Cognition, hallucination severity and hallucination-specific insight in neurodegenerative disorders and eye disease

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ABSTRACT

Introduction: Hallucinations occur across neurodegenerative disorders, with increasing severity, poorer cognition and impaired hallucination-specific insight associated with worse outcomes and faster disease progression. It remains unclear how changes in cognition, temporal aspects of hallucinations, hallucination-specific insight and distress relate to each other.

Methods: Extant samples of patients experiencing visual hallucinations were included in the analyses: Parkinson’s Disease (n = 103), Parkinson’s Disease Dementia (n = 41), Dementia with Lewy Bodies (n = 27) and Eye Disease (n = 113). We explored the relationship between factors of interest with Spearman’s correlations and random-effect linear models.

Results: Spearman’s correlation analyses at the whole-group level showed that higher hallucination-specific insight was related to higher MMSE score (rs = 0.39, p < 0.001) and less severe hallucinations (rs = −0.28, p < .01). Linear mixed-models controlling for diagnostic group showed that insight was related to higher MMSE (p < .001), to hallucination severity (p = 0.003), and to VH duration (p = 0.04). Interestingly, insight was linked to the distress component but not the frequency component of severity. No significant relationship was found between MMSE and hallucination severity in these analyses.

Conclusion: Our findings highlight the importance of hallucination-specific insight, distress and duration across groups. A better understanding of the role these factors play in VH may help with the development of future therapeutic interventions trans-diagnostically.

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Introduction

Hallucinatory visual experiences, defined as sensory perceptions in the absence of external stimuli (Teeple et al., 2009), are common in older people and are especially connected with neurodegenerative disorders, including Dementia with Lewy Bodies (DLB), Parkinson’s Disease (PD) and Parkinson’s disease dementia (PDD) (Fénelon et al., 2010; McKeith et al., 2005; Taylor et al., 2011), as well as with age-related visual impairment (eye or visual pathway disease—ffytche, 2009). There are different rates of visual hallucinations (VHs) across the different diagnostic categories, with estimates ranging between 55% and 78% in DLB, 32% and 63% in PDD (O’Brien et al., 2020), 22% and 60% in Parkinson’s Disease Psychosis (PDP) (Forsaa et al., 2010) and 15% and 60% in eye disease (ED) (ffytche, 2009).

Despite the progress made in the understanding of hallucinations across different diagnostic categories in the past decade, the relationship between cognition, hallucinations, clinical impacts (such as distress) and whether the experience is recognised as real (hallucination-specific insight) remains unclear. As highlighted by fftytche (ffytche & Aarsland, 2017) there is a link between VHs and cognitive impairment in PDP, and we know that as the disease progresses, VHs are a risk factor for developing dementia (Aarsland et al., 2003; Diederich et al., 2009). Alongside progression in cognitive decline, PDP is associated with (a) more frequent and distressing VH (that in combination are often considered as a measure of hallucination severity—Cummings et al., 1994) and that have been linked to poorer symptom management for patients and caregivers (McKinlay et al., 2008), and to (b) progressive loss of insight (i.e., the ability to discern whether these experiences reflect reality). Insight has been identified as an important factor marking the threshold at which further intervention for VH might be needed (O’Brien et al., 2020). Lack of insight or fluctuating insight is often linked to “treatment non-adherence, lower psychosocial functioning, poor prognosis, involuntary hospitalisation, and higher utilisation of emergency services” (Shad et al., 2007). Distress for both the patient themselves and their carers (Renouf et al., 2018) may be an important determinant of poor outcomes in PDP such as the move from living in the community to a care home.

It is unclear how cognition, hallucination severity and degree of insight all relate to each other. One possibility is that they all relate to advancing degenerative pathology, but that there are no causal interrelations among them. Alternatively, it could be that poorer cognitive function may make it harder for people to engage in reality-testing (Garrison et al., 2017), making them less able to discern the veracity of their experiences and thus negatively affecting hallucination-specific insight, which may, in turn, exacerbate the severity of hallucinations.

Finally, one might anticipate that some of the inter-relationships between factors will be present for all hallucinations, whatever their cause, while other inter-relationships might differ depending on the underlying condition. In ED, for example, where VH is not associated with cognitive decline or loss of insight and where hallucination frequency tends to reduce overtime, one might expect distress to associate with different factors (ffytche, 2005; Pang, 2016).

