Preprint
Published paper can be found here:
https://doi.org/10.1016/j.schres.2019.02.022

Citation:
Chouinard V-A, Shinn AK, Valeri L, Chouinard PA, Gardner ME, Asan E, Cohen BM, Ongur D (2019) Visual hallucinations associated with multimodal hallucinations. Schizophrenia Research. DOI: 10.1016/j.schres.2019.02.022

Title: Visual hallucinations associated with multimodal hallucinations, suicide attempts and morbidity of illness in psychotic disorders.

Virginie-Anne Chouinard (M.D.)[a,b], Ann K. Shinn (M.D.)[a,b], Linda Valeri (Ph.D.)[b,c], Philippe A. Chouinard (Ph.D.)[d], Margaret E. Gardner (B.A.)[a], A. Esin Asan (B.A.)[a], Bruce M. Cohen (M.D., Ph.D.)[a,b], Dost Öngür (M.D., Ph.D.)[a,b].

[a] Psychotic Disorders Division, McLean Hospital, Belmont, MA, USA.
[b] Department of Psychiatry, Harvard Medical School, Boston, MA, USA.
[c] Laboratory for Psychiatric Biostatistics, McLean Hospital, Belmont, MA, USA.
[d] Department of Psychology and Counselling, School of Psychology and Public Health, LaTrobe University, Bendigo, Victoria, Australia.

Corresponding author:
Virginie-Anne Chouinard
115 Mill Street, Mailstop 108, Belmont, MA 02478.
Tel. +16178553034
Fax +16178552895
vchouinard@mclean.harvard.edu.

Abstract

Background: Visual hallucinations (VH) are a common, but understudied symptom of psychosis, experienced by individuals across diagnostic categories of psychotic and neuropsychiatric conditions. There are limited data on VH and associated clinical phenotypes in adult idiopathic psychotic disorders, which are needed to elucidate their relevance to psychotic illness paradigms.

Method: In this cross-sectional study, we examined clinical risk factors for VH in a well-characterized sample of 766 patients with adult psychotic disorders across diagnostic categories of schizophrenia (n=227), schizoaffective disorder (n=210), and bipolar I disorder (n=329). The Structured Clinical Interview for DSM-IV-TR was used for diagnosis and symptom measurements.

Results: The prevalence of VH was 26.1% (200/766). Multivariate logistic regression showed that VH were independently associated with the presence of hallucinations in other modalities, including auditory, tactile, olfactory, and gustatory hallucinations. History of a suicide attempt and catatonic behavior were also associated with VH. In addition, specific delusions were associated with VH, in particular, delusions of control, and religious, erotomanic and jealousy delusions. Diagnosis, negative symptoms, and family history of psychosis were not independent predictors of VH.

Conclusions: Results showed the clinical and disease relevance of VH as they were associated with severe morbidity of illness, including suicide attempts and catatonic behavior. Findings also suggest a phenotype associated with hallucinations in other modalities and specific types of delusions. Based on our findings, VH may be a significant factor in assessing for suicidality and illness severity, warranting clinical attention and further study of underlying mechanisms.

Key words: hallucinations; visual; schizophrenia; schizoaffective; bipolar disorder.

1. Introduction

Hallucinations are a core diagnostic feature of psychotic disorders. They involve different sensory modalities, including auditory, visual, olfactory, tactile and gustatory hallucinations, among others (Lim et al. 2016). Visual hallucinations (VH) are commonly found across diagnostic categories of psychotic disorders (Baethge et al., 2005; Lewandowski et al., 2009; Shinn et al., 2012). Recent studies have found rates of VH in schizophrenia spectrum disorders to be between 23-38.5%, with the presence of VH early in psychotic illness (Clark et al., 2017; McCarthy-Jones et al., 2017; Waters et al., 2014). Despite their prevalence in psychotic disorders, there are limited data on this psychotic symptom, including its associated clinical phenotypes and neurobiological correlates. In working towards models of hallucinations, identifying symptomatology specifically related to VH could provide phenotypes to better understand concomitants of hallucinations across different sensory modalities. Such an approach in psychotic disorders may allow us to disentangle heterogeneity and the significance of specific hallucinatory and psychotic experiences, informing the study of underlying mechanisms. Importantly, as VH are common, a better understanding of the clinical relevance of VH may also guide clinical practice.

