

Received: 23.01.2013
Accepted: 28.06.2013

A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

CLINICAL CHARACTERISTICS AND POSSIBLE MECHANISMS UNDERLYING BEHAVIORAL AND PERSONALITY CHANGES IN FTDP-17

Michał Harciarek^{1(D,E,F)}, Emilia J. Sitek^{2,3(A,B,D,E,F,G)},
Ewa Narożańska^{2(A,B,D,E)}, Seweryna Konieczna^{4,5(B)},
Dariusz Wieczorek^{6(D)}, Bogna Brockhuis^{7(B,D)},
Piotr Lass^{7(B,D)}, Mirosława Dubaniewicz-Wyberalska^{8(B,D)},
Maria Barcikowska^{9,10(D)}, Jarosław Sławek^{1,2(A,D,E,F,G)}

¹ Department of Clinical Psychology and Neuropsychology, Institute of Psychology, University of Gdansk, Poland

² Department of Neurological and Psychiatric Nursing, Medical University of Gdansk, Gdansk, Poland

³ Department of Neurology, St. Adalbert Hospital, Gdansk, Poland

⁴ Department of Developmental Neurology, Medical University of Gdansk, Poland

⁵ Department of the History and Philosophy of Medical Science, Medical University of Gdansk, Poland

⁶ Department of Rehabilitation, Medical University of Gdansk, Gdansk, Poland

⁷ Department of Nuclear Medicine, Medical University of Gdansk, Gdansk, Poland

⁸ Department of Radiology, Medical University of Gdansk, Gdansk, Poland

⁹ Department of Neurodegenerative Diseases, Neurology Clinic, MSWiA Hospital, Warsaw, Poland

¹⁰ Department of Neurodegenerative Disorders, Mossakowski Medical Research Center, Polish Academy of Sciences, Warsaw, Poland

SUMMARY

Background:

Although the clinical and neuroanatomical characteristics of behavioral and personality changes have been well-defined in frontotemporal dementia syndromes, relatively little is known about the behavioral and personality changes in frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). Thus, the aim of this study was to longitudinally characterize the behavioral and personality abnormalities associated with FTDP-17.

Material/ Methods:

We examined three patients with a clinical diagnosis of FTDP-17 confirmed by genetic testing. In all three patients the *P301L MAPT* mutation was detected. All patients underwent neuroimaging (MRI and SPECT). Behavior and personality changes were assessed longitudinally with the Blessed Dementia Rating Scale, the Frontal Behavioral Inventory and/or the Neuropsychiatric Inventory.

Results:

All three patients demonstrated marked and progressive changes in behavior and personality, as revealed by clinical observation and longitudinal assessment. These abnormalities included mainly disinhibition, indifference, and apathy, as well as compulsive-like and utilization behavior. Nonetheless, as the disease progressed, negative symptoms dominated the clinical presentation of all cases.

Conclusions:

The common behavioral and personality abnormalities in FTDP-17 with *MAPT* seem to overlap with the behavioral variant FTD. Also, early behavioral and personality changes in FTDP-17 with *MAPT* are likely associated with the initial locus of neurodegeneration, and may represent an effect of the disease-related dynamic imbalance between the mutually inhibitory inter- and intrahemispheric processes, which may also possibly account for symptom change as the disease progresses, eventually resulting in a unified behavioral profile of negative symptoms.

Key words: frontotemporal dementia, disinhibition, apathy, interhemispheric inhibition, emotion

INTRODUCTION

Since the seminal case of Phineas Gage, a railroad construction worker who in 1848 suffered an injury to his frontal cortex (see Stuss et al., 1992), it has been well established that the frontal lobes are crucial in regulating our behavior, and that a lesion in these regions, particularly the orbitomedial parts of the frontal cortex, result in pronounced changes in one's personality and behavior (e.g. disinhibition, poor insight, defective judgement, indifference). This phenomenon has been mainly explained by the fact that there are extensive connections between the orbitofrontal cortex and other paralimbic structures primarily involved in emotional processing (e.g. amygdala, hypothalamus, insula or cingulate gyrus), and that damage to the orbitofrontal cortex would release the phylogenetically older paralimbic cortices from the inhibitory effect of phylogenetically younger orbitomedial cortex (Ongur et al., 1998). What is also striking about the consequences of lesions in orbitofrontal areas is that they may leave most cognitive skills intact, which is just opposite to lesions to the dorsolateral prefrontal cortex (Stuss et al., 2005). This double dissociation within the frontal lobes has been confirmed by both lesion and neuroimaging studies (for review see Stuss & Knight, 2002).