The overarching aim of this project is that of investigating relationships between cognition, hallucination-specific insight (during the hallucinatory episodes or in retrospect),
temporal (duration and frequency), emotional (distress) and severity (emotion × frequency) aspects of hallucinations and what aspects of the relationships might be the same or different when comparing neurodegenerative disease and eye disease. We used cross-sectional data from cohorts of patients that varied in these factors, both within and between cohorts, and looked for associations between these factors to draw inferences about their relationships, as well as similarities and differences across diagnostic groups.

Based on the evolution of cognition, insight and temporal aspects of hallucinations in PDP we anticipated:

- poorer cognitive scores will be associated with poorer hallucination-specific insight (Hypothesis A);
- poorer cognitive scores will be associated with more severe hallucinations (more frequent/ longer lasting and/or more distressing) (Hypothesis B).

We did not have specific a priori predictions whether hallucination-specific insight or temporal aspects of hallucinations would be more closely related to distress or whether the relationship between these different factors would differ between neurodegenerative conditions. In ED, where cognitive decline and loss of insight is not thought to be part of the mechanism leading to VH, we expected the association between these factors and distress to be weaker than in neurodegenerative conditions but the association with temporal factors to be stronger. An improved understanding of these relationships holds the promise of new therapeutic approaches to mitigate the poor outcomes associated with VH.

**Materials and methods**

**Participants**

We used a combination of samples from extant studies on VHs across different neurological disorders and ED (which had used the same methodology). Data on the four patient groups was derived from and described in the original published articles (Archiebald et al., 2011; Makin et al., 2013; Mosimann et al., 2008; Taylor et al., 2011; Urwyler et al., 2014). Data was only included if patients had experienced VH within the month prior to the original data collection. Ethical approval and informed consent were obtained in the original published studies and no further approval was needed for the current work. For further information on the samples (including inclusion/exclusion criteria), the reader is directed to the summary of full patient characteristics and assessments in Urwyler et al. (2016). Demographic, cognitive and clinical characteristics of all cohorts are described in Tables 1 and 2.

**Measures**

**Cognitive measures**

Participants from the different cohorts were all assessed on their level of global cognitive function using the Mini Mental State Exam (Folstein et al., 1975). This test is
Table 1. Demographics and neuropsychological assessments for the different groups.

| Variable                        | DLB (n = 27) | ED (n = 113) | PD (n = 103) | PDD (n = 41) | Statistics |
|---------------------------------|--------------|--------------|--------------|--------------|------------|
|                                 | Mean (SD)    | Mean (SD)    | Mean (SD)    | Mean (SD)    | P-value    |
| Age (years) N = 284             | 80.4 (5.62)  | 79.9 (8.27)  | 70.6 (9.78)  | 71.9 (6.58)  | p < 0.001  |
| Gender (female|male)        | 11|16       | 76|37       | 45|58       | 8|33       | p < 0.001  |
| Education (years)               | —            | —            | 10.8 (2.34)  | 11.0 (3.35)  | p = 0.450  |
| MMSE total score [max 30] *     | 18.8 (5.43)  | 27.1 (2.01)  | 28.0 (2.39)  | 23.0 (3.33)  | p < 0.001  |
| Visual acuity (decimals) N = 111 EY, N = 59 PD, N = 16 PDD | 0.169 | 0.173 | 0.401 | 0.142 | p < 0.001 |

χ², Pearson’s Chi-Square; one-way ANOVA; H, Kruskal–Wallis one-way ANOVA; SD, standard deviation. H was conducted where data violated assumption of normality (p ≤ 0.05). * Max score was 29 in the ED group.
administered quickly (<10 min) and incorporates measures of language, attention, visual construction and awareness of time and location. The overall score is used to measure general cognitive ability in patients, although it does not represent a formal diagnosis. For the ED group, the maximal MMSE score was 29 out of 30 (omission of overlapping pentagon drawing element) and 30 for all other groups as reported in the original studies.

### Clinical measures

All of the following measures reflected patients’ responses as no caregiver data were available for additional comparison across groups. Participants completed the North East Visual Hallucination Interview (NEVHI, Mosimann et al., 2008), a semi-structured interview that screens the phenomenology of VHs and assesses their emotional and behavioural impact. For details on the specific methods used in each cohort, the reader is addressed to the original cohort studies publications (Archibald et al., 2011; Makin et al., 2013; Mosimann et al., 2008; Taylor et al., 2011; Urwyler et al., 2014).