A distinguishing feature of VH is that they are commonly observed in both psychiatric and neurological conditions, including neurodegenerative disorders, such as Parkinson's disease (Fenelon and Alves, 2010) and dementia with Lewy bodies (McKeith et al., 2006). Historically, VH were once considered to be related mainly to neurological conditions. Perhaps as a result, VH have been well characterized in Parkinson's disease and other neurodegenerative disorders (Fenelon et al., 2000; Gallagher et al., 2011), even spurring the development of new treatments (Sahli and Tarazi, 2018). In contrast, VH remain an understudied symptom of psychosis in psychiatric conditions. The cross-over of VH in several neuropsychiatric conditions is a compelling feature of this psychotic symptom. In Parkinson's disease, VH are common and associated with greater severity of disease. There is also some evidence to suggest that VH are associated with more severe illness in psychotic disorders (Clark et al., 2017; Mueser et al., 1990). In childhood onset schizophrenia, a form of schizophrenia with greater genetic loading, VH are more common with a high prevalence of up to 80% (David et al., 2011). VH in childhood onset schizophrenia have been associated with markers of greater illness severity, including earlier age of onset of psychosis, lower IQ scores, and lower functional status (David et al., 2011). Although there are limited data in adult psychotic disorders, from studies with mostly small samples sizes in non-affective psychotic

disorders, these findings suggest that there may be underlying mechanisms of VH, which result in a more severe clinical phenotype, in parallel with neurodegenerative disorders. In addition, to date, in psychotic disorders, VH have been found to occur most frequently in association with other hallucinations, in particular auditory hallucinations (AH) (Bracha et al., 1989; Goodwin et al., 1971; Shinn et al., 2012). A recent study in schizophrenia spectrum disorders concluded that hallucinations in one modality, particularly AH, increased the risk of having multimodal hallucinations (Lim et al, 2016). It is possible that as multiple sensory modalities are affected, there is greater severity of psychotic illness, overall.

Given the paucity of data on VH across psychotic disorders, we studied the association of VH with other clinical features in a large, well-characterized, cross diagnostic sample of psychotic disorders. We expected that the presence of VH would be associated with hallucinations in other sensory modalities and hypothesized that VH, in this multimodal hallucinatory context, would be associated with factors of greater illness morbidity, including negative symptoms, catatonic behavior and family history of psychotic disorders. We specifically used a dimensional approach to study the significance of VH in psychosis and included patients with schizophrenia, schizoaffective and bipolar disorders. Increasing evidence from genetic, as well as physiologic studies, suggest that there are shared risk determinants across non-affective and affective psychotic disorders (Erlenmeyer-Kimling et al., 1995; International Schizophrenia Consortium et al., 2009), and that these disorders are syndromes on a continuum, rather than separate neurobiological disease processes. In support of a cross-diagnostic approach, VH are found in patients across diagnostic categories of psychotic disorders (Shinn et al., 2012). Moving beyond diagnostic classifications in psychotic disorders, and even neuropsychiatric diseases, to study VH may provide valuable clinical and psychopathological insights (Insel et al., 2010).

2. Materials and methods

2.1. Participants

We assessed 766 patients with schizophrenia (n=227), schizoaffective disorder (n=210) and bipolar I disorder with psychotic features (n=329). Participants were recruited for an ongoing genetic association study of psychotic and mood disorders at McLean Hospital. At the time of this study, patients were included if they were 18 to 89 years old and had a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder with psychotic features. There were

589 inpatients recruited from inpatient units at McLean Hospital and 177 outpatients recruited through flyers posted at McLean Hospital. Participants were excluded if their diagnosis was attributable to a general medical condition or substance use, or if they had a history of significant head trauma or developmental disorder. The study was approved by the McLean Hospital Institutional Review Board and participants provided written informed consent.

2.2. Clinical Assessments

The Structured Clinical Interview for DSM-IV-TR (SCID) (First et al., 1995) was administered with participants for diagnosis and symptom identification, including VH. This assessment was also informed by reviewing hospital records and obtaining information from family and outpatient providers. The VH group included patients with a lifetime history of VH and the non-VH group included patients without a history of VH. In both groups, patients may have additionally reported AH or other types hallucinations. Tactile, olfactory and gustatory hallucinations (TOGH) were combined into one category because of their relatively low frequency (Lewandowski et al., 2009). Psychotic symptom measures from the SCID were all based on lifetime occurrence as the SCID does not distinguish lifetime and current presence for individual psychotic symptoms. We also quantified the total number of DSM Axis I disorders diagnosed on the SCID, which has been considered a measure of global psychopathology, previously found to be associated with psychotic symptoms (Kelleher et al., 2012). SCID modules administered included mood, psychotic, anxiety and substance use disorders. Age of onset of psychotic symptoms was available for a subset of 625 patients. Psychotropic medication information was obtained from hospital records for inpatients and self-reported for outpatients. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971).

Trained research staff conducted the assessments, including research assistants, a clinical psychologist and psychiatrists. Research staff underwent monthly diagnostic reliability exercises. Perfect interrater reliability was achieved for SCID diagnoses, near-perfect agreement was observed for current (major depression, 1.0; mania, 0.93) and past mood episodes (major depression, 0.90; mania, 1.0), and excellent agreement was observed for psychotic symptoms (persecutory delusion, 0.80: auditory hallucination, 0.85).

2.3. Statistical Analyses

We performed statistical analyses using SPSS (PASW) version 22 (SPSS, Chicago, IL). We used univariate logistic regression analyses to compare demographic and clinical characteristics between VH and non-VH groups. We did not correct for multiple comparisons because of the exploratory nature of these univariate analyses. Multivariate logistic regression analysis was used as the main analysis to identify independent predictors of VH. Demographic and clinical variables that were statistically significant in univariate comparisons with a $P< 0.05$ were included in the regression model. As our sample was comprised of both inpatients and outpatients, we also carried out a multivariate regression model including inpatient status. For all analyses, we checked modeling assumptions, including normality of measures, non-constant variance, and influential points. We assessed for multicollinearity to avoid redundancy in variables, including using variance inflation factors (VIF).