Although the primary role of the orbitofrontal cortex in regulating personality, behavior and affect seems to be well documented, affective and behavioral changes have also often been noted following damage to more dorsolateral frontal regions. For example, lesions to left dorsolateral frontal cortex have been shown to result in apathy or depression (Benson, 1973; Gainotti, 1972; Goldstein, 1948; Robinson, 1998), whereas damage to the same area in the right hemisphere may produce inappropriate indifference to negative stimuli, euphoria (Babinski, 1914; Hecaen et al., 1951; Robinson et al., 1987) as well as inappropriate jocularity ("*Witzelsucht*") or moria (Oppenheim, 1889; Jastrowitz, 1888). Partly similarly to the mechanism underlying disinhibition following orbitofrontal damage, these clinical observations have been typically explained by referring to mutual interhemispheric inhibition, so that with unilateral (e.g. right) frontal damage there might be a loss of right frontal inhibition over the left frontal lobe, which becomes disinhibited (see Paçhalska et al., 2011).

As a correlate, it has been hypothesized that emotions might be organized hemispherically by valence, with right frontal lobe being dominant for negative, unpleasant emotions, and the left frontal cortex being dominant for positive, pleasant emotions (Reuter-Lorenz & Davidson, 1981). It has also been posited that these frontal hemispheric asymmetries in mediating emotional valence might be related to approach versus avoidance behaviors, so that the right frontal lobe predominantly mediates processes associated with avoidance behaviors, while the left frontal lobe is involved in approach behaviors (Davidson, 1984; Davidson et al., 1990; Fox et al., 1995; Kinsbourne, 1982). Moreover, there is evidence to suggest that the medial parts of the frontal lobes are strongly implemented in motivational/endo-evoked aspects of behavior, and that a lesion in these areas would result in apathy or abulia (see Heilman et al., 2012), sometimes misdiag-

nosed as depression (see Pačalska 2008).

Although our contemporary understanding of the neuroanatomical correlates of personality and behavior has been derived mostly from lesion studies, examining patients with neurodegenerative diseases that selectively attack the frontal lobes may be another valuable approach to better comprehend the functions of the frontal lobes. A good example of a neurodegenerative disease where the frontal lobes are primarily affected is frontotemporal dementia (FTD), a midlife onset clinical condition that was first described by Arnold Pick in 1892, and thus previously known as Pick's disease (see Kertesz, 2011). Although the clinical presentation of FTD is heterogeneous, the major FTD subtype is its behavioral variant (bvFTD), with impaired social conduct, disinhibition, stereotypic behaviors, loss of empathy, and apathy among the most prominent features associated with defective function of orbitomesial frontal cortex caused by frontotemporal lobar degeneration (FTLD) (Harciarek & Jodzio, 2005; Rascovsky et al., 2011). The second most common subtype of FTD is the language variant FTD, also described as primary progressive aphasia (PPA) (see Hodges, 2007; Mesulam, 2003). Based on the constellation of symptoms, PPA can be further divided into semantic, non-fluent/agrammatic, and logopenic variants (Gorno-Tempini et al., 2011; see also Harciarek & Kertesz, 2011; Mesulam et al., 2008). Nonetheless, in comparison to the semantic and the non-fluent/agrammatic PPA predominantly associated with FTLD, the logopenic variant has been more often linked to the pathology of Alzheimer's disease (e.g., Grossman, 2010; Rabinovici et al., 2008; Mesulam et al., 2008). Of note, since a subset of these patients also develop features of atypical Parkinsonian syndromes, such as apraxia (core feature of corticobasal syndrome, CBS) or oculomotor dysfunction (typical for progressive supranuclear palsy, PSP) (Kertesz, Davidson, McCabe, Takagi & Munoz, 2003a; Kertesz, Blair, McMonagle & Munoz, 2007), Kertesz (2011) suggested the term "Pick Complex" to unify the overlapping syndromes of FTLD and movement disorders such as CBS and PSP. Moreover, the identification of mutations in the gene encoding the microtubule-associated protein tau (*MAPT*) in the inherited forms of FTLD with parkinsonism linked to chromosome 17 (FTDP-17) established an association between tau mutations and neurodegenerative syndromes (Hutton, 2001).

