Aberrant Brain Activity in Psychopaths Links to Receptor Distribution, Gene Expression and Behavior

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To the Editor:

A recent review article discusses the role of serotonin in aggressive behavior [1]. The authors conclude that low endogenous serotonin levels represent a neurobiological trait risk factor for impulsive aggression but that further multimodal research is needed to elucidate the relationship between serotonin function and brain circuits of aggression. Recent advances in multimodal data fusion and availability of open multimodal data resources now allow for a direct evaluation of such questions at various levels integrating genetics, multimodal imaging and behavior.

Psychopathy represents an immediate model of aggression, with psychopaths disproportionally commiting sexual and nonsexual violent offenses, making up to 20–25% of the prison population, and recidivating at a rate of about 80% [2]. Here, we make use of openly available resources to provide an integrative understanding of psychopathy, combining neuroimaging meta-analyses, gene expression, *in vivo* receptor mapping as well as phenotypic information.

Analyses were based on the brain map of aberrant brain activity in psychopaths, provided by a recent meta-analysis of 155 neuroimaging experiments (Figure 1A). Increased activity converged in the fronto-insular cortex, while a consistent decrease was shown in the lateral prefrontal cortex, dorsomedial prefrontal cortex, and laterobasal amygdala (maps available at https://identifiers.org/neurovault.collection:10489) [3]. We quantified the relationship between these meta-analytic maps of generally aberrant, increased and decreased activity and the spatial distribution of various receptors systems in the healthy brain using the open-source JuSpace toolbox ($p<0.05$, FDR corrected) [4]. Correlational analyses revealed a significant positive relationship between aberrant activity in psychopaths and 5-HT_{1A} ($r=0.30$, $p=0.015$) and μ-opioid ($r=0.34$, $p=0.005$) receptors as well as dopamine ($r=0.34$, $p=0.006$) and serotonin transporters ($r=0.4$, $p<0.001$) (Figure 1B): the higher the availability of respective receptors as derived from healthy volunteer studies, the more aberrant the brain activity in psychopaths. The association with 5-HT_{1A} remained significant when testing for specificity of the respective findings in a multiple linear regression ($p=0.003$).

To test if the above relationships of aberrant activity with specific neurotransmitter systems are also observed at the gene expression level, we capitalized on the Allen Human Brain Atlas, which provides estimates of gene expression in the healthy brain. Testing for association with gene expression of the corresponding genes using the open-source MENGA toolbox [5] revealed a significant association with the 5-HT1RA gene (5-HT_{1A} receptor: mean $r=0.51$, $p=0.009$) (Figure 1C). Other associations, in contrast, were not significant (SLC6A3 (DAT): $r=-0.02$, $p=0.937$; OPRM1 (μ): mean $r=0.11$, $p=0.59$; SLC6A5 (SERT): mean $r=0.02$; $p=0.924$).

We further tested if these associations with aberrant activity are primarily linked to increased or decreased activity in psychopaths. No correlation survived correction for multiple comparisons for the map of increased activity (Figure 2A/B). In contrast, the map of decreased brain activity in psychopaths showed a significant positive correlation with distribution of the serotonergic 5-HT_{1A} ($r=0.34$; $p=0.005$) and μ-opioid ($r=0.32$; $p=0.009$) receptors (Figure 2A/B). Both associations remained significant when controlling for each other's influence using multiple linear regression (5-HT_{1A}: $p=0.002$; μ: $p=0.004$). Expression of the HT1RA gene encoding the 5-HT_{1A} receptor (mean $r=0.43$; $p=0.032$), yet not of the OPRM1 gene encoding the μ-opioid receptor (mean $r=0.02$; $p=0.914$), was significantly associated with decreased brain activity (Figure 2C).

To establish a relationship between aberrant brain activity in psychopaths and phenotypic information, we capitalized on the Neurosynth database (https://neurosynth.org) for probabilistic measures that specific terms (e.g., "attention", "emotion", and "sleep") are functionally related to

specific brain regions. This quantity mirrors how often specific terms and voxel coordinates are published in conjunction with one another. We assessed the correlation of psychopathy-related brain patterns with the individual term maps from this database. Across the pattern of aberrant brain activity, functional annotations from Neurosynth with large positive loadings were significantly related to affective processes (including “emotion regulation”, “fear”, “valence”, “arousal”, “empathy”), while terms with large negative loading were identified as related to attentional processes (Figure 1D). Querying functional annotations on increased activity yielded significant positive term associations related to thinking (e.g., “decision”, “sentence comprehension”, or “reasoning”) and affect (such as “emotion regulation”, “empathy”, or “pain”) as well as negative term associations with more perceptual processes (e.g., “visual perception” and “object recognition”) (Figure 2D). When computing the associations for the brain pattern of decreased activity, we observed significant positive loadings related to emotional processes (e.g., “emotion regulation”, “valence”, “fear”, “arousal”, “empathy”) and terms with negative loadings pertaining to motor processes (e.g., “movement” or “motor control”) and cognition (such as “imagery“, “planning” or “attention”) (Figure 2D). Taken together, the psychopathic brain pattern revealed functional profiles including valence, emotion (regulation), empathy and fear, i.e., mental functions corresponding with the deviant behavioral patterns that are pathognomonic of psychopathy.