Hallucination-specific insight scores were rated by the original interviewer from the NEVHI and measured on a 3-point scale from 3 = full insight, 2 = some insight, 1 = no insight. Hallucination duration (based on responses on the NEVHI) was measured on a 4-point scale: 1 = “less than 5 min”, 2 = “5 min to 2 h”, 3 = “more than 2 h but less than all the time”, 4 = “all the time”. Hallucination frequency (based on responses on the NEVHI) measured on a 4-point scale from 1 = never, 2 = “less than once a week”, 3 = “1–6 times a week”, 4 = “daily”. Hallucination distress (based on responses on the NEVHI) was measured as a “yes” or “no” (2 = “yes”, 1 = “no”) answer and reflect the patients’ rating about their own hallucinations. We calculated the variable of

### Table 2. Hallucination metrics and degree of insight for the different groups.

| Variable                           | DLB (n = 27) | ED (n = 113) | PD (n = 103) | PDD (n = 41) | P-value | Test     |
|------------------------------------|--------------|--------------|--------------|--------------|---------|----------|
| Hallucination severity             |              |              |              |              |         |          |
| *Mean (SD)*                         | N = 19, 4.42 (1.77) | N = 91, 3.98 (1.88) | N = 72, 3.29 (1.45) | N = 29, 4.62 (1.61) | p < 0.001 | Kruskal–Wallis |
| Hallucination Duration              |              |              |              |              |         |          |
| <5 min                             | 0 (0)        | 50 (44)      | 32 (31)      | 18 (44)      | p < 0.001 | χ² = 31.24, df = 9 |
| 5 min to 2 h                       | 16 (59)      | 44 (39)      | 40 (39)      | 9 (22)       |         |          |
| >2 h                               | 3 (11)       | 3 (2.6)      | 2 (2)        | 3 (7.3)      |         |          |
| All the time                       | 0 (0)        | 4 (3.5)      | 0 (0)        | 0 (0)        |         |          |
| Missing info                       | 8 (29)       | 12 (11)      | 29 (28)      | 11 (26.7)    |         |          |
| Hallucination frequency            |              |              |              |              |         |          |
| Never                              | 0 (0)        | 15 (13)      | 0 (0)        | 0 (0)        | p < 0.001 | χ² = 45.5, df = 9 |
| Less than once a week               | 8 (29.6)     | 14 (12)      | 31 (30)      | 8 (20)       |         |          |
| 1–6 times a week                    | 14 (52)      | 38 (34)      | 32 (31)      | 15 (36)      |         |          |
| Daily                              | 0 (0)        | 34 (30)      | 14 (14)      | 10 (24)      |         |          |
| Missing info                       | 5 (18.4)     | 12 (11)      | 26 (25)      | 8 (20)       |         |          |
| Hallucination distress             |              |              |              |              |         |          |
| Yes                                | 11 (40.8)    | 27 (24)      | 11 (11)      | 14 (34)      | p < 0.001 | χ² = 19.3, df = 3 |
| No                                 | 8 (29.6)     | 64 (57)      | 63 (61)      | 16 (39)      |         |          |
| Missing info                       | 8 (29.6)     | 22 (19)      | 29 (28)      | 11 (27)      |         |          |
| Hallucination insight              |              |              |              |              |         |          |
| Full insight                       | 4 (15)       | 32 (28)      | 42 (41)      | 5 (12)       | p < 0.001 | χ² = 33.18, df = 6 |
| Some insight                       | 7 (26)       | 18 (16)      | 25 (24)      | 20 (49)      |         |          |
| No insight                         | 7 (26)       | 2 (2)        | 25 (24)      | 4 (10)       |         |          |
| Missing info                       | 9 (33)       | 61 (54)      | 29 (28)      | 12 (29)      |         |          |

*Data are N (%). Statistics are χ² or Fisher’s exact tests apart from hallucinations severity where mean and standard deviation is provided and a Kruskal–Wallis 1-way ANOVA was run.
Hallucination Severity based on the two NEVHI measures of hallucination frequency and hallucination distress from the original datasets (temporal and emotional axes, respectively). Similar to the hallucination severity measure from the Neuropsychiatric Inventory questionnaire (NPI—Cummings et al., 1994), we multiplied the NEVHI variable of hallucination frequency and that of distress (both reflecting patients’ ratings) to get a combined severity score for the current study which ranged from 1 to 8 (higher scores indicating more severe hallucinations).