Unlike other forms of FTLD, the FTDP-17 variant is a rare neurodegenerative disorder characterized by behavioral, cognitive and motor manifestations (Foster et al., 1997; Wszolek et al., 2003). Nonetheless, since FTDP-17 is associated with mutations in *MAPT* as well as in the progranuline (*GRN*) genes (Wider, 2007; Wider & Wszolek, 2008), these patients have been often shown to have atrophy extending to the parietal lobe. Moreover, unlike kindreds with *MAPT* mutations, in most affected family members with *GRN* mutations there is a tendency for the same cerebral hemisphere to be particularly involved (Boeve & Hutton, 2008). Thus, despite some overlap with other forms of FTLD, the behavioral disturbances in FTDP-17 may sometimes not be a pure consequence of frontal and anterior temporal atrophy, but could be a result of a parietal involvement. For example, Denny-Brown and Chambers (1958) proposed a reciprocally balanced

and mutually inhibitory relationship between the frontal lobes and the posterior (temporo-parietal) regions of the brain, such that lesions of either area will result in a transcortical release of the behaviors associated with the intact region. These investigators also suggested that, with regard to emotion, posterior regions of the right hemisphere might primarily mediate approach behaviors, whereas right frontal regions might be predominantly associated with avoidance behaviors. Thus, it could be suggested that, whereas in patients with FTDP-17 with left-sided atrophy the increasing withdrawal-related behaviors (e.g. apathy or depression) could mainly result from the progressive neurodegeneration of the left frontal lobe, the same behavioral abnormalities in subjects with predominantly right hemisphere involvement could be a consequence of the atrophy of the right posterior regions. In contrast, approach-related behaviors such as disinhibition could then be most often seen in subjects with FTDP-17 presenting with predominant right frontal atrophy, similarly to what has been observed in bvFTD (Raskovsky et al., 2011; see also Harciarek & Jodzio, 2005). Hence, studying behavior in FTDP-17 could not only help to characterize behavioral and personality changes in FTL, but it could also contribute to better understanding of frontal lobe functions, both their hemispheric behavioral specificity and their mutually inhibitory relationship to more posterior (temporo-parietal) brain regions. Of note, the existence of such inter- and intrahemispheric mutually inhibitory relationships could, in turn, constitute a possible mechanism explaining not only the initial behavioral and personality changes seen at disease onset, but also the additional changes that often appear as the neurodegeneration progresses (e.g. from initially right-frontal to both-sided frontal or more generalized/parietal right hemisphere atrophy).

The aim of our study, then, was to characterize longitudinally the behavioral and personality abnormalities associated with FTDP-17, as well as to indirectly test the hypothesis that there are mutually inhibitory inter- and intrahemispheric associations related to behavioral changes in this rare FTL variant.

MATERIAL AND METHODS

Case presentations

All the patients described here have previously been reported (Sitek et al., 2009; Sitek et al., 2010, Narożańska et al., 2011; Sitek et al., 2011; Narożańska et al., 2012; Sitek et al., in press), although their behavioral profile was neither presented nor interpreted in detail in the previous publications.

Cases no. 1 and no. 2, from the first Polish family with FTDP-17, are siblings; their mother and three maternal aunts suffered from dementia (see: Narożańska et al., 2011 for pedigree). In the family of Case no. 3 both his father and grandmother probably had dementia.

In all these patients the clinical diagnosis was confirmed by genetic testing that revealed the *P301L MAPT* mutation.

CASE NO.1

Clinical description

Patient no. 1 was a right-handed man, previously employed as an electrical technician, who developed apathy and depression after being dismissed from work at the age of 48/49. Depression was thus interpreted as a psychological reaction to his life situation. A year later his spontaneous speech output became less and less elaborate. The patient withdrew from a variety of activities, such as fishing, do-it-yourself, or collecting stamps. His libido decreased. He was hospitalized for severe depression with psychomotor slowing and suicidal ideation. Hyperphagia and indifference appeared shortly after that. He stopped engaging in activities such as cooking or cleaning. Parkinsonism started at the age of 55, with left-sided resting tremor, hypomimia and initial good response to levodopa treatment. He was misdiagnosed with Parkinson's disease, as he failed to report any family history of dementia and used to come to the Movement Disorders clinic without anyone who could provide background information. He was diagnosed with FTD after his sister's hospitalization at the Neurology Unit, when his clinical diagnosis was revised. At that point autonomic dysfunctions appeared, such as tachycardia, labile blood pressure, hyperhidrosis and urinary incontinence. At the neurological examination, apart from Parkinsonian signs, he presented with vertical nystagmus and primitive reflexes. Neuropsychological evaluation showed mainly executive dysfunction and working memory impairment, accompanied by impoverished spontaneous speech output.