3. Results

The mean age was 36.5 years (SD=12.7), 56.1% were men, and 64.8% were Caucasian. The prevalence of VH was 26.1 % (n=200/766) across diagnostic categories. VH were present in 36.2% (76/210) of patients with schizoaffective disorder, 25.6% (58/227) with schizophrenia and 20.1% (66/329) with bipolar disorder. Of the 200 patients with VH, 79.5% (159/200) had AH, 53.5% (107/200) had TOGH and 12.5% (25/200) had no other types of hallucinations.

Characteristics of patients with schizophrenia, schizoaffective disorder and bipolar disorder according to visual hallucinations are presented in Table 1. In univariate logistic regression analyses, patients with VH were similar to patients without VH for most sociodemographic characteristics, including age, sex, dependency of living situation, children, employment and handedness. However, patients with VH were less likely to have graduated from college compared to patients without VH. Diagnostically, patients with VH were more likely to have schizoaffective disorder, less likely to have bipolar disorder and more likely to have an anxiety disorder. Patients with VH also had a greater total number of SCID diagnoses. There were no significant differences in substance use disorders between the two groups. We also found that patients who reported VH were less likely to be psychiatrically hospitalized at the time of the study.

From a psychopathology standpoint, patients with VH had higher rates of prior suicide attempt. Patients with VH were more likely to have other types of hallucinations, including AH and TOGH. There were significantly more delusions of reference and control, religious, erotomanic and jealousy delusions and bizarre delusions in patients with VH, compared to

those without VH. Furthermore, patients with VH were more likely to have catatonic behavior. There were no significant differences between VH and non-VH groups for negative symptoms and family history of psychotic disorders. There was a trend for age of onset to be associated with VH ($p=0.07$). As age of onset has been considered an indicator of prognosis (Juola et al., 2013; Immonen et al., 2017), we performed a posteriori logistic regression analyses to assess the effect of diagnosis on the relationship between age of onset and VH, however, diagnosis did not change these results, with age of onset remaining with a trend towards being associated with VH ($p=0.07$). In addition, there were no significant differences between groups for use of psychiatric medications at the time of the study (Table 2).

In multivariate logistic regression analysis used to identify independent predictors of VH, AH ($p<0.0001$), TOGH ($p<0.0001$), delusions of control ($p=0.006$) and religious, erotomanic and jealousy delusions ($p=0.006$) were significantly associated with VH (Table 2). In addition, history of a suicide attempt ($p=0.01$) and catatonic behavior ($p=0.04$) remained predictors of VH. Other factors, including diagnosis, total number of SCID diagnoses, anxiety and other delusions, were not found to be independently associated with VH. Inpatient status, when included in the multivariate regression model, was not associated with VH.

4. Discussion

We found that VH were common and present in 26.1% of patients across diagnostic groups of schizophrenia, schizoaffective disorder and bipolar disorder, a prevalence rate consistent with recent studies of VH in schizophrenia spectrum disorders (Clark et al., 2017; Galletti et al., 2017; McCarthy-Jones et al., 2017). Our results showed that VH were associated with multimodal hallucinations, core psychotic delusions and severe morbidity of illness, including suicide attempts and catatonic behavior. Based on our findings, where visual and multimodalities of hallucinations are present, there is greater morbidity of illness, with increased risk for mortality, in psychotic disorders. Our finding that suicide attempts were associated with VH is highly clinically relevant and may indicate greater psychological distress associated with the illness in patients with VH. A recent study by Clark et al. in patients with first episode psychosis also found higher levels of suicidal ideation in patients with VH compared to patients with AH or no hallucinations (Clark et al., 2017). This same study found that VH were associated with greater impairment in functioning and increase in risk for relapse (Clark et al., 2017). Mueser et al. showed that global severity of illness in schizophrenia was worse in patients with VH and not with other types of hallucinations (Mueser et al., 1990),

