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Correlation between cognition and symptomatic severity in patients with late-life somatoform disorders

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Objectives: Various aging associated factors, such as functional decline, psychosocial problems, and cognitive dysfunction, are risk factors for somatoform disorders (SDs) in the elderly. The aim of the present study was to evaluate how cognition is correlated with the severity of late-life SDs from a neuropsychological viewpoint.
Methods: Fifty-three patients over 60 years of age who had been diagnosed as having SDs were examined in this study. The severity of the somatic symptoms was assessed using the Hamilton Anxiety Rating Scales (HAMA). Cognitive functions were assessed using the Mini-Mental State Examination (MMSE), the Frontal Assessment Battery (FAB), and the Japanese version of the Neurobehavioral Cognitive Examination (J-COGNISTAT).
Results: The J-COGNISTAT subtest score for attention was below the cutoff point (8 points) but was not correlated with the severity of the somatic symptoms in the patients with late-life SDs. The severity of anxiety as assessed using the HAMA was significantly correlated with the calculation scores ($P < 0.005$) among the J-COGNISTAT subtests, the FAB total ($P < 0.05$), and the FAB subtest scores (similarities and motor series) ($P < 0.01$). Other factors, including the benzodiazepine dosage, antidepressant dosage, the duration of illness, and the onset age, were not significantly correlated with the symptomatic severities.
Conclusion: Patients with late-life SDs showed attention deficits, but no correlation was seen between the attention deficits and symptomatic severities. Attention deficits might be associated with the appearance of symptoms. Executive dysfunction and working memory might be associated with the severity of symptoms.

Keywords: cognitive functioning; anxiety; other disorders

Introduction

According to the current concepts of the Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision) (DSM-IV-TR), somatoform disorders (SDs) are mainly characterized by chronic multiple physical symptoms that cannot be explained in terms of an underlying organic pathology (American Psychiatric Association, 2000). Thus, patients with SDs often visit medical facilities to elucidate their pathogenesis and to receive treatment. Somatization is defined as a tendency to experience medically unexplained somatic symptoms, to attribute them to physical illness, and to seek medical help for them (Lipowski, 1988). Various beliefs or perceptions may contribute to the process of somatization, including heightened bodily sensations, physical abnormalities resulting in a heightened awareness of bodily sensations, and inappropriate illness beliefs or sickness behavior. The current view of somatization has been regarded to result from complex interactive etiological factors, including psychosocial and/or neuropsychological factors (Mayou, Bass, & Sharpe, 1995). Cognitive–behavioral models of SDs emphasize the role of inadequate body-related interpretations and health-related beliefs (Salkovskis & Warwick, 2001).

From psychosocial viewpoints, late-life SDs are related to various factors characterized by the aging process, such as a decline in bodily functions, an increase in physical illness, psychosocial problems, and life events (Harwood, Prince, Mann, & Ebrahim, 1998). The occasional experience of medically unexplainable symptoms (such as dizziness, an upset stomach, or palpitations) is common under stressful circumstances, such as various social adversities, life events, or physical illnesses, especially among the elderly. A previous study has reported that the attendance of older people with somatization is as common as that of younger people (Sheehan, Bass, Briggs, & Jacoby, 2003).

Previous studies have shown age-associated differences in the prevalence of SDs. Altamura, Carta, Tacchini, Musazzi, and Pioli (1998) reported that the prevalence of undifferentiated SD tends to increase with age. Kuwabara et al. (2007) found that the age of onset is higher in patients with hypochondriasis or pain disorder than in patients with somatization disorder or body dysmorphic disorder. The reason why such anxiety or stress-related disorders are dependent on aging has remained unclear.

From a neuropsychological viewpoint, several studies have investigated the neuropsychological performance of subjects with late-life anxiety disorder and have hypothesized that the presence or severity of anxiety is associated with a lower cognitive performance in the elderly (Beaudreau & O'Hara, 2008). According to this report, we

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hypothesized that cognitive functions might be related to the etiology of SDs. Cognitive functions decline with aging (Nilsson, 2003), especially memory, attention, and executive functions (Buckner, 2004). Among several neuropsychological tests, the Mini-Mental State Examination (MMSE) and the Frontal Assessment Battery (FAB) are useful screening tests for measuring general cognition including memory, attention, and executive functions in elderly people (Dubois, Slachevsky, Litvan, & Pillon, 2000; Folstein, Folstein, & McHugh, 1975). The Japanese version of the Neurobehavioral Cognitive Examination (J-COGNISTAT) is a brief but comprehensive test that can be used to assess multiple cognitive domains. J-COGNISTAT is a sensitive diagnostic tool for dementia (Matsuda & Nakatani, 2004). These tests are easy to administer and can be completed at the patient's bedside within a comparatively short period. These three neuropsychological tests have been established as a convenient means of screening patients and may be useful for the testing of our hypothesis.

The clarification of which neuropsychological functions are associated with symptomatic severity in patients with late-life SDs may be important for understanding their relation with aging. Therefore, the aim of the present cross-sectional study was to determine which cognitive functions are associated with disease severity in patients with late-life SDs using comparatively simple neuropsychological screening tests.

Methods

Participants

Fifty-three consecutive Japanese patients with undifferentiated SD, who were over 60 years of age and had been referred to the Jikei University Kashiwa Hospital outpatient clinic for psychiatry, were enrolled in this study. All the patients were recruited from a private general medicine practice, and the absence of any physical disease capable of explaining the somatic symptoms was confirmed. All the patients were diagnosed as having undifferentiated SD according to the DSM-IV-TR by an expert geriatric psychiatrist. Undifferentiated SD was operationalized according to whether the sufferer was unable to perform mundane activities of daily living (ADL). Focusing on undifferentiated SD seemed reasonable, since SD often appears initially as undifferentiated SD (Al-Lawati et al., 2000; Altamura et al., 1998). The exclusion criteria for the study were (1) the diagnosis of another significant axis I disorder (e.g., another anxiety-related disorder, major depressive disorder, substance abuse, somatization disorder, hypochondriasis, or pain disorder), (2) a history of major depression or other anxiety-related disorder during the last five years, (3) the presence of mild cognitive impairment (MCI) according to the diagnostic criteria for amnestic MCI (Petersen et al., 2001), (4) the presence of dementia or some other brain organic syndrome according to the DSM-IV-TR, (5) the presence of severe physical illness, or (6) the presence of psychiatric comorbidity. The present retrospective study was approved by the Ethics Committee of the Jikei University School of Medicine. Written informed consent was obtained from the patients or their designated representatives.

Psychological assessment

The severity of the somatic symptoms was assessed using the Hamilton Anxiety Scales (HAMA) (Hamilton, 1959). HAMA can be used as a scale for rating the severity of anxiety-related disorders. HAMA consists of two subscores: psychic anxiety (HAMA-PSY) (ranging from 0 to 28 points) and somatic anxiety (HAMA-SOM) (ranging from 0 to 28 points). HAMA-PSY consists of the following items: anxious mood, tension, fears, insomnia, intellectual retardation, and behavior at interview. HAMA-SOM consists of the following items: muscular symptoms, sensory symptoms, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, and autonomic symptoms (ranging from 0 to 4 points). HAMA and its subscores are reliable and valid for anxiety-related disorders (Maier, Buller, Philipp, & Heuser, 1988), and HAMA and HAMA-SOM have proven to be sensitive measures for evaluating the severity of SDs (Maier et al., 1988). Many previous studies have used HAMA to measure the severity of SDs (Müller, Mannel, Murck, & Rahlfs, 2004; Volz, Möller, Reimann, & Stoll, 2000; Volz, Murck, Kasper, & Möller, 2002), and we believe that HAMA is the most appropriate tool for measuring the severity of SDs.

Neuropsychological assessment

Mini-Mental State Examination (MMSE)

The MMSE is a well-known and widely used test for screening cognitive impairment. Possible scores range from 0 to 30. A score of 28 is the median for normal octogenarians with more than 12 years of education. Patients with an MMSE score < 24 were regarded as having dementia and were excluded from the present study.

Frontal Assessment Battery (FAB)

The FAB was recently introduced as a short screening test for exploring various functions of the frontal lobes and for evaluating executive functions (Dubois et al., 2000). The Japanese FAB version consists of six subtests: (1) similarities (conceptualization), (2) lexical fluency (mental flexibility), (3) motor series (programming), (4) conflicting instructions (sensitivity of interference), (5) go/no go (inhibition control), and (6) prehension behavior (environmental autonomy). Each subtest is rated from 0 to 3, with the total score ranging from 0 to 18.

Japanese version of the Neurobehavioral Cognitive Examination (J-COGNISTAT)

The J-COGNISTAT is a comprehensive cognitive test that consists of 10 subtests designed to convert raw scores for each subtest into age-matched standardized scores, which

are distributed with a mean of 10 and a standard deviation of 1. The cutoff point for each standardized score is set at between 8 and 9. If a subject's score is not more than 8, the score is considered to indicate an impaired level (Matsuda & Nakatani, 2004). The J-COGNISTAT can also be used as a screening tool for dementia that can be easily administered at the patient's bedside. However, the J-COGNISTAT can be used to evaluate multiple cognitive status profiles, which is useful for identifying how a certain domain has decreased in comparison with other domains. The validity of each domain of the J-COGNISTAT has been well examined (Matsuda & Saito, 2009). More intricate neuropsychological testing can impose a burden on patients with late-life SDs. Thus, we used the J-COGNISTAT to evaluate each cognitive domain relatively easily.

Assessment of other factors

Some previous studies have reported an increased risk of cognitive impairment in benzodiazepine users (Stewart, 2005). Thus, whether benzodiazepine dosage confounded the effect on cognitive functions was examined. Antidepressants also influence cognitive functions (Barch et al., 2012). The benzodiazepine and antidepressant dosage was based on the equivalent conversion table for psychometric drugs (Inagaki & Inada, 1999). In addition, we also evaluated the correlations between cognitive functions and other factors (onset age and duration of illness). As described previously, some studies have shown age-associated differences in the prevalence of SDs.

Statistical analysis

SPSS 19.0J for Windows (SPSS Japan Inc., Tokyo, Japan) was used for all the statistical analyses. To analyze the correlation between clinical parameters (HAMA score, HAMA-PSY score, and HAMA-SOM score) and cognitive parameters (MMSE total, subtest scores, FAB total, subtest scores, and J-COGNISTAT subtest scores), we performed a partial correlation analysis. The analyses were adjusted according to patient age and duration of education because some neuropsychological tests are strongly influenced by aging and education level. As an exploratory study was intended, the P-values were not initially corrected for multiple tests so that the data trends would be apparent. However, the Bonferroni-corrected P-value requirements (MMSE subtest scores: $P = 0.05/11 \fallingdotseq 0.005$; FAB subtest scores: $P = 0.05/6 \fallingdotseq 0.008$; and J-COGNISTAT subtest scores: $P = 0.05/10 = 0.005$) were reported and the effects of the correlations were noted. We also used a partial correlation analysis adjusted according to age and education level to evaluate the correlations between cognitive functions and other factors (benzodiazepine dosage, antidepressant dosage, onset age, and duration of illness).

Results

Patient characteristics

The demographic variables of the 53 late-life SD patients aged 60 years and older are summarized in Table 1.

Table 1. Subject characteristics of patients with late-life somatoform disorders.

	$n = 53$ (mean ± SD)
Sex (male/female)	9/44
Age	71.7 ± 7.2
Education (years)	12.1 ± 2.2
Duration of illness (years)	6.7 ± 6.4
Onset age	64.7 ± 8.6
HAMA total score	14.8 ± 7.2
HAMA-SOM score	8.0 ± 4.1
HAMA-PSY score	6.8 ± 4.0
MMSE total score	27.6 ± 2.0
FAB total score	16.0 ± 1.5

Note: HAMA (The Hamilton Anxiety Scale), HAMA-SOM (The Hamilton Anxiety Scale, somatic subscore), HAMA-PSY(The Hamilton Anxiety Scale, psychic subscore), MMSE (Mini-Mental State Examination), FAB (Frontal Assessment Battery)

Cognitive profiles according to J-COGNISTAT

Table 2 shows the cognitive profiles according to J-COGNISTAT. The mean J-COGNISTAT subtest score for attention was 6.2 (SD = 3.0), which was below the cutoff value (8 points). None of the other subtest scores were below the cutoff values (Table 2).