The patient did not have insight into his behavioral and cognitive problems. Compulsive shopping was one of the main behavioral problems. The patient also suffered from severe mental set-shifting difficulties, e.g. when his wife had an asthma attack and asked him for help, he responded to her after he finished preparing a sandwich, which took a couple of minutes. He often failed to follow social rules. When his wife wished the examiner Merry Christmas, the patient repeated the same wishes with his back turned to the clinician. He ate everything that was available at home, ignoring the needs of his family.

He developed unilateral neglect syndrome, which at first affected mainly personal space (e.g. dressing, shaving) and then progressed to the extrapersonal space. Aberrant motor behavior was prominent, such as folding and unfolding newspapers and tablecloths. At the age of 59 epileptic seizures began, at which time the patient's memory deteriorated significantly. The patient's left upper limb became dystonic at the age of 60 and required botulinum toxin treatment. His parkinsonism was characterized by severe bradykinesia, rigidity, and postural instability. He also suffered from dysphagia. At the age of 60 the patient was bedridden and mute. The patient died at home at the age of 62.

Neuroimaging results

An MRI was performed when the patient was 57 years and 10 months old (see: Figure 1 and Figure 2), and SPECT was performed 8 months later. The brain



Figure 1. Frontal atrophy on MRI in three cases, from the left: Case no. 3, Case no. 2, Case no. 1

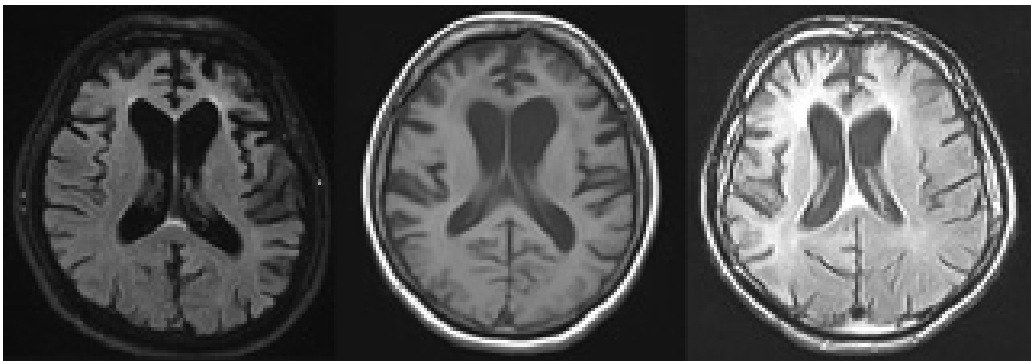


Figure 2. Cerebral atrophy on MRI in three cases, from the left: Case no. 3, Case no. 2, Case no. 1

MRI revealed diffuse cerebral atrophy, with predominance in the frontal and temporal lobes bilaterally, while SPECT showed frontotemporal hypoperfusion with right-sided predominance.

CASE NO.2

Clinical description

Patient no. 2 was a right-handed saleswoman, in whom the first behavioral changes were noticed at the age of 51. She began stealing items from the shop where she worked, just to share them with her friends. She borrowed money without obvious need. At that time, disinhibition and emotional indifference with psychomotor slowing were prominent. Hoarding and hyperphagia were also observed. One year after the onset of symptoms she ceased managing home finances. At the age of 56 she was misdiagnosed with early onset Alzheimer's disease. Once, she drank a bottle of pure grain alcohol, while previously she had hardly ever had so much as a pint of beer. On another occasion, she tore off all the leaves from the plants she had at home. When she saw her husband throw firewood to the fireplace she would start throwing paper tissues to the fireplace.

She sometimes took her husband's medication; when asked about it, she claimed that his pills looked nicer than hers. Her behavior was very difficult to control. Once, her husband asked her to rewrite prices from a supermarket leaflet just to be able to leave her in order to do his work in another room. After that, she would spend hours rewriting prices from leaflets on a daily basis. When she was 57, she was examined for the first time by a movement disorders specialist, at which time she was found to have levodopa-responsive parkinsonism with bradykinesia, left-sided cogwheel rigidity and gait disturbances. During hospitalization in the Neurology Unit she drank a whole bottle of mouthwash. She had severe posture imbalance and was incontinent. Hyperorality (including the attempt to eat stool), visual hallucinations, epileptic seizures, aberrant motor behavior and utilization behavior were also present. She died at the age of 57 in a nursing home.

