative correlations between PASAT score and cortical activations in left BA23, right BA32, and left BA7 were observed in patients only.

Conclusion: Our results show that poorer performance on the PASAT is associated with higher activation in areas connected with working memory, attention, and emotional processes during the

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fMRI assessment with PVSAT paradigm, which provides evidence for the translational validity of the PASAT in patients with RRMS.

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### **7.14 Adult brain activation during visual learning and memory tasks. An experimental approach to translational neuroscience**

Popova F, Kovacheva A, Garov P, Sivkov S, Kandilarova S, Sirakov N, Stoeva M, Velkova KG. *J Eval Clin Pract.* 2018 Aug;24(4):864-868. doi: 10.1111/jep.12911. Epub 2018 Mar 23.

Rationale, aims, and objectives: Human brain connectome is a new and rapidly developing field in neuroscience. The pattern of structural and functional connectivity in the brain is not fixed but is continuously changing in response to experiences. Exploring these phenomena opens a powerful arsenal of analyses and computational approaches that could provide important new insights into clinical and cognitive neuroscience. The aim of the present study was to investigate the activations of adult brain cortical areas during a memory task performance by using functional MRI with a specific focus on gender differences.

Methods: Twenty-nine right-handed subjects (15 men and 14 women) were scanned. The memory paradigm consisted of 4 consecutive sets of "on" and "off" blocks with a total duration of 4 minutes. The subjects were first presented with 4 pictures (fixation F-part) of the same theme-landscapes, portraits, anatomical images of internal organs, and geometric figures denoted by specific mismatching nouns (seasons, personal names, internal organs, and figures), followed by 3 of the presented pictures and questions for memory evaluation (recall R-part). For the active conditions, the participants were instructed to read the statements carefully and answer with a button press.

Results: We found reliable occipital and temporal signal responses across the block design contrasts with statistical significant differences within the groups in both genders. Statistical significance in brain cortical activation was not found between men and women.

Conclusion: The results highlighted several detailed distinctions between the genders and potential future directions in brain activation studies as part of the multidisciplinary approach in translational neuroscience.

Keywords: brain activation; connectome; fMRI; memory paradigm.

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### **7.15 EP1532. Functional MRI correlations between fatigue and cognitive performance in patients with relapsing remitting MS**

D. Iancheva, A. Trenova, G. Slavov, K. Terziyski, S. Kandilarova, S. Mantarova, Z. Zahariev. *Multiple Sclerosis Journal* 2018; 24: (S2) 738–980

The correlation between fatigue and cognitive performance in Multiple sclerosis (MS) is well reported, but the intimate mechanisms of the fatigue impact on cognition are not fully defined yet. The combined assessment with neuropsychological testing and functional MRI (fMRI) has revealed an opportunity for investigating complex compensatory mechanisms involved in cognitive functioning.

The aim of this study is to investigate blood oxygen level dependent (BOLD) activations in relapsing-remitting MS (RRMS) patients with and without cognitive dysfunction and the impact of fatigue on cortical activations. Forty-two patients diagnosed with RRMS according to McDonald's criteria (2010) in remission phase were enrolled in the study. Cognitive functioning was assessed by Symbol Digit Modalities Test (SDMT). Cut-off point of a total score of 55 on the SDMT was used to divide the patients in two groups: cognitively impaired (CI) - SDMT score equal to or below 55 points and cognitively preserved (CP) - SMDT score above 55 points. Fatigue was assessed by Modified Fatigue Impact Scale (MFIS). The fMRI scanning was performed on a 3T MRI using PVSAT paradigm as a

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cognitive task. Data were analysed with statistical parametric mapping 12 (SPM12) software. Between-group analysis revealed increased activations in left Brodmann area (BA) 40 in CP patients compared to CI ones ( $p < 0.001$  uncorrected). Regression analysis yielded increased activations in left BA 40, right BA 40 and left BA6 in patients with higher MFIS score. Stronger BOLD activation in left BA 31 was

associated with lower MFIS score (FWE,  $p < 0.05$ ). The differences in BOLD activations suggest presence of cortical reorganisation in our CP patients. The impact of fatigue on cortical activation during cognitive task is demonstrated by inconformity of activated areas depending on the MFIS score. Activation in BA 40 may represent a mechanism for diminishing fatigue impact on cognitive functioning in CP patients.

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### **7.16 Translational Functional Neuroimaging in the Explanation of Depression**

Drozdostoy Stoyanov, Sevdalina Kandilarova, Stefan Borgwardt. *Balkan Med J.* 2017 Dec 1;34(6):493-503. doi: 10.4274/balkanmedj.2017.1160. Epub 2017 Oct 11.

Translation as a notion and procedure is deeply embodied in medical science and education. Translation includes the possibility to translate data across disciplines to improve diagnosis and treatment procedures. The evidence accumulated using translation serves as a vehicle for reification of medical diagnoses. There are promising, established post hoc correlations between the different types of clinical tools (interviews and inventories) and neuroscience. The various measures represent statistical correlations that must now be integrated into diagnostic standards and procedures but this, as a whole, is a step forward towards a better understanding of the mechanisms underlying psychopathology in general and depression in particular. Here, we focus on functional magnetic resonance imaging studies using a trans-disciplinary approach and attempt to establish bridges between the different fields. We will selectively highlight research areas such as imaging genetics, imaging immunology and multimodal imaging, as related to the diagnosis and management of depression.

Keywords: Neuroscience; depression; neuroimaging functional.; translational medical research.

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## **По списък с публикации в нереферирани издания показател 8**

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### **8.1 Whether and to what extent neuroimaging methods can change modern psychiatry.**

Aryutova K., Kandilarova S., Todeva-Radneva A., Paunova R., Stoyanov D. *Medinfo.* No. 1 2021. 92-97.