Correlations between cognitive functions and disease severity

The MMSE total score was not significantly correlated with disease severity (HAMA score and HAMA-SOM score). The MMSE subtest scores were also not significantly correlated with disease severity. The FAB total score was significantly correlated with disease severity (HAMA score: $P = 0.002$; and HAMA-SOM score: $P = 0.02$). The FAB subtest scores for similarities (HAMA score: $P < 0.001$; and HAMA-SOM score: $P < 0.001$) and motor series (HAMA score: $P = 0.003$) were also significantly correlated with severity (Table 3). The J-COGNISTAT subtest score for calculation was

Table 2. Cognitive profiles of patients with late-life somatoform disorders.

	J-COGNISTAT subscores (mean ± SD)
Orientation	9.6 ± 0.9
Attention*	**6.2 ± 3.0**
Comprehension	8.5 ± 1.9
Repetition	9.9 ± 1.3
Naming	9.8 ± 0.6
Constructive ability	8.1 ± 1.5
Memory	9.6 ± 0.7
Calculation	8.9 ± 1.4
Similarities	10.1 ± 0.8
Judgment	10.7 ± 1.1
	(average)

Note: J-COGNISTAT (The Japanese version of the neurobehavioral cognitive examination)
*Attention score was below the cutoff value of J-COGNISTAT (8 points).

Table 3. Partial correlations between FAB scores and HAMA scores.

	HAMA-SOM	HAMA total
FAB total score	−0.33*	−0.46*
Subtest		
Similarities	−0.53**	−0.55**
Lexical fluency	−0.05	−0.01
Motor series	−0.36	−0.46**
Conflicting instructions	−0.08	−0.13
Go/no go	0.13	0.26
Prehension behavior	–	–

*$p < 0.05$, **Bonferoni-corrected $p < 0.05/6 = 0.008$

significantly correlated with disease severity (HAMA score: $P = 0.001$) (Table 4) Other FAB subtest scores, MMSE total and subtest scores, and J-COGNISTAT subtest scores were not significantly correlated with the HAMA score.

Correlations between cognitive functions and other factors

No significant correlation between cognitive function (FAB total score, FAB similarities, FAB motor series score, and J-COGNISTAT calculation score) and benzodiazepine dosage was seen among the patients with undifferentiated SD. The antidepressant dosage also showed no correlation with cognitive functions (FAB total score, FAB similarities, FAB motor series score, and J-COGNISTAT calculation score). These cognitive functions were not correlated with either onset age or the duration of illness.

Discussion

Summary of findings

In the present study, we investigated the correlations between cognitive functions and symptomatic severities in patients with SDs who were over 60 years of age. We found a decrease in the 'attention' average score among the J-COGNISTAT subscales. The HAMA scores were negatively correlated with the FAB total score, the FAB subtest score (similarities, motor series), and the calculation score among the J-COGNISTAT subscales. However, no other neuropsychological scores were significantly correlated with the HAMA scores. Therefore, in the present study, the symptomatic severities of late-life SDs were associated with executive function as assessed using the FAB and calculation skill as assessed using the J-COGNISTAT. Moreover, cognition and symptomatic severity in late-life SDs were not significantly influenced by the dosages of psychotropic agents (e.g., benzodiazepine and antidepressants) or other factors.

Table 4. Partial correlations between J-COGNISTAT and HAMA scores.

	HAMA-SOM	HAMA total
Orientation	0.05	0.05
Attention	0.23	0.16
Comprehension	−0.11	−0.03
Repetition	−0.20	−0.22
Naming	−0.24	−0.16
Constructive ability	0.17	0.10
Memory	−0.16	−0.15
Calculation	−0.39	−0.46*
Similarities	−0.22	−0.22
Judgment	0.04	0.05

*Bonferoni-corrected $p < 0.05/10 = 0.005$

Comparison with previous studies

In previous studies investigating cognitive declines in patients with late-life anxiety disorders, significant reductions in episodic memory and attention function were reported (Beaudreau & O'Hara, 2008). In the present study, we also found a decrease in the attention score using the J-COGNISTAT subscales, but no reduction in episodic memory was observed. The reason for this difference between the two studies is thought to be that patients with dysfunctional episodic memory were excluded from our study, based on the presence of MCI or dementia. An attention decrement was confirmed in our patients, but the decrease was not correlated with disease severity. Several possibilities may explain this result. One possibility is that a deficit in attention may have existed in our patients prior to the somatic symptoms and may have triggered the somatic symptoms, rather than being a result of the somatic symptoms. Another possibility is that attention deficits in patients with late-life SDs may be a vicarious or compensative reaction of the awareness of bodily sensations as a defense mechanism (Lipowski, 1988).

Interpretation of results

Regarding the FAB subtest score, 'similarities' reflect executive functions that enable the establishment of an abstract link between items or adherence to concrete aspects of objects. Furthermore, 'the motor series' measures the capacity to execute a sequence of actions successively in separate tasks, resembling the 'first-palm-edge' task in Luria's motor series. Therefore, we hypothesized that such disabilities of conceptualizing or executing performances in patients with late-life SDs might reflect a distortion of self-monitoring or self-correcting for physical symptoms, which might be linked to the aggravation of convinced ideations related to anxiety or dysphoria in SD patients (Nagata et al., 2009). In patients with late-life SDs, the loss of self-correction in executive functions might influence their ability to access corrective information necessary for the modification of their irrational beliefs (Kashyap, Kumar, Kandavel, & Reddy, 2012). The J-COGNISTAT score for calculation was negatively correlated with the severity of late-life SDs patients. A poorer calculation performance is caused by a dysfunction of working memory, since the calculation skill in the J-COGNISTAT requires the patient to perform single-step calculations where instructions can be repeated at the patient's

request (Gupta & Kumar, 2009). The present study showed that the severity of late-life SDs was significantly correlated with executive functions and working memory. On the other hand, attention decline was not correlated with severity. This finding suggests that attention deficits in SD patients may be a trait marker of late-life SDs; thus, impairments in executive functions and working memory may be state markers of late-life SDs.

Implications for research

From the viewpoint of coping strategies, patients with SDs may adopt somatic complaints as a mode of coping with life's vicissitudes, psychological needs and conflicts, feelings of guilt and anger, and low self-esteem (Lipowski, 1988). In other words, poor coping strategies can lead to somatization. Hall, Kuzminskyte, Pedersen, Ørnbøl, and Fink (2011) reported that coping strategies are associated with attention, working memory, and executive functions. However, the present results partially differ from this previous report. These results suggest that working memory and executive functions may contribute to coping strategies, rather than attention, in patients with late-life SDs. Further study involving a large number of patients and detailed neuropsychological test batteries is needed to clarify this hypothesis.

Implications for practice

The reason why the other FAB subtest scores were not correlated with disease severity was thought to be due to the ceiling effect of the FAB. Patients with MCI or dementia were excluded from our sample in the present study, and the FAB is somewhat limited at examining the details of cognition. This reasoning is also thought to be applicable to the J-COGNISTAT subtests.

As described previously, the HAMA score consists of the HAMA-SOM score and the HAMA-PSY score. The HAMA total score is often used to measure the severity of SDs (Volz et al., 2000; Volz et al., 2002). Therefore, we mainly used the HAMA total score to examine the severity of the SDs. Additionally, we evaluated the HAMA-SOM score to ascertain whether it can be used as an indicator of the severity of SDs. As a result, the HAMA-SOM score almost resembled the HAMA total score. However, the HAMA total score and the HAMA-SOM score were somewhat different. The HAMA total score was correlated with the 'motor series' score among the FAB subtests and with the 'calculation' score among the J-COGNISTAT subtests. On the other hand, the correlation between the HAMA-SOM score and these subtests was not statistically significant, but an associative trend was seen (former, $P = 0.01$; latter, $P = 0.005$). Some possible reasons for this difference can be considered. First, the distribution of type-I errors should be examined. To clarify this problem, further study involving a large number of patients with late-life SDs is needed. However, the HAMA total score is generally used to measure the severity of SDs (Volz et al., 2000; Volz et al., 2002), and we believe that our results are valid.

Limitations

The present study had some limitations. First, the sample size was comparatively small. Thus, we defined a valid statistical value using the Bonferroni correction to examine the association between symptomatic severity and cognitive functions. Second, we did not use normal sample data and instead investigated the cognitive profiles of late-life SD patients according to the only standardized cognitive scale available, the J-COGNISTAT subscales. Third, many other neuropsychological test batteries for evaluating executive functions exist, and these test batteries might have provided useful information. However, the FAB is one of the easiest tests to administer and can be completed at bedside without requiring any tools or instruments. J-COGNISTAT is also easy and can be used with less burden to the patients. We believe that the simplicity of these tests makes them valuable tools. Finally, the HAMA is not a specific scale for SDs. The use of more specific scale for SDs would be preferable, although a standardized specific scale is not available. Furthermore, in some previous studies, the HAMA was used to measure the severity of SDs. Thus, we believe that the use of HAMA is valid.

Conclusion

In conclusion, to elucidate the pathogenesis or to investigate risk factors for late-life SDs, we focused on the correlation between symptomatic severity and cognitive function. We found that the cognitive profiles that influenced the appearance of symptoms and symptomatic severity differed. Therefore, a subgroup of patients with a poor prognosis may exist among patients with late-life SDs based on differences in pathogenesis and the appearance of symptoms. The further development of treatment strategies targeting prognostic subgroups, rather than SD itself, is needed in the future.

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Description of authors' roles

Keisuke Inamura designed this study, examined the subjects, and wrote the manuscript. Norifumi Tsuno, Kenji Tagai, Tomoyuki Nagata and Shunichiro Shinagawa gave advice, including suggestions regarding the analysis method, and reviewed this manuscript. Kazuhiko Nakayama reviewed and commented on the final manuscript.

References

Al-Lawati, J., Al-Lawati, N., Al-Siddiqui, M., Antony, S.X., Al-Naamani, A., Martin, R.G., ... Al-Adawi, S. (2000). Psychological morbidity in primary healthcare in Oman: A

