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Viewpoint

Cerebellar involvement in hallucinations may transcend clinical conditions and perceptual modalities

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ABSTRACT

Our recent neuroimaging study identified structural differences in cerebellar subfields linked to cortical attentional networks in patients with eye disease or Parkinson's disease who experience visual hallucinations and a commentary on the study by Zorzi et al. provided additional evidence of functional cerebellar changes in Dementia with Lewy bodies. Here, we review evidence for cerebellar involvement in hallucinations across multiple clinical conditions and sensory modalities as well as examine its wider clinical and mechanistic implications. The combined structural and functional evidence is consistent with two models of cerebellar contribution to hallucination which differ in their implied direction of cause, effect and temporal sequence. Additionally, we contend that the relatively neuroanatomically localised nature of the cerebellum makes it particularly suited to identifying changes affecting distributed cortical networks using imaging techniques. As such, cerebellar subfield differences may offer value as candidate prognostic and predictive biomarkers as well as targets for neuromodulatory treatment across a range of clinical conditions.

Hallucinations are percepts in the absence of cognate external stimuli for which the underlying mechanisms remain elusive. Part of the problem has been that the range of clinical and non-clinical conditions in which they occur and the different sensory modalities involved has led to separate literature streams. This limits opportunities to explore which findings might be shared across conditions, hence perhaps revealing core hallucination mechanisms, beyond solely identifying those which are condition or modality specific. We have previously reported hallucination-related structural cerebellar and brainstem differences common to both Parkinson's disease (PD) and Charles Bonnet Syndrome (CBS) (Lawn & ffytche, 2021). In their recent commentary, Zorzi et al. provide additional evidence that reduced metabolism as measured by ^{18}F-

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FDG PET-MR in cerebellar lobules VI, VIIb, VIIIa, IX, and Crus I is linked to visual hallucinations in Dementia with Lewy Bodies (DLB) (Zorzi, Poggiali, Cecchin, & Cagnin, 2021). The commentary, taken together with structural cerebellar differences in patients with schizophrenia with and without audio-verbal hallucinations reported by Cierpka et al. (Cierpka et al., 2017), adds significant credence to the emerging picture of specific cerebellar subfield involvement in hallucinations that transcends clinical condition and sensory modality. In this Viewpoint, we speculate on the wider implications of these mechanisms in light of recent findings.

1. Outstanding issues and wider implications

1.1. *Why cerebellum not cortex?*

As discussed in our original paper (Lawn & ffytche, 2021) and supported by Zorzi et al., the cerebellar subfields altered in hallucinators have been linked to attentional mechanisms, adding support to aetiological theories of hallucinations based on dysfunctional relationships between the dorsal attentional network (DAN), ventral attentional network (VAN), and default mode network (DMN) (Collerton, Perry, & McKeith, 2005; Shine et al., 2011; Shine et al., 2014). However, although consistent with attentional theories, it remains unclear as to why the involvement of cortical DAN, VAN, and DMN has not been identified in previous VBM and metabolic studies of hallucinations. We suggest that the widely distributed nature of cortical networks such as the DAN, which spans diverse neuroanatomical regions including the frontal eye fields and superior parietal lobules in both hemispheres, makes them more difficult to detect using such methods. Furthermore, subregions of these networks may be differentially involved across patients such that techniques averaging structural or functional changes at individual voxels may miss involvement of the network as a whole. In contrast, cerebellar regions are comparatively neuroanatomically restricted. Thus, structural and functional cerebellar differences may offer a more accessible metric of network dysfunction than the cortical network itself.

1.2. *The cerebellum and hallucinations in different sensory modalities*

As well as multiple clinical conditions, cerebellar differences seem to be linked to both visual and auditory hallucinations (Table 1). Kim et al. employed a novel network-based lesion approach to map hallucinogenic lesions onto normative resting-state connectivity (Kim et al., 2021). Interestingly, while lesions associated with visual and auditory hallucinations were differentially involved with the lateral geniculate and cerebellar dentate nuclei respectively, hallucinations of both modalities fell within a single functionally connected network defined by connectivity to the cerebellar vermis, bilateral cerebellar lobule X, and right superior temporal sulcus. These cerebellar regions do not coincide directly with those found in other studies to date (Table 1). However, it does bolster arguments for the cerebellum being causally implicated in the genesis of hallucinations through some shared mechanism than transcends sensory modality.