Modern progress in neuroscience is largely due to the variety of imaging methods for studying the structure and function of the central nervous system. Functional magnetic resonance imaging (fMRI) is one of the most commonly used neuroimaging techniques in the study of the etiopathogenetic mechanisms of mental disorders. Numerous fMRI studies and the results obtained are a valuable source of information, but encounter problems in the attempts to incorporate them into clinically applicable instruments that can be applied in everyday psychiatric practice. Through a translational approach involving neuroimaging and cross-validation of a psychometric instrument (von Zerssen's paranoid-depressive scale), our team was able to create a paradigm to address this limitation by confirming the sensitivity (the ability to distinguish patients from healthy controls) and the specificity (the ability to distinguish individual disease units - paranoia and depression) of the method. By scanning and analyzing the individual fMRI modalities, we identified activations in the Default Mode Network (DMN), as well as disturbances in the connection between the

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dorsolateral prefrontal cortex and the anterior insula, which are specific to the paranoid group of patients. The results of our studies contribute to the biological understanding of psychopathological phenomena such as cognitive deficits, attention disorders and disorganized behavior, which are common signs of schizophrenia. In addition, we applied a multivariate linear model (MLM), superimposing different modalities of MRI (structural, functional at rest and during task), which allowed us to identify significant brain signatures with high discriminant value in patients with schizophrenia and depression. This type of methodology has the potential to encourage the subsequent revalidation of psychiatric classifications and assessment methods based on reliable, evidence-based neurobiological markers.

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### **8.2 Towards implementation of the model of translational validation in revisiting clinical assessment tools in psychiatry: preliminary empirical results.**

Stoyanov D, Kandilarova S, Sirakov N, Stoeva M, Velkova K, Kostianev S. World Congress of Psychiatry. Epub 2017

**Objective:** The aim of the project is to discover bridge-lows which exist between psychopathology, clinical psychology and neuroscience. The objective is to reveal convergent and discriminant validity operations across different clinical and neurobiological measures which may endorse such laws. For the moment we have discovered various significant correlations of diagnostic items on depression self-rating scale and BOLD fMRI, administered simultaneously, and observed contrasts between patients and control group.

**Methods:** The scanning of the participants was executed on a 3T MRI system – with a protocol including a structural scan – Sag 3D T1 FSPGR, slice thickness 1 mm, matrix 256x256, flip angle 120 and a functional scan – 2D EPI, slice thickness 3 mm, matrix 64x64, TR (relaxation time) – 2000 msec. TE (echo time) – 30, flip angle 90°. Before each functional scan 5 dummy time series were acquired. We used standard block design with two “on” conditions and one “off” condition and a total duration of 8 min. 32 sec. Each “on” block consisted of 4 statements presented for 8 sec each on LCD screen behind the subject or via goggles. The Diagnostically Specific (DS) blocks consisted of 4 statements from the von Zerssen depression scale and the Diagnostically Neutral (DN) blocks consisted of 4 statements from an interest questionnaire.

**Results/Discussion:** The contrast DS/DN gives activations in frontal (medial frontal cortex bilaterally) and central areas on the first level of analysis. On the second level there has been revealed significant difference between the BOLD signals in the patient group as contrasted to healthy controls during the DS item response. The brain areas involve include right anterior thalamus, middle frontal gyrus, parahippocampal gyrus, left hippocampus

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### **8.3 Psychiatry in crisis: possibilities of translational functional neuroimaging.**

Stoyanov D, Kandilarova S, Sirakov N, Stoeva M, Velkova K. Proceedings of the Second National Conference of the Scientific Society of Neuropsychopharmacology and Neuroscience. 2017

Modern psychiatry is in a prolonged crisis of its identity as a medical discipline. This crisis is fundamentally related to doubts about the validity of the applied methods and procedures for diagnosis and treatment. The other branches of medicine operate with traditional approaches to establish trans-disciplinary validity (hereinafter referred to as translational validity). One sustainable example of such an approach is the translation of data between four different disciplines (biochemistry, electrophysiology, imaging and clinical cardiology) in the diagnosis and treatment of ischemic heart disease. Among them there are regulated normative criteria for convergent and discriminant validity, which significantly support the formation of a taxonomic apparatus and therapeutic guidelines.

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The problem in psychiatry is that attempts to introduce such models to operationalize diagnostic information from various relevant disciplines (such as neurobiology, neurophysiology, and clinical psychopathology) have so far failed. The biggest progress has been made by the NIMH Research Domain Criteria project, which, however, still has a limited scope and is sharply criticized.

This report will present empirical data obtained through our model of translational validity between psychiatry and neuroscience. Our meta-empirical model suggests a study of the translational validity of von Zersen depression scale items administered simultaneously with BOLD activity recording during functional magnetic resonance imaging of the brain. The diagnostically relevant items in our paradigm are contrasted with diagnostically neutral items on a scale of interests in separate blocks. The project summarizes the results obtained on 15 patients with depressive disorders and 15 healthy controls. In the population of patients with depressive syndrome, significant above-threshold activation was found when performing diagnostically significant items in the medio-frontal cortex, which is missing when compared with healthy controls and when performing diagnostically neutral items. In our interpretation, this approach is an example of successful translational validation of a psycho-diagnostic inventory using fMRI. The same tool is often used for clinical evaluation in psychopharmacological studies. The obtained data for correlation with real-time brain activations contain the potential to optimize the choice of medication in the treatment of depressive syndrome and pharmaco-psychological monitoring of the effect of therapy.