although this study sample was small. Taken together with these findings, our results indicate that clinicians should be regularly inquiring about VH in early and later stages of psychotic disorders and that VH may be a significant factor in assessing for suicidality and illness severity. Relevant to this point, in a study of hospitalized patients with chronic schizophrenia (Bracha et al., 1989), VH were found in 32% of patients in a retrospective review of hospital charts, while there was a 56% prevalence found in patients studied prospectively, suggesting that psychiatrists may not always inquire about VH. As suicidal ideation and attempts are prevalent in psychotic disorders (Hor and Taylor, 2010), VH and its associated phenotypes should be specifically considered in studies identifying risk factors for suicide. We also found that catatonic behavior was associated with VH across psychotic disorders, despite the overall low prevalence of catatonic behavior in the sample. This finding in patients with VH is another indicator of severe morbidity, which increases the risk of mortality in psychotic disorders (Gross et al., 2008). To our knowledge, catatonic behavior has not previously been associated with VH in psychosis. The association of VH with these motor disturbances is intriguing given the high rates of VH present in primary movement disorders, such as Parkinson's Disease (Fenelon and Alves, 2010), suggesting that there may be an association between motor disturbances and VH more generally. Our findings of greater illness morbidity associated with VH are similar to findings in Parkinson's disease, where VH are associated with greater severity of disease, predict progression towards dementia and are associated with cognitive impairment in patients without dementia (Gallagher et al., 2011; Galvin et al., 2006; Hobson and Meara, 2004). On the other hand, VH in neurological disorders have several clinical features that appear to be different compared to VH in idiopathic psychotic disorders. VH in neurological disorders, such as Parkinson's Disease and Lewy body dementia, most frequently occur without hallucinations in other modalities (Fenelon and Alves, 2010; Fenelon et al., 2000; Manford and Andermann, 1998). In addition, VH in neurodegenerative disorders are usually not associated with delusions, as we found in our study, and impaired insight (Fenelon et al., 2000). Investigating markers of VH across psychotic and neurodegenerative disorders may provide insights into differing or similar pathophysiology underlying VH. Along the same lines, it may be informative to define clinical differences between patients with VH and multimodal hallucinations and the relatively few patients with VH without any other hallucinations (12.5% of patients with VH in this study).

As expected, our results showed that hallucinations across different sensory modalities were strongly associated with VH, including both AH and TOGH. We found that around 80% of patients who experienced VH, had also experienced AH. In contrast, some studies suggest

that patients with AH are less likely to experience hallucinations in other modalities (McCarthy-Jones et al., 2017; Oorschot et al., 2012). Given the high prevalence of AH in psychotic disorders, there may be a hierarchy in which sensory modalities are affected, potentially distinguishing clinical phenotypes, which may be predictive of severity of illness. VH were not only associated with multimodal hallucinations as our results showed that VH were integrated with other specific psychotic symptoms. VH were associated with delusions of control and religious, erotomanic and jealousy delusions. The strong association of VH with these delusions suggests that VH may have a specific psychotic phenomenology that has personal relevance and leads to greater distress. While studies investigating the phenomenology of VH are limited in psychotic disorders, VH often appear to be complex and have religious themes, such as images of Christ or the Virgin Mary (Chouinard and Miller, 1999; McCarthy-Jones et al., 2017). It could be that religious delusions were driving the association with this group of delusions, however, we could not separate religious, erotomanic and jealousy delusions, nor report the nature of VH images, as these are not differentiated using the SCID. A recent study in first episode psychosis found that AH and non-AH differed in their association with different types of delusions (Galletti et al., 2017), namely that AH were associated with paranoid delusions, while non-AH were associated with grandiose/religious delusions. In another study including first episode psychosis (Clark et al., 2017), patients with VH had higher scores for delusion ratings, including "outside control" domain ratings. Future research could provide more qualitative examination of convergence versus divergence in delusions and hallucinations across different sensory modalities within the same individuals. Of note, we did not find that negative symptoms were predictive of VH, thus suggesting a different pathogenesis for positive and negative symptoms.

Findings of multimodal hallucinations have implications warranting further investigation. These could indicate that hallucinations, regardless of type, may share a centralized high-level psychopathologic mechanism in psychotic disorders. This possibility is intriguing as the integration of multisensory processing is important for providing one's sense of self (Chouinard et al., 2017). This is evident in body transfer illusions, such as the rubber hand illusion (Botvinick and Cohen, 1998), in which a person's awareness of self is altered by providing false information from one sense while maintaining accurate information from a different sense, altering one's perceived reality of where their body or parts of their body are located (Chouinard et al. 2017). It then follows that the integration of information from multiple sensory modalities is important in shaping a person's self. Notably, multisensory integration is known to be important for contributing to the perceptual experience of our surroundings (Alais

et al., 2010). Recently, functional neuroimaging studies in psychotic disorders have examined patients with VH and AH compared to patients with only AH (Amad et al., 2014; Jardri et al.,2013; Rolland et al., 2015). These studies have found differing patterns of functional connectivity between these two groups. It is possible that these findings, based on which sensory modalities are affected, may explain the greater morbidity associated with VH in psychotic disorders. A better understanding of the clinical phenotypes associated with VH and multimodal hallucinations may contribute to integrating and interpreting future neuroimaging studies.