The corticocerebellar system engages multiple supratentorial regions subserving a wide range of neural processes (Diedrichsen, King, Hernandez-Castillo, Sereno, & Ivry, 2019). Roughly 40 million axons exit the neocortex, the majority of which send collaterals to pontine nuclei, which in turn innervate the 50 billion granule cells of the cerebellum; half of

Table 1 – Summary of studies directly investigating cerebellar associations with hallucination to date (VBM; Voxel Based Morphometry. GMV; Grey Matter Volume. PANNS-P; The Positive and Negative Syndrome Scale. NPI; Neuropsychiatric Inventory).

Paper	Aetiology	Modality	Method	Cerebellar hemispheric region	Hallucinators showed:
Cierpka et al. (2017)	Schizophrenia	Auditory	Structural MRI (SUIT VBM)	Right lobules VIIb and VIIIa Right lobule VIIIa	Lower GMV than healthy controls Lower GMV compared to non-hallucinators
				Right lobule VIIIa	Negative correlation between GMV and both the positive symptoms as well as thought disturbance subcomponents of the PANSS-P
Lawn and ffytche (2021)	Charles Bonnet Syndrome & Parkinson's disease	Visual	Structural MRI (SUIT VBM)	Bilateral lobules VIIIb and IX. Left lobule VIIIa Bilateral Crus 1	Lower GMV compared to non-hallucinators (PD & CBS) Lower GMV in PD than CBS
Zorzi et al. (2021)	Dementia with Lewy bodies	Visual	^{18}F-FDG PET- MR	Bilateral lobule VI, IX, and Crus I Left lobule VIIb and VIIIa	Lower glucose metabolism than non-hallucinators
				Bilateral lobule IX	Negative correlation between glucose metabolism and severity of VH (NPI)
			Structural MRI (SUIT VBM)	Right Crus I, lobule IX and X	Lower GMV compared to non-hallucinators (non- significant after multiple comparison correction)

the cells in the human brain (Azevedo et al., 2009; Diedrichsen et al., 2019). These granule cells then bifurcate and each innervate ~175,000 Purkinje cells; the output neurones of the cerebellum which, via the deep nuclei and the thalamus, feedback to neocortex (Diedrichsen et al., 2019). Therefore, the cerebellum has vast computational power and, due to the strikingly uniform cytoarchitecture, it has been argued to perform some fundamental computational process applicable across multiple domains of function: the 'universal cerebellar transform' (Schmahmann, 1996). In this framework, cerebellar contributions to both auditory and visual hallucinations would indicate some modulatory computational mechanism shared by these two sensory modalities and linked to attentional networks. One possibility is that the mechanism may relate to overweighting of perceptual priors within the emerging predictive coding framework for hallucinations (Friston, 2005; Powers, Mathys, & Corlett, 2017; Rao & Ballard, 1999).

1.3. *Cause, effect, and temporal sequence*

Zorzi et al. speculate in their commentary that the presence of significant functional but not structural differences within their DLB sample reflects the temporal sequence of functional alterations preceding structural changes in neurodegenerative disease (Zorzi et al., 2021). While we agree with this formulation, there are two distinct ways in which these structural and functional changes might be related to hallucinations, each with differing clinical and translational implications.

