What matters and what is possible in neuroimaging meta-analyses (of psychopathy)

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We thank Robert Latzmann, Christopher Patrick, and Scott Lilienfeld for their interest in and thoughtful comment [1] on our paper [2]. The commentary provides the opportunity for clarification, to prevent possible misunderstanding regarding the potential of neuroimaging meta-analyses of (not only) psychopathy with this response.

First, the authors of the comment briefly mention “a failure to distinguish among alternative measures of a target construct (i.e., psychopathy) and collapsing across non-interchangeable dependent measures (i.e., MRI-brain activations from different tasks)”, which they regard as limitations. We concur that our meta-analyses did not assess putative differences between measures that literally purport to capture the same entity (so-called psychopathy scales) or between various tasks performed by subjects with the same disorder (i.e., psychopathy). That is, our intention was not to isolate task-related differences in neural activity response in psychopathy, nor to isolate neural differences between competing psychopathy concepts. Rather, the objective of our meta-analytic study was to identify brain regions showing aberrant activity associated with psychopathy across the whole neuroimaging literature. Indeed, it also seems interesting to investigate if abovementioned differences can in fact be spotted. Unfortunately, there are simply not enough experiments available to disentangle such subtle effects in valid subanalyses presently (cf., work by Eickhoff and colleagues [3]). For instance, only 14 of the 24 experiments using an alternative measure of psychopathy (the Psychopathic Personality Inventory (PPI [4]) found any (i.e., either positive or negative) association of brain activity with the scale at all. From these 14 experiments, seven showed a positive and seven a negative relationship. Data underlying the experiments were collected in only four independent studies (i.e., samples). However, at least about 20 independent experiments would be needed for a valid activation likelihood estimation meta-analysis [3].

The main criticism raised by Latzman and colleagues, however, is the “treatment of this condition as a unitary construct, largely neglecting its heterogeneity”. To illustrate the relevance to neuroimaging, they quote three individual studies in which diverging activity corresponding to psychopathy subdimensions was found within the same brain regions.

In fact, there is a heated debate whether psychopathy is of a multidimensional or a unidimensional nature. Although there are arguments for its multidimensionality, there is also strong evidence against. The Psychopathy Checklist-Revised (PCL-R) as well as its derivative, the Psychopathy Checklist: Screening Version (PCL:SV), are arguably the most important psychometric instruments for assessing psychopathy. Most of the studies included in our meta-analyses relied on the PCL (113 out of 155 experiments). Both the PCL-R [5] and the PCL:SV [6] have been shown to be commensurate with a bifactor model of psychopathy that includes a general (*g*) factor [6]. One of the first applications of such a model to the PCL-R instruments was published by Christopher Patrick [5]. According to these models [5, 6], the items of the PCL-R/SV instruments load onto a common factor, with specific portions of variance relegated to nuisance factors. Moreover, taxometric research [7] indicates that the disorder as such (i.e., psychopathy) is a dimensional trait, not a taxon.

From this point of view, it may even be regarded as implausible to hypothesize that there should be subtraits of the disorder that do not add up to a common core and that have unique correlates in the brain. However, neuroimaging meta-analyses (of psychopathy subscales) could indeed serve as a useful tool to test if proposed subtraits are neurobiologically founded. Also for this purpose, there are unfortunately not enough experiments available from the literature.

Irrespective of the dimensionality discussion, it has to be noted that the very same regions (where aforesaid studies located diverging activity) emerged in our meta-analyses. This militates against the concern that subdivisions of psychopathy scales would lead to divergent psychopathic subgroups or distinct traits which, in turn, could cancel each other out with respect to neural correlates. Apart from that, this issue does not apply to the analyses in our paper which was looking for convergence in brain associations with psychopathy (scales). Interestingly, there was indeed strong concordance in several regions. Be it that the commentators' argument of subscales neutralizing each other is valid, then why have these scales converging neural correlates?

Moreover, our findings provide robust evidence for neural alterations associated with psychopathy and hence validate this psychological construct using rigorous neurobiological mapping. This result seems even more intriguing as similar attempts with respect to other disorders, such as depression, did not succeed [8]. In this context, we want to mention that – contrary to the presentation by Latzman and colleagues – we did not claim "that certain neural activation patterns are "pathognomonic" of psychopathy". Rather, we used a general approach, which avoids *a priori* assumptions about (putative differences between) psychological constructs and their relationship among one another as well as to neurobiology, to meta-analyze brain activation changes associated with psychopathy. In a second step, we characterized the ensuing regions functionally using independent data from healthy subjects. These analyses indicated that brain regions showing aberrant activity in psychopaths fulfill mental functions in healthy subjects which, in turn, happen to be disturbed in psychopaths. We thus stated that these *mental functions* correspond with the deviant behavioral patterns that are characteristic and pathognomonic of psychopathy. This reverse approach hence validated that the neural aberrances were associated with the (overarching construct of) psychopathy (and not with epiphenomena).

Although we provided robust evidence for a general neurobiological foundation of psychopathy, we agree that further investigations into particular aspects of this disorder are desirable. Therefore, we will wait together with Latzman and colleagues for "finer-grained meta-analyses" – for instance on psychopathy subdimensions. Many more individual studies on this topic, however, are necessary to constitute a solid basis for such endeavors. Until then, our consolidating results, establishing the robustness of a neural signature underlying common conceptualization of psychopathy, can provide guidance for future studies on the

potential heterogeneity in psychopathic traits, once sufficiently large consortium datasets will be available in the future [9].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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