There are additional topics and limitations of the study to consider. First, our data on VH and clinical characteristics are cross-sectional and do not allow us to make inferences about temporal order of symptoms or causality. Second, it is important to note that the majority of patients in our study were acutely symptomatic and hospitalized at the time of the study. We observed that VH were reported less often in patients who were hospitalized at the time of the study. However, inpatient status was not independently associated with VH in the main multivariate regression analyses and including inpatient status in these analyses did not change our results. Third, as we used the SCID for measurement of VH and psychotic symptoms, we did not have phenomenological data on the quality and content of VH, for example, simple and complex VH, frequency, severity, associated distress, among other characteristics. To inform the characterization of VH across psychotic disorders, future studies should use rating scales that have been specifically developed for the assessment of hallucinatory experiences in different modalities and even transnosographically (de Chazeron et al., 2015; Chouinard and Miller, 1990; Mitchell et al., 2017). Fourth, we did not have a complete dataset for age of onset of psychotic illness (625/766). Perhaps as a result, we found that there was only a trend for the relationship between age of onset and VH in our study. Age of onset is of particular interest in psychotic disorders as earlier age of onset has been associated with greater severity of illness and increased likelihood for neurobiological abnormalities. There are data to suggest neurodevelopmental factors may play a role in underlying mechanisms of VH. This evidence includes a high prevalence of VH in childhood onset schizophrenia, associated with earlier age of onset (David et al., 2011), as well as neuroimaging evidence for differing cortical sulcation, a brain development marker, in patients with VH compared to those with only AH (Cachia et al., 2015). Finally, we did not have assessments related to trauma, adverse childhood experiences, borderline personality disorder or other conditions that have been associated with hallucinations (Bailey et al., 2018; Niemantsverdriet et al.,2017). Childhood trauma has been associated with VH in a recent study of first episode psychosis (Solesvik et al., 2016). Notably,

auditory hallucinations have been associated with suicidal behavior in boderline personality disorder (Slotema et al., 2017). A concomitant history of trauma or borderline personality disorder would be important to examine in future studies, particularly with regards to clarifying the relationship between VH and suicide attempts.

Overall, our results show the specific clinical and disease relevance of VH across psychotic disorders, as these were associated with severe morbidity of illness, including suicide attempts and catatonic behavior. Suicide attempts and catatonic behavior both increase the risk for mortality in psychotic disorders. Based on our findings, VH may be a significant factor in assessing for suicidality and illness severity, warranting clinical attention and highlighting the importance of inquiring routinely about VH in clinical practice. Findings also suggest a clinical phenotype of VH associated with hallucinations in other modalities and specific types of delusions. Informed by these symptomatology correlates, future studies should further investigate the underlying neurobiology and cognitive mechanisms of VH across psychotic disorders and other neuropsychiatric conditions, including movement disorders.

References

Alais, D., Newell, F.N., Mamassian, P., 2010. Multisensory processing in review: from physiology to behaviour. Seeing Perceiving 23(1), 3-38.

Amad, A., Cachia, A., Gorwood, P., Pins, D., Delmarie, C., Rolland, B., Mondino, M., Thomas, P., Jardri, R., 2014. The multimodal connectivity of the hippocampal complex in auditory and visual hallucinations. Mol. Psychiatry 19(2), 184-191.

Baethge, C., Baldessarini, R.J., Freudenthal, K., Streeruwitz, A., Bauer, M., Bschor, T., 2005. Hallucinations in bipolar disorder: characteristics and comparison to unipolar depression and schizophrenia. Bipolar Disord. 7(2), 136-145.

Bailey, T., Alvarez-Jimenez, M., Garcia-Sanchez, A.M., Hulbert C., Barlow, E., Bendall, S., 2018. Childhood trauma is associated with severity of hallucinatins and delusions in psychotic disorders: a systematic review and meta-analysis. Schizophr. Bull. 44(5), 1111-1122.

Botvinick, M., Cohen, J., 1998. Rubber hands 'feel' touch that eyes see. Nature 391(6669), 756.

Bracha, H.S., Wolkowitz, O.M., Lohr, J.B., Karson, C.N., Bigelow, L.B., 1989. High prevalence of visual hallucinations in research subjects with chronic schizophrenia. Am. J. Psychiatry 146(4), 526-528.

Cachia, A., Amad, A., Brunelin, J., Krebs, M.O., Plaze, M., Thomas, P., Jardri, R., 2015. Deviation sin cortex sulcation associated with visual hallucinations in schizophrenia. Mol. Psychiatry 20(9), 1101-1107.

de Chazeron, I., Pereira, B., Chereau-Boudet, I., Brousse, G., Misdrahi, D., Fenelon, G., Tronche, A.M., Schwan, R., Lancon, C., Marques, A., Debilly, B., Durif, F., Llorca, P.M., 2015. Validation of a psychosensory hallucinations scale (PSAS) in schizophrenia and Parkinson's disease. Schizophr. Res. 161(2-3), 269-276.

Chouinard, G., Miller, R., 1999. A rating scale for psychotic symptoms (RSPS) part I: theoretical principles and subscale 1: perception symptoms (illusions and hallucinations). Schizophr. Res. 38(2-3), 101-122.

Chouinard, P.A., Sherman, J.A., Millard, A.S., Sperandio, I., 2017. Evaluating Bodily Self-Consciousness and the Brain Using Multisensory Perturbation and fMRI. Multisensory Research 30, 179-191, DOI: https://doi.org/10.1163/22134808-00002563.