**Data analysis**

All statistical tests were performed using R (R Core Team, 2013) and Python software (VanRossum and Drake - Python Software Foundation. Python Language Reference, version 3.8 (2010)). Scripts for the analyses can be found in the dedicated online repository (https://bit.ly/3vXkqNz). Observations with missing data were excluded from the analyses and the number of observations is indicated to reflect the available information for each variable per each patient group. The normal distribution of data was examined using the Shapiro–Wilk test. Means and standard deviations (SDs) were calculated. Demographic, cognitive and clinical characteristics were compared across groups using one-way ANOVA and Kruskal–Wallis one-way ANOVA (where data violated the assumption of normality). Frequencies were compared using the $\chi^2$ test.

Post-hoc power calculations for the main Spearman correlation analyses were run using G*Power (Erdfelder et al., 1996) and for the LMM using simulations in R with the “mixedpower” package (Kumle et al., 2018)—see details in the Supplementary.

**Spearman correlations**

To explore relationships between the degree of hallucination-specific insight, cognition, severity and temporal aspects of hallucinations we conducted Spearman’s correlational analyses both of all patients as a single group (Figure 1) and in each group separately (Figure 2). All reported $p$-values are two-tailed. Bonferroni correction for multiple comparisons (Curtin & Schulz, 1998) was applied to these correlation analyses.

**Linear mixed models**

We used linear mixed models (LMM) to examine associations between hallucination-specific insight, hallucination severity and/or MMSE total score across patient groups. We ran three main models to test different hypotheses and all models were specified so that each diagnostic group would get its own intercept. Notably, this specification allowed us to examine the association between hallucination severity, cognition and insight while taking into account the variation in the different groups. We specified the diagnostic group (“Group”) as a random factor in all models. Results from the main LMM analyses can be found in Tables 3–5. The Akaike Information Criterion (AIC—Akaike, 1974) measure of model quality was used to choose the best model.

The first main random-effect model (Table 3) was used to investigate the association between the variables of interest with insight as the dependent variable and main predictors being hallucination severity and its interaction with MMSE total score. The additional fixed effects (i.e., predictors) specified were the NEVHI score for duration and age. A separate additional model (see Table 4) was run with the fixed effects
including the NEVHI score for frequency of hallucinations and NEVHI scores for distress instead of the composite NEVHI score for severity (frequency × distress). A final random-effect model (Table 5) with MMSE total score as a predictor was added to test whether poorer cognitive scores will be associated with more severe hallucinations (Hypothesis 2). This same model was also run with the subcomponents of severity analysed separately—see Model 4 in Supplementary Table 6.

Results

**Spearman’s correlational analyses (Bonferroni corrected)**

Overall, in line with the predictions from our hypotheses, we found that hallucination-specific insight was positively correlated with total MMSE score, with higher cognitive scores associated with higher levels of hallucination-specific insight ($r_s = 0.39, p < 0.001$) (Hypothesis A). The results were not in line with Hypothesis B predicting more severe hallucinations with lower cognitive scores, as there was no statistically significant relationship between patients’ MMSE total score and hallucination severity ($r_s$.
Figure 2. Correlation matrix heat-map of cognitive performance and clinical variables for the four diagnostic groups. Spearman correlation coefficient value ($r$) and statistical significance level of the results are shown. Results shown after Bonferroni Correction. *No available data regarding Education (in years) for this group.

$= -0.19, \ p = 0.22$). Of the two components of hallucination severity, only distress showed a negative significant relationship with MMSE (distress $r_s = -0.25, \ p = 0.01$; frequency $r_s = 0.01, \ p = 1$). As expected, severity correlated positively with its two

Table 3. Results from the mixed model analysis with random slope looking at degree of insight as predictor. No outliers removed.

| Predictors                        | Estimates | CI          | $p$     |
|-----------------------------------|-----------|-------------|---------|
| (Intercept)                       | 2.38      | 2.27 to 2.50| $<0.001$|
| Hallucination severity            | -0.14     | -0.23 to -0.05| $0.003$ |
| MMSE total score                  | 0.27      | 0.17 to 0.36| $<0.001$|
| Hallucination severity * MMSE total score | 0.07 | -0.03 to 0.16 | 0.177 |
| Hallucination duration            | -0.09     | -0.18 to 0.01| 0.073   |
| Age                               | 0.04      | -0.05 to 0.13| 0.391   |