Neuroimaging results

SPECT was performed at the age of 56 years and 4 months, while MRI was performed 11 months later (see: Figures 1 and 2). She had diffuse cerebral atrophy with frontotemporal predominance in MRI, and right-sided hypoperfusion within the frontal and temporal lobes on SPECT.

CASE NO. 3

Clinical description

Patient no. 3 is a left-handed artist (painter) with probable specific learning difficulties (dyslexia and dysgraphia). In this patient personality changes appeared at the age of 44/45. The changes were misinterpreted as artistic nonchalance and the reaction to marital problems and subsequent divorce. Nevertheless, at the age of 48 behavioral and cognitive changes were unquestionable. He painted less and less due to lack of inspiration and then abandoned painting. He could no longer organize exhibitions or handle the sale of the paintings. He was no longer interested in his family. He presented with hyperphagia. He started gathering old newspapers, used to walk always by the same route, and constantly charged his mobile phone. His speech output became very impoverished, while his answers also reflected problems with the comprehension of complex sentences. The patient was diagnosed with FTD at the age of 50. At the age of 52, fecal incontinence emerged. Neurological examination at the age of 52 showed frontal release signs bilaterally, motor perseverations, echolalia and no parkinsonism. At the age of 53 he became apraxic; he was unable to cut or peel vegetables. Moreover, semantic problems were noted, as he tried to peel an orange with a spoon. Aberrant motor behavior was also present, especially continuously rearranging CDs, photos and books. At the age of 54 he had no parkinsonism signs, but palmomental reflex was present. He was mostly mute, and echolalia disappeared. Aberrant motor behavior and hyperorality were the most prominent features. The patient continuously re-arranged objects in the kitchen and in the rooms.

NEUROIMAGING RESULTS

MRI and SPECT (see: Figures 1 and 2) were performed at the age of 52. Brain MRI revealed significant cortical and subcortical atrophy within the frontal, temporal and parietal lobes. Atrophy was bilateral but with significant left-sided predominance, mostly pronounced within whole frontal lobes and laterally in the gray matter of the anterior and inferior temporal regions. There was also mild atrophy in the right temporal lobe and midbrain. SPECT showed diffuse hypoperfusion of the whole brain, with severe hypoperfusion within the frontal lobes and mild perfusion deficits in the left temporal and left parietal lobes.

Neurological assessment

Apart from general neurological examination, the Unified Parkinson's Disease Rating Scale (Paulson & Stern, 1997) was applied to Patients No. 1 and No. 2, who presented with parkinsonian symptoms.

Personality and behavioral assessment

In all three cases, the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) and Blessed Dementia Rating Scale (BDRS) (Blessed et al., 1968) were administered to the caregivers at least twice during the disease course. Moreover, in Patients no. 1 and no. 3 the Frontal Behavioral Inventory (FBI) was also applied (Kertesz et al., 1997; Pačhalska & MacQueen, 2000). The results of the

Table 1. The summary of clinical data

	Patient no. 1	Patient no. 2	Patient no. 3
age at onset	48	51	44
initial behavioral presentation according to the interview	apathy	disinhibition/euphoria	apathy
initial diagnosis	Parkinson's disease	early onset Alzheimer's disease	early onset Alzheimer's disease
age at initial diagnosis	55	55	50
age at FTD diagnosis	58	57	50
disease duration	14 years	6 years	10 years, ongoing
personality and behavioural changes at FTD diagnosis	apathy compulsive behaviour	disinhibition, euphoria utilization behaviour, hyperphagia	apathy, compulsive behaviour, hyperphagia
cognitive impairment at FTD diagnosis	executive and working memory impairment,	generalized cognitive decline with predominance of dysexecutive symptoms	executive dysfunction
language dysfunction at FTD diagnosis	logopenia	mild aphasia, echolalia	moderate aphasia, echolalia
motor impairment at FTD diagnosis	parkinsonism with asymmetric left-sided resting tremor, bradykinesia, rigidity, posture instability	parkinsonism with bradykinesia and rigidity, gait impairment, incontinence	no symptoms

neuropsychological testing have previously been reported (Sitek et al., in press); here, only the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Frontal Assessment Battery at bedside (FAB) (Dubois et al., 2000) are presented to show the degree of cognitive deterioration at the time of neuropsychiatric assessment. In Patient no. 1 the assessment of neuropsychiatric symptoms was performed with the assistance of the patient's wife. In Patient no. 2 her husband was the informant in the first examination; at the second examination the nursing home staff members were interviewed. In the case of Patient no. 3, the clinical information was gathered from his son, his brother and his sister-in-law. The NPI and BDRS were administered by EN or ES. The FBI was administered by ES.