preliminary study. *Journal for Scientific Research: Medical Sciences, 2*, 105–110.
Altamura, A.C., Carta, M.G., Tacchini, G., Musazzi, A., & Pioli, M.R. (1998). Prevalence of somatoform disorders in a psychiatric population: An Italian nationwide survey. Italian Collaborative Group on Somatoform Disorders. *European Archives of Psychiatry and Clinical Neuroscience, 248*, 267–271.
American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR* (4th edition, text revision). Washington, DC: American Psychiatric Association.
Barch, D.M., D'Angelo, G., Pieper, C., Wilkins, C.H., Welsh-Bohmer, K., Taylor, W., ... Sheline, Y.I. (2012). Cognitive improvement following treatment in late-life depression: Relationship to vascular risk and age of onset. *American Journal of Geriatric Psychiatry, 20*, 682–690.
Beaudreau, S.A., & O'Hara, R. (2008). Late-life anxiety and cognitive impairment: A review. *American Journal of Geriatric Psychiatry, 16*, 790–803.
Buckner, R.L. (2004). Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron, 44*, 195–208.
Dubois, B., Slachevsky, A., Litvan, I., & Pillon, B. (2000) The FAB: A Frontal Assessment Battery at bedside. *Neurology, 55*, 1621–1626.
Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975) 'Mini-mental state examination'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189–198.
Gupta, A., & Kumar, N.K. (2009). Indian adaptation of the Cognistat: Psychometric properties of a cognitive screening tool for patients of traumatic brain injury. *The Indian Journal of Neurotrauma, 6*, 123–132.
Hall, N.M., Kuzminskyte, R., Pedersen, A.D., Ørnbøl, E., & Fink, P. (2011). The relationship between cognitive functions, somatization and behavioural coping in patients with multiple functional somatic symptoms. *Nordic Journal of Psychiatry, 65*, 216–224.
Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Medical Psychology, 32*, 50–55.
Harwood, R.H., Prince, M.J., Mann, A.H., & Ebrahim, S. (1998). The prevalence of diagnoses, impairments, disabilities and handicaps in a population of elderly people living in a defined geographical area: The Gospel Oak project. *Age and ageing, 27*, 707–714.
Inagaki, A., & Inada, T. (1999). *Dose equivalence of psychometric drugs*. Tokyo: Seiwa Shoten. [In Japanese].
Kashyap, H., Kumar, J.K., Kandavel, T., & Reddy, Y.C. (2012). Neuropsychological correlates of insight in obsessive-compulsive disorder. *Acta Psychiatrica Scandinavica, 126*, 106–114.
Kuwabara, H., Otsuka, M., Shindo, M., Ono. S., Shioiri. T., & Someya T. (2007). Diagnostic classification and demographic features in 283 patients with somatoform disorder. *Psychiatry and Clinical Neurosciences, 61*, 283–289.
Lipowski, Z.J. (1988). Somatization: The concept and its clinical application. *American Journal of Psychiatry, 145*, 1358–1368.
Maier, W., Buller, R., Philipp, M., & Heuser, I. (1988). The Hamilton Anxiety Scale: Reliability, validity and sensitivity to change in anxiety and depressive disorders. *Journal of Affective Disorders, 14*, 61–68.
Matsuda, O., & Nakatani, N. (2004). *Manual for Japanese version of the Neurobehavioral Cognitive Status Examination (COGNISTAT)*. Tokyo: World Planning. [In Japanese].
Matsuda, O., & Saito, M. (2009). Multiple cognitive deficits in patients during the mild cognitive impairment stage of Alzheimer's disease: How are cognitive domains other than episodic memory impaired? *International Psychogeriatrics, 21*, 970–976.
Mayou, R., Bass, C., & Sharpe, M. (1995). Overview of epidemiology classification and aetiology. In R. Mayou, C. Bass, & M. Sharpe (Eds.), *Treatment of functional somatic symptoms* (pp. 42–65). Oxford: Oxford University Press.
Müller, T., Mannel, M., Murck, H., & Rahlfs, V.W. (2004). Treatment of somatoform disorders with St. John's wort: A randomized, double-blind and placebo-controlled trial. *Psychosomatic medicine, 66*, 538–554.
Nagata, T., Ishii, K., Ito, T., Aoki, K., Ehara, Y., Kada, H., ... Nakayama, K. (2009). Correlation between a reduction in Frontal Assessment Battery scores and delusional thoughts in patients with Alzheimer's disease. *Psychiatry and Clinical Neurosciences, 63*, 449–454.
Nilsson, L.G. (2003). Memory function in normal aging. *Acta Neurologica Scandinavica, 179*, 7–13.
Petersen, R.C., Doody, R., Kurz, A., Mohs, R.C., Morris, J.C., Rabins, P.V., ... Winblad, B. (2001) Current concepts in mild cognitive impairment. *Archives of Neurology, 58*, 1985–1992.
Salkovskis, P.M., & Warwick, H.M. (2001). Meaning, misinterpretations, and medicine: A cognitive behavioral approach to understanding health anxiety and hypochondriasis. In V. Starcevic, & D.R. Lipsitt (Eds.), *Hypochondriasis: Modern perspectives on an ancient malady* (pp. 202–222). Oxford: Oxford University Press.
Sheehan, B., Bass, C., Briggs, R., & Jacoby, R. (2003). Somatization among older primary care attenders. *Psychological Medicine, 33*, 867–877.
Stewart, S.A. (2005). The effects of benzodiazepines on cognition: Review. *Journal of Clinical Psychiatry, 66* (Suppl.), 9–13.
Volz, H.P., Möller, H.J., Reimann, I., & Stoll, K.D. (2000). Opipramol for the treatment of somatoform disorders results from a placebo-controlled trial. *European Neuropsychopharmacology, 10*, 211–217.
Volz, H.P., Murck, H., Kasper, S., & Möller, H.J. (2002). St John's wort extract (LI 160) in somatoform disorders: Results of a placebo-controlled trial. *Psychopharmacology (Berl), 164*, 294–300.

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Psychosis in Frontotemporal Dementia

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Abstract. Frontotemporal dementia (FTD) is a neurodegenerative disorder, associated with a progressive decline in behavior caused by focal degeneration of the frontal lobes. Psychosis was an underestimated symptom of FTD, however, recent genetic research has revealed a high prevalence of psychosis in certain genetic groups. The primary objective of this work is to review the literature on psychosis in FTD and to propose directions for future research, with reference to findings on psychosis in schizophrenia. A search was performed using PubMed, MEDLINE, and EMBASE. Search terms included "frontotemporal dementia", "psychosis", "schizophreni*", "psychotic symptoms", "hallucinations", and "delusions", and it identified 122 articles. Results revealed: 1) prevalence is approximately 10%, 2) TDP-43 type B and FUS pathologies might have relatively high frequency of psychosis, 3) psychosis in FTD is higher with genetic mutations of C9ORF72 and GRN, 4) imaging researches did not achieve conclusive results, and 5) no treatment for psychosis in FTD is currently available. A limitation of this systematic review is that it includes a small number of studies specifically examining psychosis in FTD. It is suggested that a possible overlap exists between FTD and schizophrenia. This potential overlap indicates a vulnerability to psychosis due to brain systems and pathways shared by these disorders.

Keywords: Frontotemporal dementia, gene mutation, neuropathology, psychosis, schizophrenia

INTRODUCTION

Frontotemporal dementia (FTD) is a neurodegenerative disorder, frequently associated with a progressive decline in behavior and language. The clinical syndromes are caused by focal degeneration of the frontal and anterior temporal lobes [1]. FTD is a common cause of early-onset dementia and has an incidence and prevalence similar to Alzheimer's disease (AD) [2]. FTD is likely an underestimated cause of dementia in both early and late-onset patients with dementia, due to a lack of general knowledge and a high rate of misdiagnosis [3].

Psychotic symptoms, such as delusions and hallucinations, are observed in dementing neurodegenerative diseases, especially in AD and dementia with Lewy bodies (DLB) [4]. Psychotic symptoms vary in type and intensity during the course of dementia and are associated with additional disability and a poorer quality of life, which, in turn, may lead to a greater burden on caregivers [5]. Physicians treating these disorders frequently encounter therapeutic difficulties in their management of these symptoms because

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antipsychotics or antidepressants may have limited efficacy or intolerance in patients with dementia [6]. Psychotic symptoms were originally thought to be a relatively rare symptom of FTD, in comparison to behavioral manifestations, such as disinhibition, stereotypic behavior, and inappropriate social behaviors. Mendez et al. reported that only 2.3% of subjects experienced delusions among 86 FTD subjects [7]. However, recent developments in genetic research have revealed a high prevalence of psychiatric symptoms in certain genetic groups, including patients with FTD who have a C9ORF72 mutation [8–11]. Moreover, considering that delusions and hallucinations are among the main symptoms of schizophrenia, recent research has considered possible associations between FTD and schizophrenia, including symptom similarity, familial co-morbidity, and genetic findings [12].

In this article, we review existing literature on psychotic symptoms in FTD, including clinical characteristics, genetic and neuroimaging findings, and treatments, while exploring the relationship between FTD and schizophrenia. Finally, based on this potential relationship, we propose future directions for research regarding the mechanisms underlying psychosis in FTD. The overlap between FTD and schizophrenia may provide a unique opportunity to explore psychosis irrespective of disease context.

METHOD

PubMed, MEDLINE, EMBASE and references from relevant studies, review articles, and books were searched using the terms "frontotemporal dementia", "psychosis", "schizophreni*", "psychotic symptoms", "hallucinations", and "delusions." Only publications written in English pertaining to psychosis in FTD were selected. The search yielded 122 articles, which formed the empirical basis of this review. The last search was conducted on Aug 12, 2013. Cross-referencing of the identified publications was also performed. The literature search was conducted independently by two of the authors (S.S. and S.N.). The results were screened for relevance, and the bibliographies of these articles were additionally screened.

RESULTS

Symptomatic studies on psychosis in FTD

Several early studies exploring the symptomatology of FTD have reported psychosis in patients with FTD before the establishment of consensus diagnostic criteria for FTD [13, 14]. After the establishment of consensus criteria for FTD by the Lund and Manchester Group in 1994 [15], and Neary et al. in 1998 [16], many studies have been conducted to compare clinical features and behavioral changes, including psychosis, between FTD and other forms of neurodegenerative dementias such as AD [17–21]. New research criteria for behavior variant FTD and the primary progressive aphasia (PPA) forms of FTD have simplified and helped to define patient cohorts likely to suffer from this disease [22, 23]. According to the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published in 2013, FTD is defined as frontotemporal neurocognitive disorders (NCD) [24]. Although the DSM criteria have not played much role in research until now, it may further facilitate studies on psychosis in FTD. Among these diagnostic criteria, the core symptoms are behavioral changes including disinhibition, apathy, loss of sympathy or empathy, stereotypic behavior, and hyperorality.

In general, the prevalence of psychotic symptoms was reported to be lower in patients with FTD than in those with AD (the estimated rate of delusions was 36% and hallucinations was 18%) [25]. Several reports failed to find psychosis among patients with FTD [26–28]. Other investigators reported relatively larger prevalence rates of delusions than hallucinations in patients with FTD [19, 29–32].

These symptomatic studies used different methodologies, including a multivariate stepwise discriminant analysis [18], original structured questionnaire [21], the Positive and Negative Syndrome Scale (PANSS) [33], and the Neuropsychiatric Inventory (NPI) [34–37]. While the NPI is a comprehensive behavioral assessment scale to compare neuropsychiatric symptoms of patients with dementia, the PANSS was originally designed for patients with schizophrenia, not psychosis in the setting of dementia. The details of these reports are summarized in Table 1.

There are several studies with larger cohorts. Omar et al. suggested that delusions were an early, prominent, and persistent feature, and that paranoid and somatic delusions were frequent. Bilateral or right-sided atrophy was found in most of the participants ($n = 56$) [32]. Mendez et al. evaluated 86 patients with FTD and reported that only 2.3% of them had delusions and none had hallucinations, which was significantly lower than patients with early onset AD ($n = 23$; delusion = 17.4% and hallucination = 4.3%) [38]. They also reviewed other reports and emphasized that psychotic symptoms were rare in FTD. They suggested that psychotic

Table 1
Delusions and hallucinations in patients with clinically diagnosed FTD

Author	n	Control	Measurement	Delusions	Hallucinations	
Lopez et al., [29]	20	AD ($n=40$)	DSM-III-R and others	20%	0%	
Levy et al., [35]	22	AD ($n=30$)	NPI	7%	0%	
Swartz et al., [18]	19	AD ($n=19$), late-life depression ($n=35$)	SCAN	Occasional (bizarre, jealous, somatic),	Rare (auditory)	
Hirono et al., [27]	24	AD ($n=240$), DLB ($n=23$)	NPI	0%	0%	
Gregory et al., [26]	15	–	CPRS	0%	0%	
Bozart et al., [19]	13	AD ($n=37$), tvFTD ($n=20$)	original questionnaire	15%	8%	
Bathgate et al., [21]	30	AD ($n=75$), CVD ($n=34$)	Informant-based behavioral questionnaire	Suspiciousness 30%, Delusions of theft 10%, False belief that people in home 10%, Misidentification phenomena 30%, Visual hallucinations/ illusions 8%, Auditory hallucinations/illusions 10%		
Boone et al., [33]	27	AD ($n=7$)	PANSS	No description about subscore, AD and FTD did not differ in positive symptom score		
Liu et al., [36]	51	Normal control ($n=20$), AD ($n=22$)	NPI	22%	13%	
Silveri et al., [119]	11	AD ($n=29$)	SPAS and NPI	Psychotic symptoms: SPAS 36% NPI 63%		
Mourik et al., [37]	63	–	NPI	12.7%	6.3%	
Engelborghs et al, [30]	29	AD ($n=205$), mixed dementia ($n=39$), DLB ($n=23$)	BEHAVE-AD	17.2%	6.9%	
Le Ber et al., [31]	68	–	detailed behavioral inventory (original)	5%	2%	
Mendez et al., [28]	74	–	psychiatric checklist (original)	Psychotic symptoms	2.7%	
Mendez et al., [7]	86	EOAD ($n=23$)	original questionnaire	2.3%	0%	
Omar et al., [32]	56	–	DSM-IV	14% (paranoid and somatic)	9%	2 cases have pathological confirmation
Lillo et al., [120]	43	FTD-ALS ($n=18$)	DSM-IV	19%	12%	

AD, Alzheimer's disease; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Scale; CPRS, Comprehensive Psychopathological Rating Scale; CVD, cerebrovascular dementia; DLB, dementia with Lewy bodies; DSM, Diagnostic and Statistical Manual of Mental Disorders; EOAD, early onset Alzheimer's disease; FTD-ALS, frontotemporal degeneration with amyotrophic lateral sclerosis; NPI, Neuropsychiatric Inventory; PANSS, Positive and Negative Syndrome Scale; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SPAS, Subsets of Survey Psychiatric Assessment Schedule; tvFTD, temporal variant frontotemporal dementia.

symptoms in patients with AD involved the temporal limbic area, a region which links perception to emotional states [38], while patients with FTD have relative sparing of this system, resulting in their difference in rate of psychotic symptoms [39]. Finally, Velakoulis et al. reviewed 199 studies and reported that the prevalence of psychosis was 6.5% in 751 patients with FTD [40]. Patients with FTD with psychosis were younger than those without psychosis at the age of onset and experienced a longer delay between onset of psychosis and their subsequent presentation of apparent cognitive decline. Taken together, the evidence indicates that the prevalence rate of psychosis in patients with FTD is lower than in patients with AD. Delusions are relatively more common than hallucinations in patients with FTD and younger age may be a risk factor for psychosis in FTD.