Random effects

$\sigma^2$ | 0.33 |

$\eta^2$ Group | 0.01 |

$N_{Group}$ | 4 |

Observations | 169 |

Marginal $R^2$/Conditional $R^2$ | 0.259/0.270 |

AIC | 315 |

Bold font indicates a significance of $p < 0.05$. 
components, frequency and distress. Hallucination-specific insight was negatively correlated with hallucination severity, with lower insight associated with more severe hallucinations ($r_s = -0.28$, $p = 0.01$). Of the two components of severity, only distress showed a significant negative relationship with insight (distress $r_s = -0.34$, $p < 0.001$; frequency $r_s = 0.001$, $p = 1$). We also examined hallucination duration, another temporal measure that, unlike frequency, is not included in the severity metric. Notably, duration was not strongly associated with the subcomponents of frequency ($r_s = 0.13$, $p = 1$) or distress ($r_s = 0.15$, $p = 0.101$), but was significantly associated with overall hallucination severity ($r_s = 0.22$, $p = 0.04$). Finally, duration was not linked to hallucination-specific insight ($r_s = -0.21$, $p = 0.28$) after Bonferroni correction. Education level was positively associated with MMSE ($r_s = 0.29$, $p < 0.001$), but the significance level for the association with the other variables of interest was not met after multiple-comparison correction.

**Table 4.** Results from the mixed model analysis with random slope and degree of insight as predictor.

| Predictors                  | Estimate | CI             | $p$   |
|-----------------------------|----------|----------------|-------|
| (Intercept)                 | 2.38     | 2.26 to 2.51   | **<0.001** |
| Hallucination frequency     | −0.00    | −0.11 to 0.10  | 0.939 |
| Hallucination distress      | −0.17    | −0.26 to −0.08 | **<0.001** |
| Hallucination duration      | −0.10    | −0.19 to −0.00 | 0.044 |
| MMSE total score            | 0.26     | 0.16 to 0.35   | **<0.001** |
| Age                         | 0.04     | −0.05 to 0.13  | 0.337 |

**Random effects**

|                      |          |               |
|----------------------|----------|---------------|
| $\sigma^2$          | 0.33     |               |
| $\tau_{00\text{ Group}}$ | 0.01     |               |
| $N_{\text{Group}}$  | 4        |               |
| Observations         | 169      |               |
| Marginal $R^2$/Conditional $R^2$ | 0.273/0.288 |
| AIC                  | 312      |               |

Notes: This model allows to look at the two components of severity (distress and frequency) separately. No outliers removed. Bold font indicates a significance of $p < 0.05$.

**Table 5.** Results from the mixed model analysis with random slope looking at total MMSE score as predictor.

| Predictors                  | Estimate | CI             | $p$   |
|-----------------------------|----------|----------------|-------|
| (Intercept)                 | −0.38    | −1.07 to 0.32  | 0.292 |
| Hallucination severity      | 0.07     | −0.05 to 0.19  | 0.242 |
| Degree of insight           | 0.27     | 0.14 to 0.39   | **<0.001** |
| Hallucination duration      | 0.04     | −0.08 to 0.16  | 0.536 |
| Hallucination severity * Degree of insight | −0.04 | −0.15 to 0.07 | 0.480 |
| Age                         | −0.12    | −0.23 to 0.00  | **0.048** |

**Random effects**

|                      |          |               |
|----------------------|----------|---------------|
| $\sigma^2$          | 0.52     |               |
| $\tau_{00\text{ Group}}$ | 0.49     |               |
| $N_{\text{Group}}$  | 4        |               |
| Observations         | 169      |               |
| Marginal $R^2$/Conditional $R^2$ | 0.070/0.522 |
| AIC                  | 399.5    |               |

Note: No outliers removed. Bold font indicates a significance of $p < 0.05$. 

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**Table 4.** Results from the mixed model analysis with random slope and degree of insight as predictor.

| Degree of insight | Estimates | CI             | $p$   |
|-------------------|-----------|----------------|-------|
| (Intercept)       | 2.38      | 2.26 to 2.51   | **<0.001** |
| Hallucination frequency | −0.00    | −0.11 to 0.10  | 0.939 |
| Hallucination distress | −0.17    | −0.26 to −0.08 | **<0.001** |
| Hallucination duration | −0.10    | −0.19 to −0.00 | 0.044 |
| MMSE total score  | 0.26      | 0.16 to 0.35   | **<0.001** |
| Age               | 0.04      | −0.05 to 0.13  | 0.337 |

**Random effects**

|                      |          |               |
|----------------------|----------|---------------|
| $\sigma^2$          | 0.33     |               |
| $\tau_{00\text{ Group}}$ | 0.01     |               |
| $N_{\text{Group}}$  | 4        |               |
| Observations         | 169      |               |
| Marginal $R^2$/Conditional $R^2$ | 0.273/0.288 |
| AIC                  | 312      |               |

Notes: This model allows to look at the two components of severity (distress and frequency) separately. No outliers removed. Bold font indicates a significance of $p < 0.05$. 

