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Letter to the Editor

Midbrain dysfunction in anorexia nervosa

Anorexia nervosa (AN) is a serious psychiatric condition associated with significant disturbances in the experiences of one's own body weight or shape. Unlike many other mental illnesses, there is a lack of empirical evidence and neurobiological rationale justifying the use interventions specifically targeting underlying neurobiological dysfunction in AN, including pharmacological treatments and brain stimulation techniques, as the neurobiological contributions to the illness have thus far not been clear. However, our recent findings have suggested dysfunction of midbrain regions in individuals with AN.

The midbrain has not been a specific area of great interest in the study of AN, and we therefore report the findings of a series of studies undertaken by our group in the same group of acute AN participants, relative to healthy controls, to demonstrate the consistencies across different techniques. Midbrain regions are involved in initiating and inhibiting eye movements, and our recent behavioural findings have uncovered distinctive eye movement abnormalities in AN (Phillipou et al., 2014; Phillipou et al., 2016b). In addition, we have reported more direct indicators of midbrain dysfunction in AN, including reduced grey matter volumes (Phillipou et al., 2018a) and white matter microstructural deficits (Phillipou et al., 2018a).

Disrupted structure and function of particular midbrain regions may contribute to illness symptoms in AN. The substantia nigra (SN) is involved in response to rewarding stimuli and deficits in this region may be related to the anhedonia experienced in the illness. The SN projects to and from various cortical and subcortical regions, including the superior colliculus which is particularly involved in multisensory integration. As the SN projects to and from various brain regions, functional connectivity of this area to other brain regions may be impaired in AN. Functional connectivity to the inferior parietal lobe (IPL) is of particular interest as the IPL is involved in visuospatial perception and multisensory integration, particularly vision and somatic sensation, which may be related to the disturbance in body image experienced in AN.

Utilising a region of interest (ROI) approach, we aimed to identify functional connectivity differences of the SN, in individuals with AN compared to healthy controls (HC). Participant characteristics, and magnetic resonance imaging (MRI) protocols and analyses are described in detail in this journal (Phillipou et al., 2016a). Briefly, 26 right-handed females with AN and 27 age-, gender- and handedness-matched HC underwent an MRI scan that included a resting state functional MRI (fMRI) sequence. The functional connectivity analysis involved a right (MNI coordinates 10, −16, −12) and left (−9, −16, 12) SN ROI-to-whole brain analysis undertaken in the CONN functional connectivity toolbox in Matlab.

Significantly reduced connectivity between the left SN and clusters in the left inferior parietal lobule/supramarginal gyrus (65 voxels; peak MNI coordinates −60, −40, 48) and the right posterior cingulate gyrus (97 voxels; peak MNI coordinates 8, −32, 44) were found in AN compared to HC. Reduced functional connectivity in AN was also found between the right SN and left middle frontal gyrus (105 voxels; peak MNI 42, 34, 34) (all p-FWE $< .05$). The AN group did not demonstrate any regions of increased functional connectivity to the SN, relative to HC. In addition, no significant correlations were found between functional connectivity of the SN and illness duration, body mass index or Eating Disorder Examination Questionnaire scores, for either group. Given the role of these regions, correlational analyses with measures more specific to body image disturbance and anhedonia should be investigated in the future.

Reduced communication between the SN and IPL in AN may contribute to the atypical eye movement findings observed in the illness, as well as the body image distortion experienced. Individuals with AN have been found to demonstrate a discrepancy between the sizes they feel and think they are (Phillipou et al., 2016c), which may be contributed to by reduced functional connectivity of visual (i.e. SN) and somatosensory (i.e. IPL) regions.

Reduced functional connectivity was also found between the SN and the posterior cingulate gyrus, an area thought to be involved with regulating the focus of attention; and between the SN and the middle frontal gyrus, which corresponds to the frontal eye fields (FEF). The FEF are involved in saccadic eye movement production and in maintaining fixation, and send signals to and from the superior colliculus via the SN. Similarly to the findings relating the IPL, reduced functional connectivity of this region could also explain the atypical eye movements reported in AN. Further, the FEF is also involved in visual attention and may play a role in attentional deficits reported in AN, including the focus on body regions associated with weight.

Overall, the findings of this study reveal reduced functional connectivity in individuals with AN between the SN and other brain regions. Findings from our other research in the same group of AN participants revealed reduced grey matter volumes (Phillipou et al., 2018b) and reduced white matter integrity of midbrain regions (Phillipou et al., 2018a), suggesting that structural differences may contribute to functional connectivity changes, and may, theoretically, be involved in the underlying deficits that lead to body image distortion in the illness. It must, however, be noted that the findings across these different studies were from the same group of participants and require replication in other samples.

The findings of this research are important as the brain regions of focus are not involved only in eye movement production, but also in multi-sensory integration and body image; which are key deficits and arguably the driving-force behind AN behaviour. These findings also suggest that brain stimulation techniques, such as high definition transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS), applied to regions such as the left IPL may be beneficial to individuals with AN by potentially increasing connectivity to midbrain regions, and consequently improving body image disturbances. Further research confirming the role of the midbrain in AN is required, as well as research assessing the efficacy of utilising non-

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invasive brain stimulation techniques to target midbrain dysfunction in individuals with AN.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2018.11.004.

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