However, most of symptomatic studies shown in Table 1 examined neuropsychiatric symptoms in patients with FTD and thus, few studies specifically focused on psychosis [40]. In addition, the definition of psychosis differed among these studies and some did not provide a detailed definition of psychosis. Moreover, most of the studies diagnosed FTD and examined psychotic symptoms only based on clinical symptoms. Patients with FTD may have made false statements based on their delusions or confabulations. A delusion is a systematic fixed belief formation that is false but firmly held, in contrast, confabulations production of fabricated, misinterpreted memories which is more isolated, fleeting, and variable. A retrospective chart survey by Mendez et al. demonstrated that 8.3% of patients with FTD ($n=48$) made false reports about their own experience [41]. They found that patients with FTD might have both fantastic and wish-fulfilling confabulations, and typical content-specific delusions. Both phenomena may be a result of disturbances in the ventromedial prefrontal cortex, an area highly implicated in FTD. The disturbances in these brain areas may result in deficits of source monitoring and in activating an automatic tagging for false reports.

Furthermore, in patients with FTD, behavioral and personality changes are the most prominent symptoms and usually precede their cognitive disabilities. Clinical symptoms, such as disinhibition, inappropriate social behaviors, repetitive compulsion behaviors, and lack of insight are very heterogeneous. The heterogeneity of these clinical characteristics of FTD may lead clinicians to misdiagnose FTD, not only as psychiatric disorders, such as late-onset schizophrenia, atypical psychosis, and depression [42], but also as neurologic diseases, such as cerebrovascular disorders [3, 7, 28, 42]. One study at a specialized clinic for neurodegenerative diseases revealed that patients with FTD received a prior inaccurate psychiatric diagnosis more often than patients with AD (FTD, 50.7% versus AD, 23.1%; $p<0.001$) [3]. There is also a problem with referral. For example, in a nationwide study examining reasons for referral to geriatric psychiatric hospitals, patients with FTD who had paranoid syndromes (3% out of 75 FTD patients) were more likely to be hospitalized rather than referred to memory clinics [43]. Thus, the clinical report of psychotic symptoms in FTD may have been potentially influenced by 1) misdiagnoses due to subjective false reports and confabulations, or caregivers' misunderstandings, 2) misdiagnoses due to their behavioral symptoms, as well as 3) referral bias to memory clinic or psychiatric hospital.

Research studies based only on clinical symptoms alone have potential confounds related to misdiagnosis, and also have the potential to underrepresent patients in whom psychosis is the diseases' earliest manifestation. Given that biological confirmation of disease pathology has become increasingly developed, clinico-pathological studies are required to accurately diagnose FTD and to clarify the prevalence of psychotic symptoms.

Clinico-pathological reports on psychosis in FTD

Recent reports on the clinico-pathological features of patients suspected of suffering from FTD have revealed that FTD is associated with a variety of pathological conditions. In general, patients with FTD can be subdivided into the following three subcategories, which are based on the presence of specific pathologies: 1) tau, 2) transactive response DNA binding protein 43 kDa (TDP-43) and 3) Fused in Sarcoma (FUS) [44]. Even today, a small number of patients diagnosed with FTD do not show any of these FTD-related specific pathologies. In these cases, other co-existing neurodegenerative diseases, including AD and DLB, may become apparent with microscopy, particularly in older patients. Changes in the pathological classification of FTD syndromes are still in progress [44, 45].

There have been relatively few studies of psychosis in FTD where the cohort had pathological confirmation. These studies suggest several underlying histopathological backgrounds for psychosis in FTD. However, some of the early studies of FTD with psychosis did not employ immunostaining methods or the latest classification of pathological changes in these FTD syndromes. Furthermore, there is a possibility that

pathological classification will be changing from now on.

The tau pathology

The tau pathology includes Pick's disease, FTD with MAPT mutations (FTDP-17), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and argyrophilic grain disease. Several case reports noted that patients with FTD who presented with psychotic symptoms had the neuropathology of Pick's disease [46–48]. However, their ages at onset and clinical presentations differed. Cases with FTDP-17 will be described in a later section discussing genetics.

The TDP-43 pathology

Tartaglia et al. and Loy et al. reported that patients with FTD with psychosis had the neuropathology of TDP-43 [49, 50]. Later, Claassen et al. reported six patients with FTD presenting DLB-like visual hallucinations; two of them were diagnosed with the TDP-43 pathology [51]. Velakoulis et al. also reported that among 17 pathologically proven patients with early-onset FTD, 5 had presented with a psychotic illness (schizophrenia/schizoaffective disorder = 4, bipolar disorder = 1) an average of 5 years prior to the diagnosis of FTD. Further, these patients with schizophrenia exhibited neuropathological changes consistent with the TDP-43 pathology [40].

The FUS pathology

Urwin et al. reported that 36% of 34 patients with FTD with psychosis presented with the FUS pathology, a relatively high frequency [52].

Other reports

Rohrer et al. studied a pathologically ascertained cohort of 95 patients with FTD (51%, 44%, and 5% had the TDP-43, tau, and FUS pathology, respectively) [53]. They reported that delusions and hallucinations existed mostly among patients in the TDP-43 type A pathology group, one patient in the TDP-43 type B pathology group showed delusions, and one patient with Pick's pathology showed an alteration of visual perception.

By contrast, some clinico-pathological reports without genetic information found low frequencies of psychosis in patients with FTD. According to Passant et al. no delusions and hallucinations were found among 19 patients (corticobasal degeneration = 1, frontotemporal lobe degeneration = 16, and Pick's disease = 2) [42]. Liscic et al. also reported that 4 patients experienced delusions, but none presented with hallucinations among 48 patients with pathologically proven FTD (only FTD = 37, FTD + AD = 11) [54]. This study was limited in that the information utilized to classify patients' detailed neuropathologies, such as tau-positive or tau-negative, was insufficient, and the behavioral assessments employed were not focused on psychosis.

Mendez et al. examined the relationship between psychosis in FTD and pathologies among 107 patients with clinically diagnosed FTD [55]. Among them, 95 had definite pathological findings, including 23 tau-positive patients, 51 tau-negative patients, and 21 patients with the AD pathology; 17 patients studied presented with psychosis. They found that patients with the AD pathology were more likely to have psychosis than other pathologies (28% versus 15%) and speculated that patients with the AD pathology might be misdiagnosed with FTD if they have an early age at onset and prominent neuropsychiatric features. This study did not contain more detailed neuropathology-based classification (subtype of the tau-positive pathology or tau-negative pathology) and does not discuss genetic information.

As a whole, patients with FTD who have the TDP-43 type B pathology are more likely to show psychosis compared to those with other pathology subtypes. This is associated with linkage to genetic mutation of C9ORF72 described below. Patients with FTD who have FUS pathology may also likely show psychosis, although the underlying mechanisms still remain elusive. Further studies that include genetic information, along with structural and functional imaging information, will be required to elucidate the relationships with FTD.

Genetic reports on psychosis in FTD

Recent advances in genetic research have revealed that approximately 40% of patients with FTD have a positive family history of dementia, suggesting a strong genetic component contributing to FTD [56]. Genes recognized to play an important role in the autosomal dominant FTD include 1) MAPT, encoding the microtubule-associated protein tau, 2) GRN, encoding the protein progranulin, 3) C9ORF72, a recently identified hexanucleotide repeat expansion on chromosome 9 open reading frame 72 [57, 58], and 4) other minor mutations.

MAPT mutation

More than 40 mutations in the MAPT gene have been identified in families with FTD and parkinsonism

Table 2
Frequency of delusions and hallucinations in FTD cases with C9ORF72 mutations

Author	Subject	Control	Delusions	Hallucinations
Sha et al., [9]	FTD ($n=15$)	FTD non-carriers ($n=48$)	21%*	–
Snowden et al., [8]	FTD ($n=19$) PPA ($n=4$) FTD-MND ($n=9$)	non-carriers ($n=366$)	50%	19%
Mahoney et al., [10]	FTD ($n=12$) PPA ($n=1$) FTD-MND ($n=3$)	–	<12%	<12%
Hsiung et al., [75]	FTD ($n=15$) FTD-MND ($n=7$) ALS ($n=8$)	–	3%	0%
Boeve et al., [11]	FTD ($n=16$) FTD-MND ($n=3$) ALS ($n=1$)	–	45%	50%
Simon-Sánchez et al., 2012 [74]	FTD ($n=28$) PPA ($n=8$) FTD-MND ($n=6$)	–	0%	5%
Galimberti et al., [121]	FTD ($n=29$) PPA ($n=2$) FTD-MND ($n=8$)	non-carriers ($n=37$)	12%	15%
Le Ber et al., [122]	FTD, PPA, PSP/CBDS, FTD-ALS ($n=202$)	–	–	7%

*at the first observation. ALS, amyotrophic lateral sclerosis; C9ORF72, chromosome 9 open reading frame 72; FTD, frontotemporal degeneration; FTD-ALS, FTD with ALS; FTD-MND, FTD with motor neuron disease; PPA, primary progressive aphasia; PSP/CBDS, progressive supranuclear pulsy/corticobasal degeneration syndrome.

linked to chromosome 17q (FTDP-17), accounting for 10–15% of familial FTD subjects [58]. Some studies reported cases or families with the MAPT gene mutation at S356T presenting psychosis from a very early age and being subsequently diagnosed as FTD [48, 59]. This S356T mutation leads to atypical FTD-P pathology with more 3R tau and classical Pick bodies. Given that a few case studies addressed this gene mutation, it remains uncertain whether the type of MAPT mutation or the age at which this mutation is expressed is a determining factor in the presentation of psychosis.

GRN mutation

More than 60 mutations in the GRN gene on chromosome 17 have been identified, responsible for a relatively large proportion of patients with familial FTD. Patients with FTD with the GRN mutation account for approximately 5–10% of all patients with FTD, and approximately 20% of patients with familial FTD [60]. Their neuropathology is characterized by the tau-negative and TDP-43-positive linear nuclear inclusions. Several case and family reports suggested a relationship between GRN gene mutation and psychosis in patients with FTD [61, 62]. Le Ber et al. found GRN mutations in 10 out of 210 patients with FTD. They also identified that 30% of GRN mutations carriers had visual hallucinations, and 20% had delusions during the course of the disease [63]. Later, they analyzed 502 probands with FTD and related disorders, and found that 32 had a GRN mutation. Among them, visual hallucinations were found in 8 patients (25%) and delusions were found in 2 patients (6%). They suggested that hallucinations may help differentiate GRN mutation carriers from other FTD patients [64].

C9ORF72 mutation

C9ORF72 is considered to be one of the most frequent genetic causes of FTD, FTD with motor neuron disease (FTD-MND), and amyotrophic lateral sclerosis (ALS) [65, 66]. C9ORF72 mutations are pathologically associated with the deposition of the FTLD-TDP type B, although some patients have a pattern that looks more like FTLD-TDP type A [67]. Additionally, in these patients there are Tau, FUS, and TDP-43 negative but P62-positive aggregates in hippocampal, thalamic, and cerebellar regions. There are many clinico-pathological-genetic studies reporting that patients with FTD with C9ORF72 mutation have a high prevalence of psychotic features (hallucinations or delusions) up to 50%, as well as other neuropsychiatric features, such as depression or anxiety, suggesting that these symptoms could be markers of this mutation [8, 9, 11].