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**Table 5.** Results from the mixed model analysis with random slope looking at total MMSE score as predictor.

| MMSE total score | Estimates | CI             | $p$   |
|------------------|-----------|----------------|-------|
| (Intercept)      | −0.38     | −1.07 to 0.32  | 0.292 |
| Hallucination severity | 0.07     | −0.05 to 0.19  | 0.242 |
| Degree of insight | 0.27     | 0.14 to 0.39   | **<0.001** |
| Hallucination duration | 0.04     | −0.08 to 0.16  | 0.536 |
| Hallucination severity * Degree of insight | −0.04     | −0.15 to 0.07 | 0.480 |
| Age              | −0.12     | −0.23 to 0.00  | **0.048** |

**Random effects**

|                      |          |               |
|----------------------|----------|---------------|
| $\sigma^2$          | 0.52     |               |
| $\tau_{00\text{ Group}}$ | 0.49     |               |
| $N_{\text{Group}}$  | 4        |               |
| Observations         | 169      |               |
| Marginal $R^2$/Conditional $R^2$ | 0.070/0.522 |
| AIC                  | 399.5    |               |

Note: No outliers removed. Bold font indicates a significance of $p < 0.05$. 

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Spearman correlation analyses were then also run to assess the statistical significance of these relationships in each group separately (Figure 2). The negative association between hallucination-specific insight and hallucination severity was present in all diagnostic groups but did not reach significance after Bonferroni correction. Of the two components of severity, a negative association between insight and distress was significant for PD ($r_s = -0.38, p = 0.03$) but not in the other groups. In the PD group, the duration of hallucinations was negatively related to education ($r_s = -0.49, p < 0.001$) and positively to the degree of insight ($r_s = 0.40, p = 0.02$).

After Bonferroni correction, distress was not associated with cognition in any of the groups.

**Linear mixed model analyses**

**Random-effect models**

The models were built to investigate the relationship between hallucination severity, cognitive decline and hallucination-specific insight across the different diagnostic groups when the variable of diagnosis/group was controlled for. For the first model, the proportion of total variance accounted for by the random-effect of “Group” was very small at around 3% (calculated by taking the variance for the random-effect $\tau_{00\text{ Group}}$ and dividing it by the total variance—for example, the Group variance $\tau_{00\text{ Group}}$ plus the residual variance $\sigma^2$), with the greater remaining variance explained by the specified fixed effects in the model.

As can be seen in Table 3, hallucination-specific insight was significantly associated with MMSE score ($p < 0.001$) and hallucination severity ($p = 0.003$) indicating that higher cognitive score was related to greater insight while increased hallucination severity was associated with poorer insight. Neither age, duration or the interaction of MMSE and severity were significantly associated with insight. We further tested whether it was possible to disentangle the relative contribution of the distress and frequency components of hallucination severity in a separate random-effect model (see Table 4). Results from this model indicated that distress was related to hallucination-specific insight ($p < 0.001$) but this was not the case for hallucination frequency ($p = 0.93$). When the severity score was subdivided into its subcomponents, the relationship between insight and hallucination duration became significant ($p = 0.04$), with longer duration linked to more impaired insight.

A final model allowed us to test the relationship between cognitive score and hallucination severity (Table 5) by having the total MMSE score as the predictor variable. Results from this model indicated MMSE score was predicted by age ($p = 0.048$) and by insight ($p < 0.001$) as expected from the previous analyses. However, hallucination severity was not related to cognitive scores ($p = 0.242$), and neither were its components of frequency ($p = 0.761$) and distress ($p = 0.193$) when tested in an additional model with severity score subdivided into its subcomponents (see Table 6 in Supplementary).

**Discussion**

This is the first study to explore relationships between VH severity (as indexed by temporal and emotional aspects), cognition and hallucination-specific insight in a large
trans-diagnostic sample. The findings help us to understand how these factors inter-relate and how they differ in ED and neurodegeneration.