Clark, M.L., Waters, F., Vatskalis, T.M., Jablensky, A., 2017. On the interconnectedness and prognostic value of visual and auditory hallucinations in first-episode psychosis. Eur. Psychiatry 41, 122-128.

David, C.N., Greenstein, D., Clasen, L., Gochman, P., Miller, R., Tossell, J.W., Mattai, A.A., Gogtay, N., Rapoport, J.L., 2011. Childhood onset schizophrenia: high rate of visual hallucinations. J. Am. Acad. Child Adolesc. Psychiatry 50(7), 681-686 e683.

Erlenmeyer-Kimling, L., Squires-Wheeler, E., Adamo, U.H., Bassett, A.S., Cornblatt, B.A., Kestenbaum, C.J., Rock, D., Roberts, S.A., Gottesman, I.I., 1995. The New York High-Risk Project. Psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow-up. Arch. Gen. Psychiatry 52(10), 857-865.

Fenelon, G., Alves, G., 2010. Epidemiology of psychosis in Parkinson's disease. J. Neurol. Sci. 289(1-2), 12-17.

Fenelon, G., Mahieux, F., Huon, R., Ziegler, M., 2000. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain 123 (Pt 4), 733-745.

First, M.B., Sptizer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured clinical interview or DSM-IV Axis I Disorders. New York State Pscyhiatric Institute, Biometrics Research, New York.

Gallagher, D.A., Parkkinen, L., O'Sullivan, S.S., Spratt, A., Shah, A., Davey, C.C., Bremner, F.D., Revesz, T., Williams, D.R., Lees, A.J., Schrag, A., 2011. Testing an aetiological model of visual hallucinations in Parkinson's disease. Brain 134(Pt 11), 3299-3309.

Galletti, C., Paolini, E., Tortorella, A., Compton, M.T., 2017. Auditory and non-auditory hallucinations in first-episode psychosis: Differential associations with diverse clinical features. Psychiatry Res. 254, 268-274.

Galvin, J.E., Pollack, J., Morris, J.C., 2006. Clinical phenotype of Parkinson disease dementia. Neurology 67(9), 1605-1611.

Goodwin, D.W., Alderson, P., Rosenthal, R., 1971. Clinical significance of hallucinations in psychiatric disorders. A study of 116 hallucinatory patients. Arch. Gen. Psychiatry 24(1), 76-80.

Gross, A.F., Smith, F.A., Stern, T.A., 2008. Dread complications of catatonia: a case discussion and review of the literature. Prim. Care Companion J. Clin. Psychiatry 10(2); 153-155.

Hobson, P., Meara, J., 2004. Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. Mov. Disord. 19(9), 1043-1049.

Immonen, J., Jaaskelainen, E., Korpela, H., Miettunen, J., 2017. Age at onset and outcomes in schizophrenia: a systematic review and meta-analysis. Early Interv. Psychiatry 11(6), 453-460.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010.

Research domain criteria(RDoC): toward a new classification framework for research on mental disorders. Am. J. Psychiatry 167(7):748–51.

Hor, K., Taylor, M., 2010. Review: suicide and schizophrenia: a systematic review of rates and risk factors. J. Psychopharmacol. 24 (4), 81-90.

International Schizophrenia Consortium, Purcell, S.M., Wray, N.R., Stone, J.L., Visscher, P.M., O'Donovan, M.C., Sullivan, P.F., Sklar, P., 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460(7256), 748-752.

Jardri, R., Thomas, P., Delmaire, C., Delion, P., Pins, D., 2013. The neurodynamic organization of modality-dependent hallucinations. Cereb. Cortex (5), 1108-1117.

Juola P., Miettunen J., Veijola J., Isohanni M., Jääskeläinen E., 2013. Predictors of short–and long- term clinical outcome in schizophrenic psychosis—The Northern Finland 1966 Birth Cohort study. European Psychiatry 28(5), 263–268.

Kelleher, I., Keeley, H., Corcoran, P., Lynch, F., Fitzpatrick, C., Devlin, N., Molloy, C., Roddy, S., Clarke, M.C., Harley, M., Arseneault, L., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., Cannon, M., 2012. Clinicopathological significance of psychotic experiences in nonpsychotic young people: evidence from four population-based studies. Br. J. Psychiatry. 201(1), 26-32.

Lewandowski, K.E., DePaola, J., Camsari, G.B., Cohen, B.M., Ongur, D., 2009. Tactile, olfactory, and gustatory hallucinations in psychotic disorders: a descriptive study. Ann. Acad. Med Singapore 38(5), 383-385.

Lim, A., Hoek, H.W., Deen, M.L., Blom, J.D., GROUP Investigators, 2016. Prevalence and classification of hallucinations in multiple sensory modalities in schizophrenia spectrum disorders. Schizophr. Res. 176(2-3), 493-499.

Manford, M., Andermann, F., 1998. Complex visual hallucinations. Clinical and neurobiological insights. Brain 121 (10), 1819-1840.