Table 2 summarizes reports on the frequency of delusions and hallucinations in patients with C9ORF72 mutations, including FTD. This table includes studies on FTD, primary progressive aphasia (PPA), FTD-MND, and ALS. Studies only investigating FTD-MND and ALS were excluded. Among the included studies, delusions and hallucinations were reported in 0% to 50% of the patients with C9ORF72 mutations.

Prominent psychotic symptoms were observed in carriers with C9ORF72 expansion as early manifestations. Snowden et al. found that psychotic symptoms were found more frequently in carriers (38%) than in non-carriers (<4%), which led to initial diagnoses of delusional psychosis, somatoform psychosis, or paranoid schizophrenia of mutation groups [8]. The delusions were somatic and alterations in temperature perception, preoccupation with bowel movements, and leg pain contributed to the delusional disorder, although there is still discussion whether we can define these changes in perception as delusions. Sha et al. compared clinical symptoms between C9ORF72 mutation carriers and non-carriers and reported delusions were more frequently reported as the initial neuropsychiatric symptoms in the carriers (21%) than the non-carriers (0%) [9]. Contrary to the findings of

Snowden et al., delusions were of the paranoid type and included delusions of jealousy; somatic delusions were not observed. Interestingly, significant differences in delusions between carriers and non-carriers disappeared when using the NPI at evaluation, suggesting that delusions could be attributed to C9ORF72 mutations when they were reported as the first symptom. Hallucinations were not reported as initial neuropsychiatric symptoms in C9ORF72-associated disease, and were also uncommon at evaluation.

Moreover, there are several case reports describing the relationship between C9ORF72 mutation and psychosis, including clinico-pathological studies [67], imaging studies [68], and kindred reports [69]. Furthermore, some case reports suggested that psychosis may precede the development of dementia, indicating that psychosis may potentially be prodromal or an early symptom of FTD with C9ORF72 mutation [70]. Within these case reports, subjects in whom psychosis preceded dementia included three atypical psychiatric patients [71], one patient with delusions of pregnancy [72], and one patient with bipolar affective disorder [73].

By contrast, some other studies suggested a lower prevalence rate of psychosis in carriers with the C9ORF72 mutation. For example, Simón-Sanchez et al. found that only two out of 42 mutation carriers presented with hallucinations and none had delusions [74]. Mahoney et al. reported that the prevalence of psychotic symptoms was approximately 10% in patients with C9ORF72 mutation [10]. In this study, delusions were late manifestations in mutation carriers. Delusions were not observed in the initial assessment, whereas hallucinations were reported in about one-half of patients at the initial assessment. Hsiung et al. reported one FTD mutation carrier out of 30 that presented with delusions, who was initially diagnosed with psychosis/schizophrenia [75]. The wide-variety in the results coming from these studies may suggest different ways to detect and code the delusions and hallucinations, different timing of appearance of the symptoms during the illness, and variety of the persistence of symptoms.

Other mutations related to psychosis in FTD

Several other genetic mutations were also reported. Mosca et al. described a proband of the transactive response DNA-binding protein (TARDBP) mutation carriers that developed hallucinations [76]. Tang-Wai et al. identified a presenilin 1 (PSEN1) gene mutation in one allele in a kindred consisting of three FTD cases presenting with delusions and illusions [77]. Gourzis et al. found a genetic defect on chromosome 1 (46, XX, 1qh-) in a patient with early-onset FTD who had been misdiagnosed with schizophrenia [78].

As a whole, C9ORF92 mutation, which is related to the TDP-43 type B pathology, may be the most common genetic factor in patients with FTD presenting psychosis. GRN mutation, which is related to the TDP-43 type A pathology, may be the second most common. However, some additional factors, such as anatomical distinctions, within these specific genetic groups may have contributed to the development of psychosis.

Neuroimaging studies on psychosis in FTD

Several neuroimaging studies have investigated patients with C9ORF72; this mutation is reported to be associated with a high frequency of psychosis in FTD. These studies emphasized thalamic and cerebellar atrophy in mutation carriers [9, 10, 79]. Thalamic and cerebellar projections could be related to the psychosis associated with the C9ORF72 mutation although further research is warranted [10, 45].

Chan et al. examined relationships between predominant right temporal lobe atrophy (RTLA) and clinical profiles in patients with FTD. They found that predominant RTLA (i.e., mean volume reduction of 41% and 51% in the right hippocampus and amygdala, respectively) is associated with a higher rate of visual hallucinations (10%) in patients with FTD compared to those with semantic dementia (left dominant atrophy patients) (0%) [80]. These results suggest a relationship between right temporal damage and the presence of psychotic symptoms.

Some of the recent studies addressed the condition FTD phenocopy syndrome [81], which has similar behavioral disturbances to "real FTD" but shows normal structural and functional neuroimaging findings, and a slow progression over many years [82, 83]. However, the relationship between these phenocopy groups and psychosis are still uncertain.

Altogether, there is still a lack of clear evidence regarding anatomical correlation of psychosis using neuroimaging methods.

Treatment for psychosis in FTD

To date, there is no specific disease modifying treatment or preventative treatment for FTD. Medications for AD and psychiatric disorders are frequently used as off-label treatments for FTD [84]. Current pharmacological studies on FTD mainly focus on treating behavioral symptoms, such as compulsions, repetitive

behaviors, stereotypical movements, eating abnormalities, and apathy, using various kinds of psychotropics, including acetylcholinesterase inhibitors, antidepressants, atypical antipsychotics, and NMDA glutamate receptor antagonists [85, 86]. No systematic studies confirmed that they are effective for psychosis in patients with FTD, only several case studies exist to date. There are two case reports of patients with FTD with Cotard's syndrome, which had not responded to pharmacotherapy but were subsequently improved by electroconvulsive therapy [87, 88]. While several open label studies examined the effects of alternative medicines on delusions and hallucinations in FTD [89, 90], the sample size is too small and further research is warranted.

Atypical antipsychotics are still widely used for behavioral symptoms of patients with FTD, however, there are no large scale systematic studies about the effectiveness of these drugs. Adverse effects often limit the use of these drugs for FTD, and the decision to use them should be made with caution. An important concern is the increased susceptibility to extrapyramidal symptoms induced by antipsychotics in patients with FTD [91]. Age and long-term antipsychotic exposure are risk factors for development of treatment-resistant tardive dyskinesia [92–94]. Additionally, a meta-analysis of randomized, placebo-controlled trials suggested that antipsychotic treatment of elderly patients with dementia is associated with a 1.6- to 1.7-fold increase in mortality secondary to cardiac events or infection, which in turn prompted the Food and Drug Administration to place a 'black-box warning' on their use. Thus, given the absence of treatment for psychosis in FTD, further research is needed to elucidate the mechanisms underlying psychosis in FTD in order to develop new therapeutic options for this symptom.

DISCUSSION

Relationships between FTD and schizophrenia

In summary, we have described the following: 1) psychosis is a clinically relevant symptom accompanying FTD, with a prevalence rate of approximately 10–15%; 2) psychosis in FTD may be related to genetic mutations of C9ORF72 and GRN; 3) neuroimaging studies did not achieve conclusive results; and 4) no treatment is currently available for psychosis in FTD.

Psychotic symptoms are seen in multiple different neurodegenerative and neuropsychiatric disorders, including AD, DLB, epilepsy, schizophrenia, and bipolar disorder. A similar pathophysiology for susceptibility to psychosis may exist in these various illnesses. Taking into consideration that psychosis is among the most frequent symptoms in schizophrenia, the potential link between FTD and schizophrenia should be further investigated in order to elucidate the mechanisms underlying psychosis in FTD. Current reports regarding the relationship between FTD and schizophrenia identify potential overlaps in clinical presentation, neuroimaging, neuropsychology, and genetics, while significant differences are found with regard to pathology [12, 95].

First, typical behavioral symptoms in FTD, such as inappropriate social behaviors and repetitive compulsion-like behaviors, symptomatically resemble to confusion and disorganization seen in patients with schizophrenia. Similarly, apathy and deficits in emotional expression in FTD resemble affective flattening and lack of motivation in schizophrenia. Also, it is reported that nearly half of FTD patients with mutations in C9ORF72 experience delusions or hallucinations [8, 11]. Second, neuroimaging research on schizophrenia demonstrates structural and functional alterations in frontal and temporal lobes when compared to healthy controls. Previous studies employing structural MRI report volume reductions in frontal, temporal, limbic, striatal, and thalamic regions in patients with schizophrenia [96]. A meta-analysis of 18 first episode schizophrenia studies (555 patients and 621 control subjects) and 20 studies of FTD (311 patients and 431 control subjects) reveals a spatial overlap of structural brain changes. Both disorders share gray matter deficits in the bilateral caudate, left insula, and bilateral uncus regions [97], although the degree of atrophy differs between symptomatic FTD and schizophrenia. Functional brain imaging in schizophrenia shows altered function and impaired functional connections in frontal and temporal regions [98], similar to what has been found in FTD. Third, neuropsychological data shows poor frontal-executive function in patients with schizophrenia, as demonstrated through tests of set-shifting abilities or selective attention [99]; this impairment is typical of FTD. Finally, certain genetic reports suggest that relatives of probands with GRN or VCP mutations who present with FTD may have a high family history frequency of schizophrenia [62, 100]. Schoder et al. report that the morbid risk for schizophrenia is significantly higher in relatives of probands with FTD (1.35) than in relatives of probands with AD (0.32). Some questions regarding this finding arise due to the fact that the rate of schizophrenia in this genetic group is only 1.1%, which is comparable to the general population. It is also

unclear whether the individuals with these mutations will continue to have typical FTD-like presentations. Huey et al. studied samples of 192 unrelated subjects with schizophrenia to assess the presence of C9ORF72 mutation. None of the subjects with schizophrenia had the pathogenic expansion [101]. It remains elusive whether schizophrenia should be viewed as related to these mutations. The available literature suggests that a link between FTD and schizophrenia may exist although more studies are needed [102].

This link between FTD and schizophrenia is indicative of potential vulnerability to psychosis in brain systems and pathways shared by both disorders. For example, dysfunction in frontal-subcortical circuits has been implicated in the loss of executive behavioral control in both groups of patients. This dysfunction may lead to alterations in affective state, disinhibition, and specific manners of thinking, such as a tendency to jump to conclusions, which may increase the risk of formation of psychosis in both diseases [103, 104]. Further, thalamic dysfunction may also result in a reduced ability to adjust one's sensory responsiveness to ongoing behaviors in patients with schizophrenia [105]. Psychosis is associated with source-monitoring deficits whereby self-initiated behaviors become attributed to outside sources. A function of the thalamus is to adjust sensory responsiveness in accordance with behavioral contextual cues. Thus, the vulnerability potentially shared by FTD and schizophrenia, including the dysfunction in the frontal cortex and thalamus, may clinically represent psychosis in both types of patients.

Further research

Based on the limitations of previous studies, further research on psychosis in patients with FTD needs to be conducted in larger cohorts with biologically confirmed disease pathologies using clear and standardized definitions of psychosis. Focusing on a specific target potentially related to psychosis, structural and functional neuroimaging studies should compare patients with or without psychosis. Longitudinal follow-up studies from the early stage before the onset of dementia are also required as psychosis often precedes cognitive decline in patients with FTD.