**Overall results and interpretations**

Our results help confirm the hypothesised relationship between cognition and hallucination-specific insight. Lower MMSE scores were associated with lower hallucination-specific insight at the whole-group level (Figure 1 of Spearman’s correlation) and in the LMM models (Tables 3 and 4). Another aspect under investigation was the relationship between hallucination-specific insight and hallucination severity. Whole-group level Spearman correlations showed that more severe hallucinations were related to decreased/lower insight. This relationship held in the LMM analyses controlling for diagnosis and was stronger for the emotional (distress) component than the frequency component of severity (Tables 3 and 4). Surprisingly, it seemed that the temporal aspect of duration was more closely linked to one’s degree of insight than the commonly used measure of frequency—a pattern of results that is further discussed in the clinical implications section.

Finally, when testing our hypothesis that poorer cognitive scores would be associated with increased hallucination severity (both composite and as separate components), we found no statistically significant results either with the LMM (Tables 5 and 6 in Supplementary) or with the Spearman’s correlation analyses.

A possible interpretation as to why we see a pattern of results linking lower cognition to more impaired insight and lower insight to more severe hallucinations might be related to the impact of cognition on reality-testing (Garrison et al., 2017). Although we did not have a direct measure of reality-testing, we know from the literature that problems in source monitoring are linked to impaired cognitive abilities (Anselmetti et al., 2007). Furthermore, patients with reality-testing deficits are more likely to perceive their hallucinations as real (Garrett & Silva, 2003). Therefore, it could be the case in our patients that their cognitive decline adversely impacted their reality-testing abilities and thus their ability to judge whether their hallucinatory experiences were real or not, which may, in turn, have exacerbated the severity of hallucinations by affecting its subcomponent of perceived distress. This latter point is supported by work done on the important role of attribution in cognitive models of psychosis (Garety et al., 2001).

Cognitive behavioural formulations of VH take as their starting point that distress reflects a person’s understanding (usually called an attribution) of their hallucinatory experiences, which does not necessarily depend on the content of the hallucination (Wilson et al., 2016). A positive understanding is associated with positive emotions, and a negative one, negative emotions. Therefore, if the person sees the hallucination as a threat, then they are fearful or angry. If they see it as protection, then they are comforted. In this model, lack of hallucination-specific insight is not necessarily positive or negative but depends on the attribution. A positive attribution can occur without insight (“Here is an angel who will look after me” or “My dead wife comes to comfort me”), while a negative attribution can occur with insight preserved (“I am having hallucinations which are a sign of madness, so I am going mad” or “These hallucinations are very distracting and stop me concentrating on the TV, so I am irritated by them”). In this formulation, the alternative option to what we discussed above is that a lack of insight
would not necessarily lead to distressing hallucinations. However, this approach does not address other sources of distress associated with hallucinations such as reactions of other people or the distressing nature of the hallucination content itself (Garety et al., 2001). The evidence from our study suggests that, in a clinical setting, hallucination-specific insight and distress are related although the nature of this relationship remains unclear.

**ED group**
In addition, we had also set out to investigate this triad of factors with specific hypotheses for the ED group. We had anticipated that we would not find associations between VH severity, cognition and insight in ED where cognitive decline and loss of insight are not thought integral to the mechanism of VH. There was not an obvious difference between ED and neurodegenerative conditions in these associations and the mixed-effect models suggested only a small contribution of diagnosis to the variance. Similarly, another prediction was that temporal factors would contribute more to the severity in ED than other conditions and while a strong relationship between hallucination frequency and severity was only found in ED ($r_s = 0.76, p < 0.001$), duration and severity were not significantly related ($r_s = 0.33, p = 0.052$). Taken together, the results suggest that factors linking distress, cognition and hallucination-specific insight are the same in ED as other conditions and apply generally and trans-diagnostically. However, it is of note that some patients in the ED group had no or partial insight and some of their mean cognitive scores suggested that they may have had an early or covert neurodegenerative disorder that might account for the overall similarity in ED and neurodegenerative results. Furthermore, multivariate analyses were done for each group separately (see Table 7 in Supplementary Material) showed that MMSE had a stronger association with insight for groups of patients with a diagnosis of dementia (namely DLB and PDD). Speculatively, this pattern of results could indicate that cognitive decline measured by the MMSE is more strongly associated with hallucination-specific insight in those with more advanced cognitive impairments, while the severity of hallucinations might be more closely related to hallucination-specific insight in those with mild cognitive problems. The interaction between MMSE and severity in PD ($p = 0.022$) and DLB ($p = 0.017$) in Table 7 is consistent with this view.