RESULTS

Patient no. 1

At the first neuropsychiatric assessment the patient was moderately demented; at follow-up his cognitive state had deteriorated to the stage of severe dementia according to BDRS. In this patient psychomotor slowing and apathy were the most prominent features. Aberrant motor behavior was also present throughout the reported observation period. During the course of the disease, mild delusions and hallucinations appeared. At last examination the patient was bed-ridden and almost mute, but no observable signs of anxiety or depression were reported by the caregiver. At this stage the negative behavior score was higher than the disinhibition score on FBI. Since the baseline assessment some signs of environmental dependency were seen, such as echopraxia.

Patient no. 2

This patient was severely demented at the time of both neuropsychiatric assessments. In this patient apathy and aberrant motor behavior predominated in the clinical picture. Psychomotor slowing was not so remarkable as in her brother (Patient no. 1). Delusions and hallucinations decreased in the observation period, as did agitation and euphoria. In this patient utilization behavior was very prominent throughout the disease course.

Patient no. 3

This patient was moderately demented at the first neuropsychiatric assessment and severely demented at follow-up. Depressed mood and signs of euphoria were clearly present at baseline, but they were not reported afterwards by the patient's family and caregiver. Aberrant motor behavior and apathy were present throughout the reported observation period. In this patient no psychotic symptoms were observed. Agitation and irritability were mild and present only at the second assessment. The negative behavior score was higher than the disinhibition score on two FBI assessments. Signs of environmental dependency were present after the first assessment and increased over time.

Table 2. Neuropsychiatric Inventory (NPI) and Unified Parkinson's Disease Rating Scale (UPDRS) assessment of the patients

	Patient No. 1						Patient No. 2						Patient No. 3					
	58/5		59/0		59/6		60/1		57/2		57/10		52/0		53/2		54/11	
	freq	sev	freq	sev	freq	sev	freq	sev	freq	sev	freq	sev	freq	sev	freq	sev	freq	sev
age at examination years/months	9	10	11	11	14	20	21	4	1	1	4	1	4	1	1	1	1	1
time since onset (years)	9	10	11	11	14	20	21	4	1	1	4	1	4	1	1	1	1	1
Blessed DRS	11	17	16.5	20	20	11	11	11	11	11	11	11	11	11	11	11	11	11
MMSE	24	21	20	11	14	20	21	4	1	1	4	1	4	1	1	1	1	1
FAB	-	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
NPI	0	1	1	0	4	0	0	0	3	0	0	0	0	0	0	0	0	0
delusions	0	0	1	1	0	0	0	0	3	0	0	0	0	0	0	0	0	0
hallucinations	1	1	2	1	2	1	0	0	3	1	1	1	0	0	0	0	0	0
agitation	4	3	0	0	0	0	3	1	3	0	0	0	0	0	2	2	0	0
depression / dysphoria	0	0	4	1	3	2	0	0	1	1	2	2	3	2	0	0	0	0
anxiety	2	2	0	0	0	0	0	0	3	1	0	0	0	0	0	0	0	0
euphoria / elation	4	1	0	0	0	0	0	0	4	2	0	0	4	1	0	0	0	0
apathy / indifference	4	3	4	2	4	3	4	3	4	3	4	2	4	1	4	1	4	2
disinhibition	3	3	0	0	1	1	0	0	4	3	1	2	0	0	1	1	0	0
irritability / lability	2	1	0	0	0	0	0	0	1	1	0	0	0	0	2	2	0	0
aberrant motor behaviour	4	3	4	2	4	1	4	1	4	3	4	2	4	1	4	1	4	2
UPDRS	14	NA	NA	NA	25	NA	NA	NA	30	20	20	20	0	0	0	0	NA	
part I	36				41				50	18	18	18	0	0	0	0	NA	
part III	2				3				0	0	0	0	0	0	0	0	NA	
part IV	52				69				80	38	38	38	0	0	0	0	NA	
parts II-IV																		
Medications related to clinical presentation of FTDP-17, daily dose (mg)	Levodopa 300 Sertralium 50						Levodopa 300 Sertralium 75						Levodopa 200 Carbamazepine 400 Promazine 25 Fluoxetine 20					
	Memantine 20						Memantine 20						Memantine 20					