1.3.1. *Functional differences precede structural differences: a disease driven susceptibility model*

One interpretation of the DLB findings is that functional cerebellar changes confer susceptibility to hallucinations and are the result of the DLB neurodegenerative process, evolving into structural changes as the disease progresses. This raises the question as to why structural changes are present in the PD patient sample but not the DLB patient sample. This might reflect the longer disease duration in the PD patients studied than those with DLB, as pointed out by Zorzi et al. but might also reflect the progression in PD (but not DLB) of pathology from brainstem to cortex and, hence, cerebellar involvement preceding cortical involvement and hallucinations in PD (Beach et al., 2009). The neurodegenerative account also explains why some individuals with PD or DLB hallucinate but others do not. Heterogeneity in the location of pathology may drive variation in hallucination susceptibility; for example, those patients who show sufficient disruption of the DAN may be those who go on to hallucinate. Such explanations work less well for CBS and schizophrenia where neurodegeneration, if present at all, is not a prominent feature. However, it is also plausible some individuals have pre-existing genetic or environmental factors which confer susceptibility to hallucinate. These may modulate attentional networks, including cerebellar regions, and onset of disease could unmask this pre-existing susceptibility. Whether through a longer-term predisposition or disease-related changes, such accounts consider functional and structural changes within the cerebellum as part of the causal mechanism of hallucinations and thus present before hallucination onset (Fig. 1).

1.3.2. *Structural and functional differences are a consequence of hallucinations: a hallucination driven model*

The likely absence of neurodegenerative changes in CBS and schizophrenia gives rise to another interpretation of the data. Might it be that the cerebellar changes identified are not the direct cause of the hallucinations but a downstream secondary effect (Fig. 2)? Hallucinations could result in changes in attention, eye movements, or other behaviours that lead to

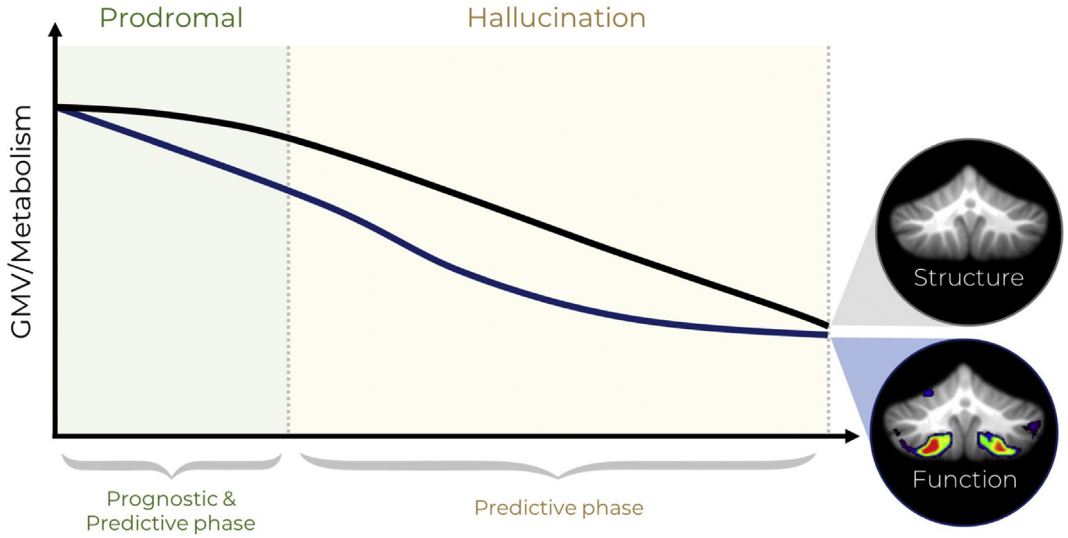

Fig. 1 – Functional differences precede structural differences: a disease driven susceptibility model. During the prognostic phase, structural and functional cerebellar differences may indicate future propensity to hallucinate. During the predictive phase, they may inform potential treatment responses.