Our findings extend the results from previous, smaller-sized PET studies and support the conclusions of da Cunha-Bang and Knudsen pointing to the association of psychopathy and aggression with serotonergic neurotransmission [1,10,11] by identifying a specific link between psychopathy-related brain activity and 5-HT_{1A} receptor distribution, encoded by the HTR1A gene [12,13]. Promoter polymorphism of this gene modulates human anxiety levels via altering parasympathetic nervous functioning [14], which is likely disrupted in psychopaths, given the inverse relationship of resting heart rate and psychopathy [15,16]. Our analyses interconnect these findings by linking distribution of the 5-HT_{1A} receptor, which modulates both anxiety and associated autonomic changes [17], to the pattern of altered brain activity in psychopaths; and this pattern, in turn, to behavioral domains such as anxiety and fear, which are affected in psychopathy.

Importantly, recent studies have raised various methodological concerns regarding many openly available resources including some used in the above example. Among other, an appropriate control of type 1 errors in spatial correlation analyses as well as the generalizability of some of the resources were discussed. Besides the obvious need for further methodological improvements, integration of evidence from different resources and at different levels as demonstrated here may provide a way forward to increase the confidence in single findings as well as to provide comprehensive and integrative insights into specific research questions.

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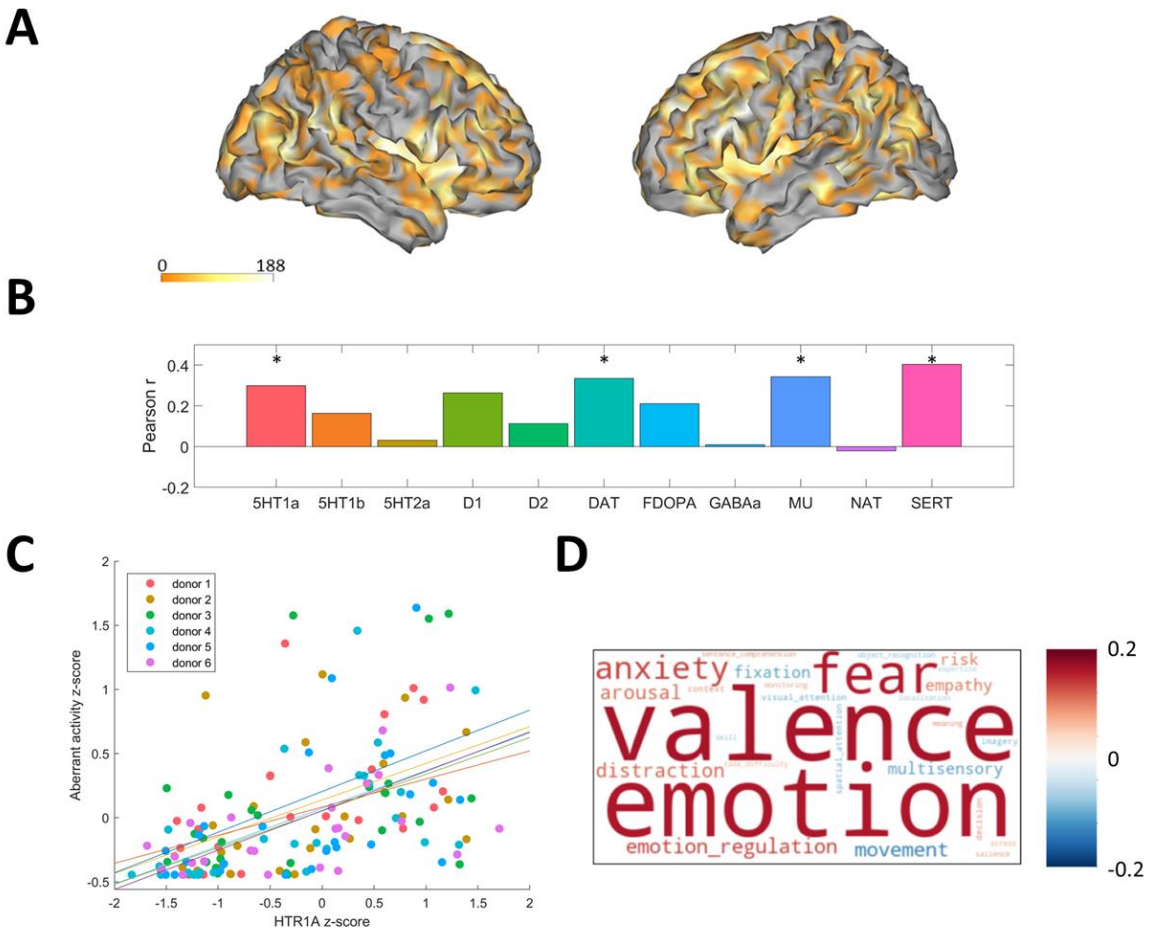
Figure legends