Also, based on the potential linkage between FTD and schizophrenia, future research that references current findings on psychosis in schizophrenia should help to elucidate the mechanisms underlying psychosis in FTD. For example, on the neurotransmitter level, positron emission tomography studies have shown that dopamine synthesis capacity, dopamine release, and baseline dopamine levels are elevated in the striatum in patients with schizophrenia [106]. Similar studies have not been performed in FTD. In addition, increased glutamate signaling in the striatum has been reported in subjects at ultra-high risk for psychosis and in those with first-episode psychosis using magnetic resonance spectroscopy [107]. These increases in dopamine and glutamate in the striatum have been linked to positive symptoms, such as hallucinations and delusions in schizophrenia. Patients with FTD generally show presynaptic deficiencies in striatal dopamine neurotransmitter systems [108, 109], while no consistent finding is reported on the relationship between glutamate and psychosis in FTD. However, only a few studies have examined the relationship between dopaminergic or glutamatergic systems and psychosis in FTD. For example, Engelborghs et al. examined the relationship between cerebrospinal fluid (CSF) levels of dopamine metabolites (DOPAC and HVA) and neuropsychiatric symptoms in patients with FTD ($n = 25$) [110]. They found that CSF DOPAC levels correlated with neuropsychiatric symptoms. Vermeiren et al. examined the relationship between CSF levels of glutamate and neuropsychiatric symptoms in patients with FTD ($n = 32$) [111]. They demonstrated that CSF levels of glutamate negatively correlated with verbally agitated behavior in patients with FTD. These findings suggest that abnormal dopaminergic or glutamatergic neurotransmission may be associated with neuropsychiatric symptoms in FTD. However, no study has specifically focused on the relationship between psychosis in FTD and these neurotransmitter systems.

Thus, further research is required to elucidate the mechanisms underlying psychosis in FTD, with a focus on the systems to which psychosis in schizophrenia is attributed.

Limitations

This review has to be considered in light of the limitations within the literature in addition to the aforementioned limitations in each section. First, research techniques such as neuroimaging, immunostaining, and genetics, were recently developed. Thus, the clinical and pathological concept of FTD continues to change, altering the diagnosis and classification of FTD. Ultimately, this has resulted in various groups employing differing methods to diagnose and classify FTD. Further, few studies specifically addressed psychosis in patients with FTD and the definition of psychosis differed across them. Symptoms comprising

psychosis in FTD may be different among individuals as well as genetic groups. Second, with regard to the genetic roles, East-Asian patients with FTD are known to have fewer family histories [112, 113], and no C9ORF72 mutations cases were found in 75 Japanese subjects with FTD, PSP, and CBD and 75 Korean subjects with FTD [114, 115]. Thus, genetic background may have different roles in the presentation of psychosis between Western and East-Asian patients with FTD. This may be one explanation why symptomatic studies in Asia failed to find psychosis among patients with FTD [27]. Further studies are needed on psychosis in patients with FTD between different ethnic groups.

Third, the sample sizes of most of the references are relatively small. Also, many studies relied on retrospective review of clinical records, and thus, information bias issues should be considered. Fourth, despite the presence of a potential overlap in FTD and schizophrenia in terms of neuropsychology and neuroimaging, significant differences are found between them with regard to pathology [12, 95]. FTD is a neurodegenerative disorder and the degree of neuronal loss is clearly different in FTD from that in schizophrenia, as there is little evidence of large scale neuronal loss in the latter [116]. In addition, this overlap should be explored with caution given that schizophrenia is a syndrome presenting psychosis and FTD presents psychosis as a symptom with a relatively low prevalence.

Moreover, evidence of cognitive decline and the development of dementia in patients with schizophrenia is still unclear, although cognitive impairment is shared by both disorders. The majority of studies on cognition and schizophrenia are uncontrolled. Patients with schizophrenia have many confounding dementia risk factors, including lifestyle, diet, smoking, antipsychotic use, and alcohol and substance abuse [117]. While controversial, it is suggested that patients with schizophrenia do not experience acceleration in cognitive aging [118], rather schizophrenia appears to be a disorder marked by generalized cognitive dysfunction. Finally, frontal areas are influenced in other neuropsychiatric and neurodegenerative diseases. This suggests that the frontal involvement in aforementioned findings, implicated in psychosis, may not be specific to FTD and schizophrenia.

CONCLUSION

Important advances in research exploring the genetics and molecular mechanisms of FTD over the last decades have led to changes in the concept of FTD. As such, the recognition and diagnosis of this disease has increased. Also, recent advances in understanding the genetic mechanisms of FTD reveal that FTD patients with specific genetic background, such as C9ORF72 mutation, have a higher frequency of psychosis than do patients with other mutations. In addition to the frontal dysfunction common in patients with FTD, additional factors in this genetic group may contribute to the development of psychosis.

Psychosis is a common symptom in several neurodegenerative and neuropsychiatric diseases, including FTD and schizophrenia, which may have common vulnerability and endophenotypic mechanisms. These genetic cases that are linked to FTD can be instrumental in clarifying the mechanism of psychosis beyond FTD and may offer principles for understanding the biological correlates of psychosis.

Additionally, psychosis in patients with FTD contributes to worse clinical outcomes, social dysfunction, poorer quality of life, and greater caregivers' burden. Given that no treatment is currently available for psychosis in FTD, there is an urgent need to identify new therapeutic strategies that target these symptoms. Interventions aimed at specific targets shared by FTD and schizophrenia may be effective for the treatment of psychosis in both disorders. Still, no decisive conclusions have been made regarding the biological mechanism of psychosis in FTD. Further research is warranted to elucidate this mechanism, with reference to findings pertaining to psychosis in schizophrenia.

DISCLOSURE STATEMENT

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REFERENCES

[1] Shinagawa S (2013) Phenotypic variety in the presentation of frontotemporal lobar degeneration. *Int Rev Psychiatry* **25**, 138-144.

[2] Ratnavalli E, Brayne C, Dawson K, Hodges JR (2002) The prevalence of frontotemporal dementia. *Neurology* **58**, 1615-1621.

[3] Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP (2011) The diagnostic challenge of psychiatric symptoms in neurodegenerative disease. *J Clin Psychiatry* **72**, 126-133.

[4] Bhat R, Rockwood K (2011) Psychiatric complications of dementia. *Can J Psychiatry* **56**, 398-407.

[5] Matsumoto N, Ikeda M, Fukuhara R, Shinagawa S, Ishikawa T, Mori T, Toyota Y, Matsumoto T, Adachi H, Hirono N, Tanabe H (2007) Caregiver burden associated with behavioral and psychological symptoms of dementia in elderly people in the local community. *Dement Geriatr Cogn Disord* **23**, 219-224.

[6] Ihl R, Frölich L, Winblad B, Schneider L, Burns A, Möller H-J (2011) World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the biological treatment of Alzheimer's disease and other dementias. *World J Biol Psychiatry* **12**, 2-32.

[7] Mendez MF, Shapira J, Woods RJ, Licht EA, Saul RE (2008) Psychotic symptoms in frontotemporal dementia: Prevalence and review. *Dement Geriatr Cogn Disord* **25**, 206-211.

[8] Snowden J, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, Jones M, Gerhard A, Davidson YS, Robinson A, Gibbons L, Hu Q, DuPlessis D, Neary D, Mann DM, Pickering-Brown SM (2012) Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. *Brain* **135**, 693-708.

[9] Sha SJ, Takada LT, Rankin KP, Yokoyama JS, Rutherford NJ, Fong JC, Khan BK, Karydas A, Baker MC, DeJesus-Hernandez M, Pribadi M, Coppola G, Geschwind DH, Rademakers R, Lee SE, Seeley WW, Miller BL, Boxer AL (2012) Frontotemporal dementia due to C9ORF72 mutations: Clinical and imaging features. *Neurology* **79**, 1002-1011.

[10] Mahoney CJ, Beck J, Rohrer JD, Lashley T, Mok K, Shakespeare T, Yeatman T, Warrington EK, Schott JM, Fox NC, Rossor MN, Hardy J, Collinge J, Revesz T, Mead S, Warren JD (2012) Frontotemporal dementia with the C9ORF72 hexanucleotide repeat expansion: Clinical, neuroanatomical and neuropathological features. *Brain* **135**, 736-750.

[11] Boeve BF, Boylan KB, Graff-Radford NR, DeJesus-Hernandez M, Knopman DS, Pedraza O, Vemuri P, Jones D, Lowe V, Murray ME, Dickson DW, Josephs KA, Rush BK, Machulda MM, Fields JA, Ferman TJ, Baker MC, Rutherford NJ, Adamson J, Wszolek ZK, Adeli A, Savica R, Boot B, Kuntz KM, Gavrilova R, Reeves A, Whitwell JL, Kantarci K, Jack CR, Parisi JE, Lucas JA, Petersen RC, Rademakers R (2012) Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. *Brain* **135**, 765-783.

[12] Harciarek M, Malaspina D, Sun T, Goldberg E (2013) Schizophrenia and frontotemporal dementia: Shared causation? *Int Rev Psychiatry* **25**, 168-177.

[13] Miller BL, Cummings JL, Villanueva-Meyer J, Boone KB, Mehringer CM, Lesser IM, Mena I (1991) Frontal lobe degeneration: Clinical, neuropsychological, and SPECT characteristics. *Neurology* **41**, 1374-1382.

[14] Miller BL, Chang L, Mena I, Boone KB, Lesser IM (1993) Progressive right frontotemporal degeneration: Clinical, neuropsychological and SPECT characteristics. *Dementia* **4**, 204-213.

[15] The Lund, Manchester Group (1994) Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *J Neurol Neurosurg Psychiatry* **57**, 416-418.

[16] Neary D, Snowden J, Gustafson L, Passant U, Stuss D, Black SE, Freedman M, Kertesz A, Robert PH, Albert M, Boone KB, Miller BL, Cummings JL, Benson DF (1998) Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. *Neurology* **51**, 1546-1554.

[17] Gregory CA, Hodges JR (1996) Clinical features of frontal lobe dementia in comparison to Alzheimer's disease. *J Neural Transm Suppl* **47**, 103-123.

[18] Swartz JR, Miller BL, Lesser IM, Booth R, Darby A, Wohl M, Benson DF (1997) Behavioral phenomenology in Alzheimer's disease, frontotemporal dementia, and late-life depression: A retrospective analysis. *J Geriatr Psychiatry Neurol* **10**, 67-74.

[19] Bozeat S, Gregory CA, Ralph MAL, Hodges JR (2000) Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry* **69**, 178-186.

[20] Snowden J, Bathgate D, Varma A, Blackshaw A, Gibbons ZC, Neary D (2001) Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *J Neurol Neurosurg Psychiatry* **70**, 323-332.

[21] Bathgate D, Snowden J, Varma A, Blackshaw A, Neary D (2001) Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurol Scand* **103**, 367-378.

[22] Rascovsky K, Hodges JR, Knopman DS, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EGP, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini M-LL, Rosen HJ, Prioleau-Latham CEC, Lee AA, Kipps CM, Lillo PP, Piguet OO, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt V, Lebert FF, Pijnenburg YA, Chow TW, Manes F, Grafman JJ, Cappa SF, Freedman M, Grossman M, Miller BL (2011) Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* **134**, 2456-2477.

[23] Gorno-Tempini M-LL, Hillis AE, Weintraub S, Kertesz A, Mendez MF, Cappa SF, Ogar JM, Rohrer JD, Black SE, Boeve BF, Manes F, Dronkers NF, Vandenberghe R, Rascovsky K, Patterson K, Miller BL, Knopman DS, Hodges JR, Mesulam M, Grossman M (2011) Classification of primary progressive aphasia and its variants. *Neurology* **76**, 1006-1014.

[24] American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, American Psychiatric Publishing, Washington, DC.

[25] Ropacki SA, Jeste DV (2005) Epidemiology of and risk factors for psychosis of Alzheimer's disease: A review of 55 studies published from 1990 to 2003. *Am J Psychiatry* **162**, 2022-2030.

[26] Gregory CA (1999) Frontal variant of frontotemporal dementia: A cross-sectional and longitudinal study of neuropsychiatric features. *Psychol Med* **29**, 1205-1217.

[27] Hirono N, Mori E, Tanimukai S, Kazui H, Hashimoto M, Hanihara T, Imamura T (1999) Distinctive neurobehavioral features among neurodegenerative dementias. *J Neuropsychiatry Clin Neurosci* **11**, 498-503.

[28] Mendez MF (2006) Functional neuroimaging and presenting psychiatric features in frontotemporal dementia. *J Neurol Neurosurg Psychiatry* **77**, 4-7.

[29] Lopez OL, Gonzalez MP, Becker JT, Charles R, Sudilovsky A, DeKosky ST (1996) Symptoms of depression and psychosis in Alzheimer's disease and frontotemporal dementia. *Neuropsychiatry Neuropsychol Behav Neurol* **9**, 154-161.

[30] Engelborghs SS, Maertens K, Nagels G, Vloeberghs E, Mariën P, Symons A, Ketels V, Estercam S, Somers N, De Deyn P (2005) Neuropsychiatric symptoms of dementia: Cross-sectional analysis from a prospective, longitudinal Belgian study. *Int J Geriatr Psychiatry* **20**, 1028-1037.