McCarthy-Jones, S., Smailes, D., Corvin, A., Gill, M., Morris, D.W., Dinan, T.G., Murphy, K.C., Anthony, O.N.F., Waddington, J.L., Australian Schizophrenia Research Bank, Donohoe, G., Dudley, R., 2017. Occurrence and co-occurrence of hallucinations by modality in schizophrenia-spectrum disorders. Psychiatry Res. 252, 154-160.

McKeith, I.G., Dickson, D.W., Lowe, J., Emre, M., O'Brien, J.T., Feldman, H., Cummings, J., Duda, J.E., Lippa, C., Perry, E.K., et al. Diagnosis and management of dementia with lewy bodies: Third report of the dlb consortium. Neurology 2005, 65, 1863–1872

Mitchell, C.A.A., Maybery, M.T., Russell-Smith, S.N., Collerton, D., Gignac, G.E., Waters, F., 2017. The structure and measurement of unusual sensory experiences in different modalities: the multimodality unusual sensory experiences questionnaire (MUSEQ). Front. Psychol. 8, 1363.

Mueser, K.T., Bellack, A.S., Brady, E.U., 1990. Hallucinations in schizophrenia. Acta. Psychiatr. Scand. 82(1), 26-29.

Niemantsverdriet, M.B.A, Slotema, C.W., Blom, J.D., Franken, I.H., Hoek, H.W., Sommer, I.E.C., van der Gaag, M., 2017. Hallucinations in borderline personality disorder: prevalence, chacteristics and associations with comorbid symptoms and disorders. Sci. Rep. 7, 13920.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9(1), 97-113.

Oorschot, M., Lataster, T., Thewissen, V., Bentall, R., Delespaul, P., Myin-Germeys, I., 2012. Temporal dynamics of visual and auditory hallucinations in psychosis. Schizophr. Res. 140(1-3), 77-82.

Rolland, B., Amad, A., Poulet, E., Bordet, R., Vignaud, A., Bation, R., Delmarie, C., Thomas, P., Cottencin, O., Jardri, R., 2015. Resting-state functional connectivity of the nucleus accumbens in auditory and visual hallucinations in schizophrenia. Schizophr. Bull. 41(1), 291-309.

Sahli, Z.T., Tarazi, F.I., 2018. Pimavanserin: novel pharmacotherapy for Parkinson's disease psychosis. Expert Opin. Drug Discov. 13(1), 103-110.

Shinn, A.K., Pfaff, D., Young, S., Lewandowski, K.E., Cohen, B.M., Ongur, D., 2012. Auditory hallucinations in a cross-diagnostic sample of psychotic disorder patients: a descriptive, cross-sectional study. Compr. Psychiatry 53(6), 718-726.

Slotema, C.W., Niemantsverdriet, M.B., Blom, J.D., van der Gaag, M., Hoek, H.W., Sommer, I.E., 2017. Suicidality and hospitalisation in patients with borderline personality disorder who experience auditory verbal hallucinations. Eur. Psychiatry 41,47-52.

Solesvik, M., Joa, I., Larsen, T.K., Langeveld, J., Johannessen, J.O., Bjornestad, J., Anda, L.G., Gisselgard, J., Hegelstad, W.T., Bronnick, K., 2016. Visual hallucinations in first-episode psychosis: association with childhood trauma. PLoS One 11(5), e0153458.

Thaler, L., Arnott, S.R., Goodale, M.A., 2011. Neural correlates of natural human echolocation in early and late blind echolocation experts. PLoS One 6(5), e20162.

Waters, F., Collerton, D., Ffytche, D.H., Jardri, R., Pins, D., Dudley, R., Blom, J.D., Mosimann, U.P., Eperjesi, F., Ford, S., Laroi, F., 2014. Visual hallucinations in the psychosis spectrum and comparative information from neurodegenerative disorders and eye disease. Schizophr. Bull. 40 Suppl 4, S233-245.

Table 1. Characteristics of Patients with Schizophrenia, Schizoaffective Disorder and Bipolar Disorder According to Visual Hallucinations (VH)