Figure 1. Relationship of aberrant brain activity in psychopaths with neurotransmitter systems, gene expression and behavior. *Meta-analytically derived aberrant brain activity (A) was spatially related to distribution of 5-HT_{1A} and μ-opioid receptors as well as dopamine and serotonin transporters (B). The color bar represents threshold-free cluster enhancement (TFCE) values as weighted sums of the entire local clustered signal on the unthresholded brain map. Then, Pearson correlations were computed between z-transformed gene expression estimates obtained from the Allen Human Brain Atlas and the respective altered activity maps. Significance testing was performed using a meta-analytic z-test of p-values across all six donors [5]. This association analysis revealed a link between the meta-analytically derived map and 5-HTR1A gene expression, encoding the respective receptor (C). We then queried the Neurosynth database to assess significant similarity between a given ontological term's functional activity patterns and the meta-analytically derived aberrant brain activity maps of psychopaths by applying a spatially-constrained null framework ($p<0.05$) [6–9] (D; red/blue = positive/negative correlation, range = [-0.2, 0.2]). Word size represents relative magnitude of a given significant association.*

Figure 2. Relationship of increased/decreased brain activity in psychopaths with neurotransmitter systems, gene expression and behavior. *While there were no significant associations with increased activity, the meta-analytically derived map of decreased brain activity (A) was spatially related to distribution of 5-HT_{1A} and μ-opioid receptors (B). The color bar represents threshold-free cluster enhancement (TFCE) values as weighted sums of the entire local clustered signal on the unthresholded brain maps. The meta-analytically derived brain map of decreased activity in psychopaths was also linked to 5-HTR1A gene expression, encoding the respective receptor (C). Querying the Neurosynth database to assess significant similarity between a given ontological term's functional activity patterns and the meta-analytically derived maps of increased/decreased activity in psychopaths revealed several behavioral associations (D; red/blue = positive/negative correlation, range = [-0.2, 0.2]). Word size represents relative magnitude of a given significant association.*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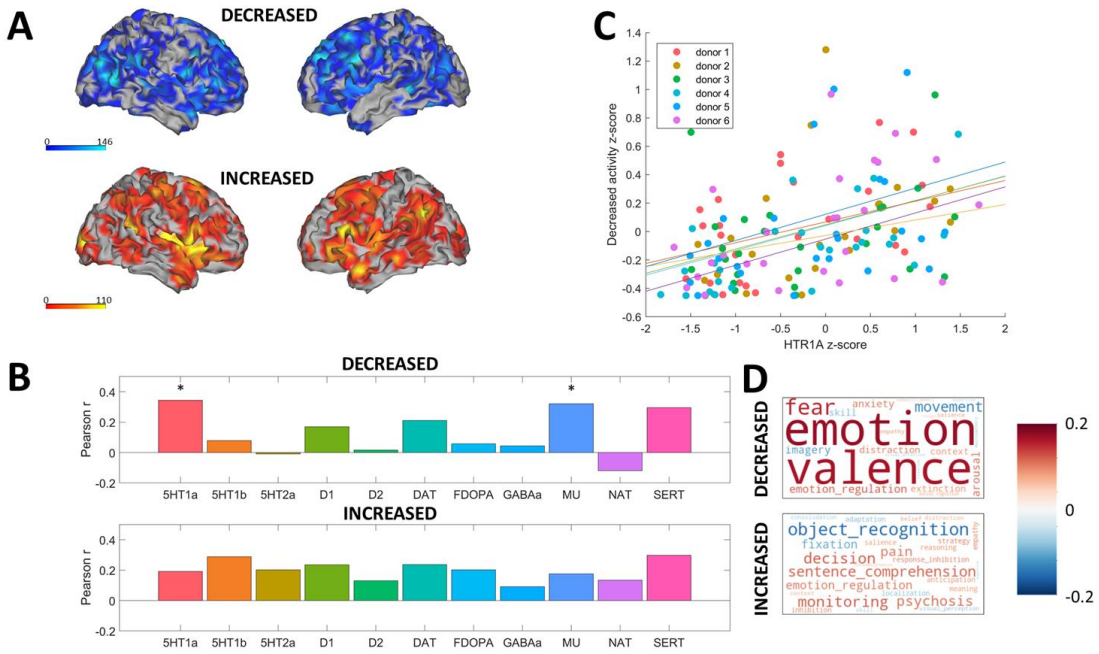
[Figure 1]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[Figure 2]