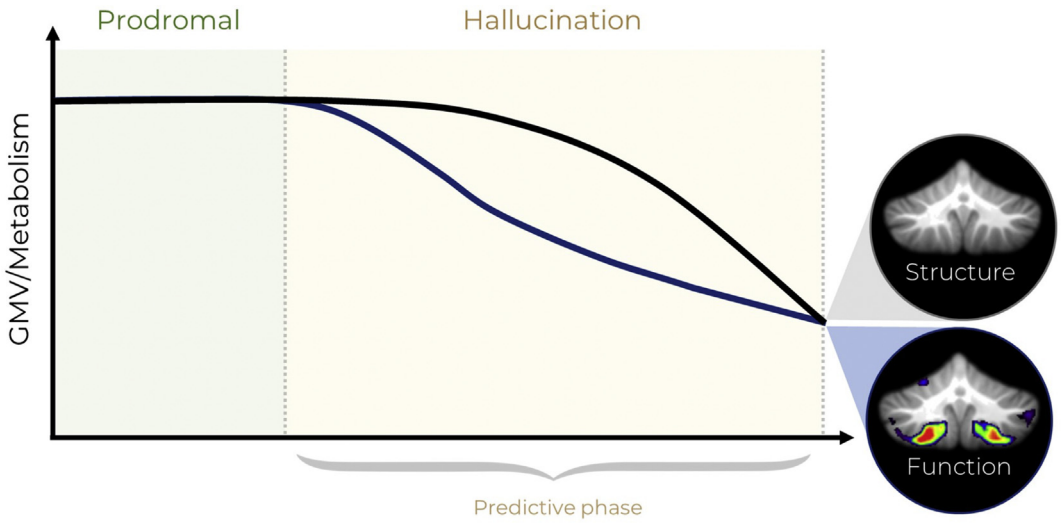

Fig. 2 – Functional differences precede structural differences: a hallucination driven model. During the predictive phase, structural and functional cerebellar differences may inform potential treatment responses.

cerebellar changes that are not reflective of the underlying causal mechanism. This would also be consistent with the DLB findings reported by Zorzi et al. where one might argue that the onset of hallucinations has led to functional changes that have not yet evolved into structural changes, with the longer duration of hallucinations in the PD and CBS groups accounting for the structural changes identified. Contrasting with the causal neurodegenerative disease driven model, by this interpretation cerebellar alterations in function and structure are epiphenomena that follow the onset of hallucinations rather than precede them.

1.4. *Diagnostic, prognostic, and predictive clinical value*

Irrespective of which account of directional causality gains further empirical support in future studies, it remains important to consider potential translational utility of the cerebellar differences beyond elucidation of mechanisms and the use of structural, functional, and related cognitive differences between individuals as biomarkers.

If cerebellar changes are part of a hallucinatory mechanism then, prior to their onset, differences between individuals may offer prognostic value in delineating those more likely to develop hallucinations and the associated poorer long-term outcomes. Functional or structural cerebellar differences would need to be sufficiently robust to identify future hallucinators from non-hallucinators with high sensitivity and specificity as, once patients are already experiencing hallucinations, diagnostic and prognostic biomarkers are superseded by patient self-report. The functional and structural cerebellar differences may also be associated with specific cognitive deficits which would offer another way of identifying the future hallucinator subgroup using existing or modified psychometric tests as a fast, cost-effective, and scalable option for clinical application.

Whilst there is a current paucity of effective treatments for hallucinations, it may be possible that the cerebellar changes identified, whether present before or after the onset of hallucinations, may offer predictive value for response to intervention. Both functional MRI-based neurofeedback and repetitive transcranial magnetic stimulation have shown some therapeutic promise for treatment of hallucination (Merabet, Kobayashi, Barton, & Pascual-Leone, 2003; Orlov et al., 2018; Slotema, Blom, Van Lutterveld, Hoek, & Sommer, 2014). However, the optimal neural targets of these interventions have yet to be ascertained and cerebellar subregions may be suitable candidates for hallucinations across clinical conditions and sensory modalities. Within heterogeneous clinical populations, some individuals with structural, functional, or cognitive cerebellar deficits may demonstrate more robust responses to such targeted interventions.

The findings in PD, CBS, schizophrenia, and now broadened to include DLB by Zorzi et al. make a compelling case for greater research focus on cerebellar contributions to hallucinations across all modalities and the need to incorporate the cerebellum into the wider network-based theories of hallucinations.

Declaration of competing interest

The authors declare no competing financial interests.

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