**Clinical implications**
The findings suggest that therapeutic interventions targeting hallucination-specific insight might help reduce the distress caused by VH to patients and caregivers and mitigate poor outcomes such as they move into a care home setting. These interventions would need to be tailored “according to the level of insight and cognitive impairment” (Renouf et al., 2018) in these patient groups as patients will vary in their ability to understand the concepts and retain the information required. Previous research has shown that insight is predictive of outcomes in cognitive behavioural therapy for psychosis (Kuller et al., 2012). The findings from Kuller et al. (2012) also show that insight should be highlighted early on in the diagnosis of psychosis across diseases.

Another important clinical implication of our findings is the spotlight that it shines on how to best conceptualise “severity” of hallucinations, especially with regards to its temporal aspects. In fact, although there are several ways in which VH might be considered...
to vary in their “severity”, the construct has been operationalised in the NPI as a composite of how frequent hallucinations occur and how distressing they are. In this formulation, severity is therefore thought to depend on how frequently an experience happens and how distressing each experience is, and combining the two measures might provide a better index of severity than either measure separately. However, our combined findings suggest that frequency poorly correlates with distress, VH-specific insight or cognition. In contrast, duration (how long the hallucinations last) was better related to these factors but is not typically included as a measure of VH severity or outcome. Our findings suggest that this needs to be reconsidered and greater attention paid to VH duration as a clinical metric.

**Limitations and future directions**

An important limitation of the current study was that it was restricted to the use of the MMSE total score (which is not the best measure of executive functioning) as the only cognitive variable available across all groups of patients. In the future, it would be useful to either have a test with sufficient sensitivity to be able to also detect mild cognitive impairments (Bak, 2006) or to have a complete cognitive battery to reliably detect small changes in performance across different underlying cognitive domains that are known to be linked to VHS in patients with neurodegenerative disorders (e.g., executive function, working memory and visuo-spatial tasks—Montagnese and Leptourgos, 2021). Furthermore, future research should examine what kinds of specific cognitive deficits are predictive of poor insight.

When looking at each group separately, the correlation between MMSE and degree of insight did not survive Bonferroni correction. However, given the robust results found in both the bigger sample and in the LMM accounting for diagnostic differences, one could speculate that a lack of statistical significance at each group level between MMSE and degree of insight might be due to the more limited sample sizes and to the higher rate of false negatives due to the conservative multiple-comparison approach employed. Future research should look at reproducing these analyses with larger sample sizes.

Another limitation was that distress was only measured on a 2-point scale and hallucination-specific insight on a 4-point scale. These limited the types of analyses that could be performed and do not provide nuanced, fine-grain detail of patients’ beliefs about their hallucinatory episodes nor the nature of the distress. Future studies should select better measures of distress and insight, especially so that they can be more sensitive to both partial insight and fluctuating insight, as well as providing qualitative and quantitative information.

Another limitation is the use of cross-sectional data to make inferences about factors driving longitudinal hallucination progression. It will be crucial to establish that a change in insight or lengthening of hallucination duration translates into more distressing hallucinations for individual patients. In the current study, there was also not enough data to include other subgroups that were partly available in the original datasets, such as “Eye disease + dementia”. These would be interesting comorbidity groups to explore in future research in order to investigate how different underlying pathological mechanisms might interact in such cases and whether they would affect the associations between cognition, severity and hallucination-specific insight found here. Finally, as multimodal
hallucinations (i.e., hallucinations occurring in different sensory modalities, both simultaneously and serially in time—Montagnese and Vignando, 2021) tend to be associated with a more advanced stage of the hallucinatory symptomatology and are perceived as more frightening and veridical than unimodal ones (Dudley et al., 2018; Laloyaux et al., 2019), it would be important for future studies to also collect information about multimodality in order to explore whether the associations across insight, severity and cognition found in our study would differ as a function of multimodality.

**Conclusion**

The severity of VH across ED and neurodegenerative diseases and its subcomponent of distress are related to impaired hallucination-related insight, which is itself associated with cognitive decline. Whether reduced insight is causally related to distress or whether the association reflects other factors remains unclear. The same associations between hallucination-specific insight, severity and cognition applied to VH in ED, although this may relate to undiagnosed neurodegenerative disease in the ED group and temporal aspects of hallucinations seem to play a greater role in ED than in neurodegenerative disease. How frequently hallucinations occur seems to be a less important measure of VH severity or distress in neurodegenerative disease than previously thought while, in contrast, a relatively unexplored aspect of VH timing—the duration of individual hallucination episodes—seems a better indicator of disease progression. Overall, our findings point to possible new approaches to mitigate the poor outcomes linked to VH, targeting treatment to improve hallucination-specific insight and VH duration.

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Data availability statement

Data available on request from the authors.

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