	VH (N=200)	Non-VH (N=566)	OR (95%CI)	P value
Sociodemographic characteristics				
Age, mean (SD), y	36.4 (12.5)	36.5 (12.8)	0.99 (0.98-1.01)	0.88
Male sex, No.(%)	104 (52.0)	326 (57.6)	0.79 (0.57-1.10)	0.17
Left-handed, No.(%)	30 (15.5)	87 (15.8)	0.97 (0.62-1.53)	0.92
Never married, No.(%)	140 (70.7)	402 (71.4)	0.96 (0.67-1.38)	0.85
No children, No.(%)	152 (76.4)	432 (76.7)	0.98 (0.67-1.43)	0.92
Not living independently, No.(%)	92 (46.5)	275 (49.6)	0.88 (0.63-1.21)	0.44
Did not graduate college, No.(%)	142 (71.7)	346 (61.5)	1.59 (1.11-2.26)	0.01
Unemployed, No.(%)	125 (62.8)	330 (58.7)	1.18 (0.85-1.65)	0.31
Clinical characteristics				
Diagnosis- No.(%)				
Schizophrenia	58 (29.0)	169 (29.9)	1.36 (0.91-2.04)	0.12
Schizoaffective Disorder	76 (38.0)	134 (23.7)	2.26 (1.53-3.33)	<0.0001
Bipolar I Disorder	66 (33.0)	263 (46.5)		<0.0001
Age of onset, mean (SD), y	20.5 (7.1)	21.7 (7.5)	0.98 (0.95-1.00)	0.07
Prior suicide attempt, No.(%)	92 (49.7)	187 (34.8)	1.85 (1.32-2.60)	<0.0001
Family history of psychosis No.(%)	48 (24.6)	144 (25.9)	0.93 (0.64-1.36)	0.72
Anxiety disorder, No.(%)	79 (39.5)	141 (24.9)	1.96 (1.39-2.76)	<0.0001
Alcohol use disorder, No.(%)	73 (36.5)	236 (41.7)	0.80 (0.57-1.12)	0.19
Cannabis use disorder, No.(%)	79 (39.5)	189 (33.4)	1.30 (0.93-1.81)	0.12
Any substance use disorder, No.(%)	114 (57.0)	327 (57.8)	0.96 (0.69-1.34)	0.84
Total SCID diagnoses, mean (SD)	1.88 (1.27)	1.65 (1.05)	1.18 (1.03-1.36)	0.02
Inpatient status, No. (%)	141 (70.5)	448 (79.2)	0.63 (0.44-0.91)	0.01
Psychotic symptoms				
Auditory Hallucinations, No.(%)	159 (79.5)	287 (50.7)	3.77 (2.57-5.51)	<0.0001
Tactile, Olfactory and Gustatory Hallucinations, No.(%)	107 (53.5)	100 (17.7)	5.36 (3.77-7.62)	<0.0001
Delusions, No.(%)				
Persecution	132 (66.0)	340 (60.1)	1.30 (0.93-1.83)	0.12
Reference	158 (79.0)	389 (68.7)	1.80 (1.22-2.65)	0.003
Control	86 (43.0)	113 (20.0)	3.02 (2.13-4.27)	<0.0001
Religious, erotomanic, jealousy	109 (54.5)	206 (36.5)	2.08 (1.50-2.88)	<0.0001
Bizarre	46 (23.0)	66 (11.7)	2.38 (1.56-3.64)	<0.0001
Catatonic Behavior, No.(%)	21 (10.9)	27 (4.9)	2.36 (1.30-4.28)	0.005
Negative Symptoms, No.(%)	62 (32.8)	162 (29.8)	1.14 (0.80-1.63)	0.44

Abbreviations: SZ, schizophrenia; SZA, schizoaffective disorder; BD, bipolar disorder ; SCID, Structured Clinical Interview for DSM-IV-TR.

Table 2. Psychiatric Medication Use According to Visual Hallucinations (VH)

Medications, No. (%)	VH (N=200)	Non-VH (N=566)	OR (95%CI)	P value
Atypical antipsychotic	160 (80.0)	457 (80.7)	0.82 (0.54-1.26)	0.38
Typical antipsychotic	34 (17.0)	81 (14.3)	1.19 (0.76-1.84)	0.43
Clozapine	25 (12.5)	77 (13.6)	0.88 (0.54-1.43)	0.66
Two or more atypical antipsychotics	29 (14.5)	87 (15.4)	0.91 (0.57-1.43)	0.68
Mood stabilizer	105 (52.5)	321 (56.7)	0.80 (0.57-1.10)	0.43
CPZ	436.97 (339.39)	436.42 (287.51)	1.00 (1.00-1.00)	0.38

Abbreviations: CPZ, chlorpromazine equivalents.

Table 3. Logistic Regression Predicting Visual Hallucinations in Patients with Schizophrenia, Schizoaffective and Bipolar Disorders

Characteristic[a]	OR (95% CI)	P Value
Diagnosis		
Schizophrenia	1.35 (0.78-2.33)	0.15
Schizoaffective disorder	1.52 (0.87-2.66)	0.27
Bipolar disorder		0.32
Did not graduate college	1.48 (0.94-2.34)	0.09
Auditory hallucinations	2.95 (1.79-4.87)	<0.0001
Tactile, olfactory and gustatory hallucinations	2.99 (1.94-4.63)	<0.0001
Delusions of reference	1.09 (0.68-1.76)	0.72
Delusions of control	1.93 (1.21-3.08)	0.006
Religious, erotomanic, and jealousy delusions	1.80 (1.18-2.73)	0.006
Bizarre delusions	1.57 (0.90-2.75)	0.11
Catatonic behavior	2.26 (1.01-5.09)	0.04
Prior suicide attempt	1.68 (1.10-2.56)	0.01
Anxiety Disorder	1.61 (0.92-2.83)	0.09
Total SCID diagnoses	0.90 (0.72-1.15)	0.42

[a] Variables different ($P<0.05$) in univariate comparisons.

Abbreviations: SCID, Structured Clinical Interview for DSM-IV-TR.