[31] Le Ber I, Guedj E, Gabelle A, Verpillat P, Volteau M, Thomas-Antérion C, Decousus M, Hannequin D, Véra P, Lacomblez L, Camuzat A, Didic M, Puel M, Lotterie J-A, Golfier V, Bernard A-M, Vercelletto M, Magne C, Sellal

F, Namer I, Michel B-F, Pasquier J, Salachas F, Bochet J, French Research Network on FTD, FTD-MND, Brice A, Habert M-O, Dubois B (2006) Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia. *Brain* **129**, 3051-3065.

[32] Omar R, Sampson EL, Loy CT, Mummery CJ, Fox NC, Rossor MN, Warren JD (2009) Delusions in frontotemporal lobar degeneration. *J Neurol* **256**, 600-607.

[33] Boone KB, Miller BL, Swartz RR, Lu PP, Lee AA (2003) Relationship between positive and negative symptoms and neuropsychological scores in frontotemporal dementia and Alzheimer's disease. *J Int Neuropsychol Soc* **9**, 698-709.

[34] Cummings JL, Mega MS, Gray KK, Rosenberg-Thompson SS, Carusi DAD, Gornbein JJ (1994) The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology* **44**, 2308-2314.

[35] Levy ML, Miller BL, Cummings JL, Fairbanks LA, Craig AA (1996) Alzheimer disease and frontotemporal dementias. Behavioral distinctions. *Arch Neurol* **53**, 687-690.

[36] Liu W, Miller BL, Kramer JH, Rankin KP, Wyss-Coray C, Gearhart R, Phengrasamy L, Weiner M, Rosen HJ (2004) Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. *Neurology* **62**, 742-748.

[37] Mourik JC, Rosso SM, Niermeijer MF, Duivenvoorden HJ, van Swieten JC, Tibben A (2004) Frontotemporal dementia: Behavioral symptoms and caregiver distress. *Dement Geriatr Cogn Disord* **18**, 299-306.

[38] Mendez MF, Lauterbach ECE, Sampson SMS (2008) An evidence-based review of the psychopathology of frontotemporal dementia: A report of the ANPA Committee on Research. *J Neuropsychiatry Clin Neurosci* **20**, 130-149.

[39] Rosen HJ, Gorno-Tempini M-LL, Goldman WP, Perry RJ, Schuff N, Weiner M, Feiwell RR, Kramer JH, Miller BL (2002) Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology* **58**, 198-208.

[40] Velakoulis D, Walterfang M, Mocellin R, Pantelis C, McLean C (2009) Frontotemporal dementia presenting as schizophrenia-like psychosis in young people: Clinicopathological series and review of cases. *Br J Psychiatry* **194**, 298-305.

[41] Mendez MF, Fras IAI, Kremen SA, Tsai P-H (2011) False reports from patients with frontotemporal dementia: Delusions or confabulations? *Behav Neurol* **24**, 237-244.

[42] Passant U, Elfgren C, Englund E, Gustafson L (2005) Psychiatric symptoms and their psychosocial consequences in frontotemporal dementia. *Alzheimer Dis Assoc Disord* **19**(Suppl 1), S15-S18.

[43] Ibach B, Poljansky S, Barta W, Koller M, Wittmann M, Hajak G (2004) Patterns of referring of patients with frontotemporal lobar degeneration to psychiatric in- and out-patient services. *Dement Geriatr Cogn Disord* **17**, 269-273.

[44] Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, Kovacs GG, Ghetti B, Halliday GM, Holm IE, Ince PG, Kamphorst W, Revesz T, Rozemuller AJM, Kumar-Singh S, Akiyama H, Baborie A, Spina S, Dickson DW, Trojanowski JQ, Mann DMA (2010) Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: An update. *Acta Neuropathol* **119**, 1-4.

[45] Mackenzie IR, Neumann M, Baborie A, Sampathu DM, Plessis Du D, Jaros E, Perry RH, Trojanowski JQ, Mann DMA, Lee VMY (2011) A harmonized classification system for FTLD-TDP pathology. *Acta Neuropathol* **122**, 111-113.

[46] Waddington JL, Youssef HA, Farrell MA, Toland J (1995) Initial 'schizophrenia-like' psychosis in Pick's disease: Case study with neuroimaging and neuropathology, and implications for frontotemporal dysfunction in schizophrenia. *Schizophr Res* **18**, 79-82.

[47] Kremen SA, Solis OE, Shapira J, Vinters HV, Mendez MF (2010) "Fantastic thinking" in pathologically proven Pick disease. *Cogn Behav Neurol* **23**, 130-134.

[48] Khan BK, Woolley JD, Chao S, See T, Karydas AM, Miller BL, Rankin KP (2012) Schizophrenia or neurodegenerative disease prodrome? Outcome of a first psychotic episode in a 35-year-old woman. *Psychosomatics* **53**, 280-284.

[49] Tartaglia MC, Kertesz A, Ang L-C (2008) Delusions and hallucinations in frontotemporal dementia: A clinicopathologic case report. *Cogn Behav Neurol* **21**, 107-110.

[50] Loy CT, Kril J, Trollor JN, Kiernan MC, Kwok JB, Vucic S, Halliday GM, Hodges JR (2010) The case of a 48 year-old woman with bizarre and complex delusions. *Nat Rev Neurol* **6**, 175-179.

[51] Claassen DO, Parisi JE, Giannini C, Boeve BF, Dickson DW, Josephs KA (2008) Frontotemporal dementia mimicking dementia with Lewy bodies. *Cogn Behav Neurol* **21**, 157-163.

[52] Urwin HH, Josephs KA, Rohrer JD, Mackenzie IR, Neumann M, Authier A, Seelaar H, van Swieten JC, Brown JM, Johannsen PP, Nielsen JEJ, Holm IE, Dickson DW, Rademakers R, Graff-Radford NR, Parisi JE, Petersen RC, Hatanpaa KJ, White CL, Weiner MF, Geser FF, Van Deerlin VM, Trojanowski JQ, Miller BL, Seeley WW, van der Zee J, Kumar-Singh S, Engelborghs SS, De Deyn P, Van Broeckhoven C, Bigio EH, Deng H-XH, Halliday GM, Kril J, Munoz DG, Mann DMA, Pickering-Brown SM, Doodeman VV, Adamson GG, Ghazi-Noori SS, Fisher EMCE, Holton JLJ, Revesz T, Rossor MN, Collinge J, Mead S, Isaacs AM (2010) FUS pathology defines the majority of tau- and TDP-43-negative frontotemporal lobar degeneration. *Acta Neuropathol* **120**, 33-41.

[53] Rohrer JD, Lashley T, Schott JM, Warren JE, Mead S, Isaacs AM, Beck J, Hardy J, de Silva R, Warrington EE, Troakes CC, Al-Sarraj SS, King AA, Borroni B, Clarkson MJM, Ourselin SS, Holton JLJ, Fox NC, Revesz T, Rossor MN, Warren JD (2011) Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. *Brain* **134**, 2565-2581.

[54] Liscić RM, Storandt MM, Cairns NJ, Morris JC (2007) Clinical and psychometric distinction of frontotemporal and Alzheimer dementias. *Arch Neurol* **64**, 535-540.

[55] Mendez MF, Joshi AA, Tassniyom KK, Teng E, Shapira J (2013) Clinicopathologic differences among patients with behavioral variant frontotemporal dementia. *Neurology* **80**, 561-568.

[56] Borroni B, Alberici A, Archetti S, Magnani E, Di Luca M, Padovani A (2010) New insights into biological markers of frontotemporal lobar degeneration spectrum. *Curr Med Chem* **17**, 1002-1009.

[57] Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, Isaacs AM, Authier A, Ferrari R, Fox NC, Mackenzie IR, Warren JD, de Silva R, Holton J, Revesz T, Hardy J, Mead S, Rossor MN (2009) The heritability and genetics of frontotemporal lobar degeneration. *Neurology* **73**, 1451-1456.

[58] Seelaar H, Rohrer JD, Pijnenburg YA, Fox NC, van Swieten JC (2011) Clinical, genetic and pathological heterogeneity of frontotemporal dementia: A review. *J Neurol Neurosurg Psychiatry* **82**, 476-486.

[59] Momeni P, Wickremaratchi MM, Bell J, Arnold R, Beer R, Hardy J, Revesz T, Neal JW, Morris HR (2010) Clinical Neurology and Neurosurgery. *Clin Neurol Neurosurg* **112**, 917-920.

[60] Rohrer JD, Warren JD (2011) Phenotypic signatures of genetic frontotemporal dementia. *Curr Opin Neurol* **24**, 542-549.

[61] Arosio B, Abbate C, Galimberti D, Rossi PD, Inglese S, Fenoglio C, Ridolfi E, Gussago C, Casati M, Tedone E, Ferri E, Serpente M, Scarpini E, Mari D (2013) GRN Thr272fs clinical heterogeneity: A case with atypical late onset presenting with a dementia with Lewy bodies phenotype. *J Alzheimers Dis* **35**, 669-674.

[62] Momeni P, DeTucci K, Straub RE, Weinberger DR, Davies P, Grafman J, Hardy J, Huey ED (2010) Progranulin (GRN) in two siblings of a Latino family and in other patients with Schizophrenia. *Neurocase* **16**, 273-279.

[63] Le Ber I, van der Zee J, Hannequin D, Gijselinck I, Campion D, Puel M, Laquerrière A, De Pooter T, Camuzat A, Van den Broeck M, Dubois B, Sellal F, Lacomblez L, Vercelletto M, Thomas-Antérion C, Michel B-F, Golfier V, Didic M, Salachas F, Duyckaerts C, Cruts M, Verpillat P, Van Broeckhoven C, Brice A, French Research Network on FTD, FTD-MND (2007) Progranulin null mutations in both sporadic and familial frontotemporal dementia. *Hum Mutat* **28**, 846-855.

[64] Le Ber I, Camuzat A, Hannequin D, Pasquier F, Guedj E, Rovelet Lecrux A, Hahn-Barma V, van der Zee J, Clot F, Bakchine S, Puel M, Ghanim M, Lacomblez L, Mikol J, Deramecourt V, Lejeune P, la Sayette de V, Belliard S, Vercelletto M, Meyrignac C, Van Broeckhoven C, Lambert J-C, Verpillat P, Campion D, Habert M-O, Dubois B, Brice A, French Research Network on FTD, FTD-MND (2008) Phenotype variability in progranulin mutation carriers: A clinical, neuropsychological, imaging and genetic study. *Brain* **131**, 732-746.

[65] DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker MC, Rutherford NJ, Nicholson AM, Finch NA, Flynn HH, Adamson J, Kouri NN, Wojtas A, Sengdy P, Hsiung G-YR, Karydas AA, Seeley WW, Josephs KA, Coppola G, Geschwind DH, Wszolek ZK, Feldman HH, Knopman DS, Petersen RC, Miller BL, Dickson DW, Boylan KB, Graff-Radford NR, Rademakers R (2011) Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron* **72**, 245-256.

[66] Renton A, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, Schymick JC, Laaksovirta H, van Swieten JC, Myllykangas LL, Kalimo HH, Paetau AA, Abramzon Y, Remes AM, Kaganovich AA, Scholz SWS, Duckworth JJ, Ding JJ, Harmer DWD, Hernandez D, Johnson JO, Mok K, Ryten MM, Trabzuni DD, Guerreiro R, Orrell RWR, Neal JJ, Murray A, Pearson JJ, Jansen IEI, Sondervan DD, Seelaar H, Blake DD, Young KK, Halliwell NN, Callister JB, Toulson GG, Richardson AA, Gerhard AA, Snowden J, Mann DMA, Neary D, Nalls MAM, Peuralinna TT, Jansson LL, Isoviita V-MV, Kaivorinne A-LA, Hölttä-Vuori MM, Ikonen EE, Sulkava RR, Benatar MM, Wuu JJ, Chiò A, Restagno G, Borghero G, Sabatelli MM, Heckerman DD, Rogaeva E, Zinman LL, Rothstein JDJ, Sendtner MM, Drepper CC, Eichler EEE, Alkan CC, Abdullaev ZZ, Pack SDS, Dutra AA, Pak EE, Hardy J, Singleton AA, Williams NM, Heutink P, Pickering-Brown SM, Morris HR, Tienari PJP, Traynor BJ (2011) A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* **72**, 257-268.

