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Commentary: Expanding the collection of neuroimaging tools in psychiatry

Georg S. Kranz[1,2] & Jack JQ Zhang[1]

[1]*Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong, China*
[2]*Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria*
Correspondence to: Georg.kranz@polyu.edu.hk

The commonly used distinction between "mental" and "neurological" disorders in psychiatry and neurology, respectively, demonstrates the necessity for a continued effort to ground psychiatry as a medical faculty and to emphasize psychiatric disorders as brain disorders. Public confusion over the nature of psychiatric disorders is not surprising, considering that diagnoses are still only symptom-based. Likewise, the field has little benefit from the considerable degree of symptom heterogeneity within a single psychiatric diagnosis. For example, several hundreds of symptom combinations can meet DSM criteria for major depression. We are still far from utilizing objective pathognomonic markers in daily routine, a necessity for personalized treatment achieved in neurology and many disciplines in general medicine. Part of the problem lies in the nature and complexity of psychiatric disorders itself. As an information-processing organ, the brain is highly plastic and susceptible to change. Almost every incoming information leaves a trace and has the potential to shape functional and structural neural properties permanently. On the one hand, neural plasticity reminds us of the importance of non-biological factors in the etiology of psychiatric disorders. On the other hand, it emphasizes the brain as imprint of our inner personal

experience, an imprint that should provide quantifiable and objective information, if studied carefully with appropriate instruments.

Neuroimaging is a highly promising approach, as it allows for the investigation of the human brain in vivo with little discomfort for patients (Linden and Thome 2011). The last decades have seen a steep rise in publications using EEG, MRI or PET yielding essential information that constitutes most of what we know about the functioning of the living human brain today. However, despite major effort of many researchers utilizing these tools within the last decades, attempts to find reliable markers have been unfruitful so far. In their review, Drepper et al. (2017) summarize and evaluate the use of transcranial sonography (TCS) for psychiatry, a neuroimaging tool that has gained significance in neurological diagnosis in recent years (Berg et al. 2008). TCS enables the visualization of midbrain and brainstem structures at axial scanning planes with an in-plane image resolution of approximately 0.7x1mm. For example, via an acoustic window in the temporal bone, the brainstem raphe nuclei can be detected as an echogenic continuous line within the butterfly-shaped mesencephalic brainstem. Drepper et al. thoroughly summarize evidence of ultrasound abnormalities in several psychiatric disorders including schizophrenia, bipolar disorder and major depression, among others. Most convincing is their demonstration of a reduced echogenicity of the brainstem raphe nuclei in major depression, a finding that is supported by eight of nine studies as depicted in their second table (Drepper et al. 2017). As an illustration, we extracted the frequency scores from the nine individual studies and calculated a pooled odds ratio using random-effects model meta-analysis (see Figure). The summary effects estimate clearly demonstrated a pronounced hypoechogenicity of the brainstem raphe region

(pooled OR: 15.36; 95% CI: (7.71, 30.59), which translates to a Hedges' *g* of 1.49). There was no sign of publication bias, as indicated by funnel plot and Egger regression test (P=0.322).

A Hedges' *g* of 1.49 is a very large effect. Indeed, the brainstem raphe hypoechogenicity seems to be three times as strong as the reduction of serotonin transporter binding in this region in major depression, as recently demonstrated by our group (Gryglewski et al. 2014). Moreover, the observed effect is almost double the effect size of increased striatal dopamine synthesis capacity in schizophrenia (Howes et al. 2012). It is worth noting that two of the nine included studies did not comment on examiner blinding. This is important because image acquisition is subjective, depends for example on the correct plane chosen, and should thus be performed only by a well-experienced operator. However, being aware of the patients' appearance, the operator may be influenced and image acquisition biased. Moreover, although image analysis can be done in a blinded manner after acquisition, it consists of a semi-quantitative visual assessment and is thus not entirely objective.

Drepper et al. mention these drawbacks in their review and cite work that attempts to overcome them. They also give an overview on the potential causes of changes in echogenicity, an issue whose outcome will greatly enrich our understanding of the pathophysiology of psychiatric disorders. In any case, the review by Drepper et al. clearly shows that TCS is a highly promising imaging tool with the potential to detect pathognomonic biological markers in daily routine. TCS is cheap, widely available, easy and harmless to apply and less affected by movement compared to other imaging techniques. Psychiatric disorders are estimated to be the leading global burden in terms of years lived with disability (Vigo et al. 2016). We need to increase our research effort

to get a better understanding of these disorders. In this sense, TCS is a most welcome candidate to expand the collection of neuroimaging tools in psychiatry.

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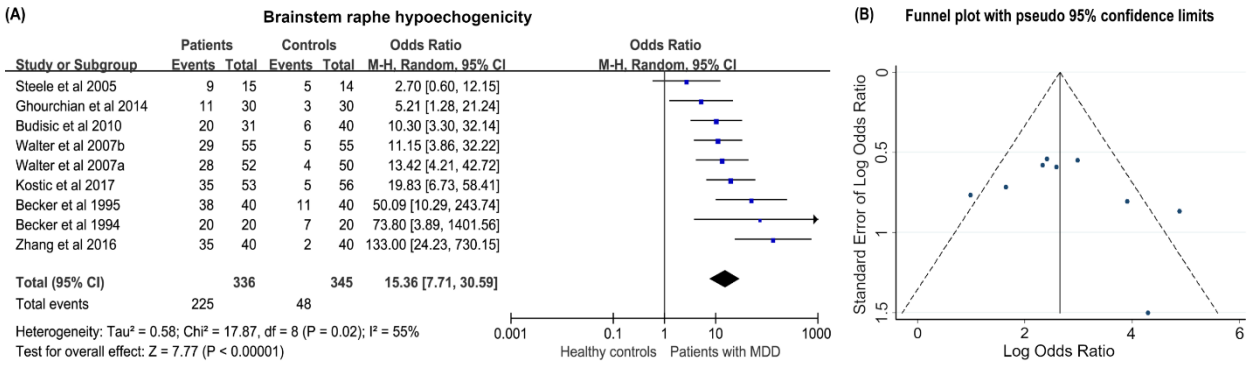

Figure legend

Hypoechogenicity in the brainstem raphe region in patients with major depressive disorder (MDD) compared to healthy controls. (A) Forest plot of TCS studies investigating the frequency of brainstem raphe hypoechogenicity in MDD and healthy controls summarizing to a pooled odds ratio of 15.36. (B) The corresponding funnel plot displays study precision as a function of effect estimate. The funnel plot appears symmetrical except for an outlier at the right bottom.