[67] Dobson-Stone C, Hallupp M, Bartley L, Shepherd CE, Halliday GM, Schofield PR, Hodges JR, Kwok JB (2012) C9ORF72 repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts. *Neurology* **79**, 995-1001.

[68] Khan BK, Yokoyama JS, Takada LT, Sha SJ, Rutherford NJ, Fong JC, Karydas A, Wu T, Ketelle R, Baker MC, DeJesus-Hernandez M, Coppola G, Geschwind DH, Rademakers R, Lee SE, Rosen HJ, Rabinovici GD, Seeley WW, Rankin KP, Boxer AL, Miller BL (2012) Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion. *J Neurol Neurosurg Psychiatry* **83**, 358-364.

[69] Takada LT, Pimentel MLVM, DeJesus-Hernandez M, Fong JC, Yokoyama JS, Karydas AA, Thibodeau M-PM, Rutherford NJ, Baker MC, Lomen-Hoerth C, Rademakers R, Miller BL (2012) Frontotemporal dementia in a Brazilian kindred with the c9orf72 mutation. *Arch Neurol* **69**, 1149-1153.

[70] Takada LT, Sha SJ (2012) Neuropsychiatric features of C9orf72-associated behavioral variant frontotemporal dementia and frontotemporal dementia with motor neuron disease. *Alzheimers Res Ther* **4**, 38-38.

[71] Arighi A, Fumagalli GG, Jacini FF, Fenoglio CC, Ghezzi L, Pietroboni AMA, De Riz MM, Serpente M, Ridolfi EE, Bonsi R, Bresolin N, Scarpini E, Galimberti D (2012) Early onset behavioral variant frontotemporal dementia due to the C9ORF72 hexanucleotide repeat expansion: Psychiatric clinical presentations. *J Alzheimers Dis* **31**, 447-452.

[72] Larner AJ (2013) Delusion of pregnancy: A case revisited. *Behav Neurol* **27**, 293-294.

[73] Floris G, Borghero G, Cannas A, Stefano FD, Murru MR, Corongiu D, Cuccu S, Tranquilli S, Marrosu MG, Chiò A, Marrosu F (2013) Bipolar affective disorder preceding frontotemporal dementia in a patient with C9ORF72 mutation: Is there a genetic link between these two disorders? *J Neurol* **260**, 1155-1157.

[74] Simón-Sánchez J, Dopper EGP, Cohn-Hokke PE, Hukema RK, Nicolaou N, Seelaar H, de Graaf JRA, de Koning I, van Schoor NM, Deeg DJH, Smits M, Raaphorst J, van den Berg LH, Schelhaas HJ, De Die-Smulders CEM, Majoor-Krakauer D, Rozemuller AJM, Willemsen R, Pijnenburg YA, Heutink P, van Swieten JC (2012) The clinical and pathological phenotype of C9ORF72 hexanucleotide repeat expansions. *Brain* **135**, 723-735.

[75] Hsiung G-YR, DeJesus-Hernandez M, Feldman HH, Sengdy P, Bouchard-Kerr P, Dwosh E, Butler R, Leung B, Fok A, Rutherford NJ, Baker MC, Rademakers R, Mackenzie IR (2012) Clinical and pathological features of familial frontotemporal dementia caused by C9ORF72 mutation on chromosome 9p. *Brain* **135**, 709-722.

[76] Mosca L, Lunetta C, Tarlarini C, Avemaria F, Maestri E, Melazzini M, Corbo M, Penco S (2012) Wide phenotypic spectrum of the TARDBP gene: Homozygosity of A382T mutation in a patient presenting with amyotrophic lateral sclerosis, Parkinson's disease, and frontotemporal lobar degeneration, and in neurologically healthy subject. *Neurobiol Aging* **33**, 1846.e1-4.

[77] Tang-Wai DF, Lewis P, Boeve BF, Hutton M, Golde T, Baker M, Hardy J, Michels V, Ivnik RJ, Jack CR, Petersen RC (2002) Familial frontotemporal dementia associated with a novel presenilin-1 mutation. *Dement Geriatr Cogn Disord* **14**, 13-21.

[78] Gourzis P, Skokou M, Polychronopoulos P, Soubasi E, Triantaphyllidou IE, Aravidis C, Sarela A-I, Kosmaidou Z

(2012) Frontotemporal dementia, manifested as schizophrenia, with decreased heterochromatin on chromosome 1. *Case Rep Psychiatry* **2012**, 937518.

[79] Mahoney CJ, Downey LE, Ridgway GR, Beck J, Clegg S, Blair M, Finnegan S, Leung KK, Yeatman T, Golden H, Mead S, Rohrer JD, Fox NC, Warren JD (2012) Longitudinal neuroimaging and neuropsychological profiles of frontotemporal dementia with C9ORF72 expansions. *Alzheimers Res Ther* **4**, 41.

[80] Chan D, Anderson V, Pijnenburg YA, Whitwell JL, Barnes J, Scahill R, Stevens JM, Barkhof F, Scheltens P, Rossor MN, Fox NC (2009) The clinical profile of right temporal lobe atrophy. *Brain* **132**, 1287-1298.

[81] Pennington C, Hodges JR, Hornberger M (2011) Neural correlates of episodic memory in behavioral variant frontotemporal dementia. *J Alzheimers Dis* **24**, 261-268.

[82] Davies R, Kipps CM, Mitchell J, Kril J, Halliday GM, Hodges JR (2006) Progression in frontotemporal dementia: Identifying a benign behavioral variant by magnetic resonance imaging. *Arch Neurol* **63**, 1627-1631.

[83] Kipps CM, Nestor PJ, Fryer TD, Hodges JR (2007) Behavioural variant frontotemporal dementia: Not all it seems? *Neurocase* **13**, 237-247.

[84] Hu B, Ross LL, Neuhaus J, Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, Miller BL, Boxer AL (2010) Off-label medication use in frontotemporal dementia. *Am J Alzheimers Dis Other Demen* **25**, 128-133.

[85] Caselli RJ, Yaari R (2008) Medical Management of Frontotemporal Dementia. *Am J Alzheimers Dis Other Demen* **22**, 489-498.

[86] Mendez MF (2009) Frontotemporal dementia: Therapeutic interventions. *Front Neurol Neurosci* **24**, 168-178.

[87] Kobayashi T, Inoue K, Shioda K, Kato S (2012) Effectiveness of electroconvulsive therapy for depression and Cotard's syndrome in a patient with frontotemporal lobe dementia. *Case Rep Psychiatry* **2012**, 1-4.

[88] Fázzari G, Benzoni O, Sangaletti A, Bonera F, Nassini S, Mazzarini L, Pacchiarotti I, Sani G, Koukopoulos AE, Sanna L, Gasparotti R, De Rossi P, Lazanio S, Savoja V, Girardi P (2009) Improvement of cognition in a patient with Cotard's delusions and frontotemporal atrophy receiving electroconvulsive therapy (ECT) for depression. *Int Psychogeriatr* **21**, 600.

[89] Kimura T, Hayashida H, Murata M, Takamatsu J (2011) Effect of ferulic acid and Angelica archangelica extract on behavioral and psychological symptoms of dementia in frontotemporal lobar degeneration and dementia with Lewy bodies. *Geriatr Gerontol Int* **11**, 309-314.

[90] Kimura T, Hayashida H, Furukawa H, Miyauchi D, Takamatsu J (2009) Five cases of frontotemporal dementia with behavioral symptoms improved by Yokukansan. *Psychogeriatrics* **9**, 38-43.

[91] Kerssens CJ, Kerrsens CJ, Pijnenburg YA (2008) Vulnerability to neuroleptic side effects in frontotemporal dementia. *Eur J Neurol* **15**, 111-112.

[92] Nakajima S, Gerretsen P, Takeuchi H, Caravaggio F, Chow TW, Le Foll B, Mulsant B, Pollock B, Graff-Guerrero A (2013) The potential role of dopamine D3 receptor neurotransmission in cognition. *Eur Neuropsychopharmacol* **23**, 799-813.

[93] Miller DD, McEvoy JP, Davis SM, Caroff SN, Saltz BL, Chakos MH, Swartz MS, Keefe RS, Rosenheck RA, Stroup TS, Lieberman JA (2005) Clinical correlates of tardive dyskinesia in schizophrenia: Baseline data from the CATIE schizophrenia trial. *Schizophr Res* **80**, 33-43.

[94] Novick DD, Haro JMJ, Bertsch JJ, Haddad PMP (2010) Incidence of extrapyramidal symptoms and tardive dyskinesia in schizophrenia: Thirty-six-month results from the European schizophrenia outpatient health outcomes study. *J Clin Psychopharmacol* **30**, 531-540.

[95] Pose M, Cetkovich M, Gleichgerrcht E, Ibáñez A, Torralva T, Manes F (2013) The overlap of symptomatic dimensions between frontotemporal dementia and several psychiatric disorders that appear in late adulthood. *Int Rev Psychiatry* **25**, 159-167.

[96] Fornito A, Yücel M, Pantelis C (2009) Reconciling neuroimaging and neuropathological findings in schizophrenia and bipolar disorder. *Curr Opin Psychiatry* **22**, 312-319.

[97] Olabi BB, Ellison-Wright I, Bullmore ET, Lawrie SMS (2012) Structural brain changes in first episode schizophrenia compared with fronto-temporal lobar degeneration: A meta-analysis. *BMC Psychiatry* **12**, 104-104.

[98] Brown GG, Thompson WK (2010) Functional brain imaging in schizophrenia: Selected results and methods. *Curr Top Behav Neurosci* **4**, 181-214.

[99] Kalkstein SS, Hurford II, Gur RCR (2010) Neurocognition in schizophrenia. *Curr Top Behav Neurosci* **4**, 373-390.

[100] Schoder D, Hannequin D, Martinaud O, Opolczynski G, Guyant-Marechal L, Le Ber I, Campion D (2010) Morbid risk for schizophrenia in first-degree relatives of people with frontotemporal dementia. *Br J Psychiatry* **197**, 28-35.

[101] Huey ED, Nagy PL, Rodriguez-Murillo L, Manoochehri M, Goldman JS, Lieberman J, Karayiorgou M, Mayeux R (2013) C9ORF72 repeat expansions not detected in a group of patients with schizophrenia. *Neurobiol Aging* **34**, 1309.e9-10.

[102] Cooper JJ, Ovsiew F (2013) The relationship between schizophrenia and frontotemporal dementia. *J Geriatr Psychiatry Neurol* **26**, 131-137.

[103] Forman MS, Farmer J, Johnson JK, Clark CM, Arnold SE, Coslett HB, Chatterjee A, Hurtig HI, Karlawish JH, Rosen HJ, Van Deerlin VM, Lee VMY, Miller BL, Trojanowski JQ, Grossman M (2006) Frontotemporal dementia: Clinicopathological correlations. *Ann Neurol* **59**, 952-962.

[104] Kapur S, Agid O, Mizrahi R, Li M (2006) How antipsychotics work-from receptors to reality. *NeuroRx* **3**, 10-21.

[105] Vukadinovic Z, Rosenzweig I (2012) Abnormalities in thalamic neurophysiology in schizophrenia: Could psychosis be a result of potassium channel dysfunction? *Neurosci Biobehav Rev* **36**, 960-968.

[106] Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S (2012) The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry* **69**, 776-786.

[107] Poels EMP, Kegeles LS, Kantrowitz JT, Slifstein M, Javitt DC, Lieberman JA, Abi-Dargham A, Girgis RR (2014) Imaging glutamate in schizophrenia: Review of findings and implications for drug discovery. *Mol Psychiatry* **19**, 20-29.

[108] Huey ED, Putnam KT, Grafman J (2006) A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. *Neurology* **66**, 17-22.

[109] Nikolaus S, Antke C, Müller H-W (2009) *In vivo* imaging of synaptic function in the central nervous system: I. Movement disorders and dementia. *Behav Brain Res* **204**, 1-31.

[110] Engelborghs SS, Vloeberghs E, Le Bastard N, Van Buggenhout M, Mariën P, Somers N, Nagels G, Pickut BA, De Deyn P (2008) The dopaminergic neurotransmitter system