¹NA- not available

Table 3. Frontal Behavioural Inventory (FBI) assessment of the patients

		Patient no. 1	Patient no. 3	
	age at examination (years/ months)	60/1	53/2	54/11
	time since onset (years)	11	9	10
	FBI- overall	45	51	41
	FBI negative behaviour score	33	32	28
	FBI disinhibition score	12	19	13
FBI – Negative behaviour				
1	apathy	3	3	3
2	aspontaneity	3	3	3
3	indifference, emotional flatness	3	3	2
4	inflexibility	3	3	3
5	personal neglect	3	2	0
6	disorganization	3	3	3
7	inattention	3	3	3
8	loss of insight	3	3	3
9	logopenia	3	3	3
10	semantic dementia	0*	3	3
11	aphasia and verbal apraxia	3	3	3
12	alien hand and / or apraxia	3	0	0
FBI – Disinhibition				
13	perseverations, obsessions	3	3	3
14	irritability	0	1	0
15	excessive jocularity	0	2	0
16	impulsivity / poor judgement	0	3	0
17	hoarding	0	2	0
18	inappropriateness	0	0	0
19	restlessness / roaming	0	0	2
20	aggression	0	1	0
21	hyperorality	3	2	3
22	hypersexuality	0	0	0
23	utilization behaviour	3	3	2
24	incontinence	3	2	3

*impossible to access

DISCUSSION

The main aim of our study was to better characterize and understand the nature of the progressive behavioral and personality changes in FTDP-17. Overall, the results of a prospective assessment of three cases of FTDP-17 with *MAPT* revealed that behavioral and personality abnormalities are common in this subtype of FTLD, and may be present relatively early in the course of the disease (see also Ghetti et al., 2008). Further, this study shows that apathy, indifference, and disinhibition, as well as compulsive and utilization behaviors, are among the most frequently seen behavior and personality changes in patients with FTDP-17 with *MAPT*, although the early behavioral profile strongly depends on the initial locus of neurodegeneration. Moreover, the behavioral profile of our cases was also related to the actual stage of the disease, and the results from the behavioral assessment with FBI have provided converging evidence for more negative symptoms at later disease stages.

In regard to the clinical symptoms and diagnosis of bvFTD, the Lund and Manchester clinical criteria (The Lund and Manchester Groups, 1994) have typ-

ically been used. These criteria indicate that impaired insight, disinhibition, loss of mental flexibility, stereotyped, perseverative and utilization behavior, hyperorality, distractibility as well as impulsivity are among the most sensitive diagnostic behavioral features. Further, recently revised criteria for bvFTD also imply that for the diagnosis of “possible” bvFTD at least three out of six of the following discriminating features are required: disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviors, hyperorality, and dysexecutive neuropsychological profile (Raskovsky et al., 2011). It may be worth mentioning here that Kertesz et al. (2003b) have demonstrated that such behavioral quantitation may be even more sensitive than neuropsychological testing in detecting FTD. In the present study, patients with FTDP-17 presented with 5 out of the 6 discriminating features proposed by Raskovsky et al. (2011). Thus the results of our study provide additional support for a substantial overlap in behavioral and personality changes between bvFTD and FTDP-17 with *MAPT*. Of note, whereas the behavioral and personality abnormalities in FTDP-17 with *MAPT* seem to be one of the hallmarks of this condition, they have been shown to be relatively less common in FTDP-17 with *GRN* mutation (Ghetti et al., 2008).

In contrast to FTD patients carrying *MAPT* mutations, neuroimaging studies have revealed strikingly asymmetric atrophy in the brains of FTD subjects with *GRN* (Rohrer & Warren, 2011; Rohrer et al., 2011; Whitwell et al., 2012). This asymmetry is often detected in the frontal, temporal and parietal regions, and the rate of atrophy in the left hemisphere seems to be higher than that in the right (Rohrer et al., 2012), suggesting an association of specific FTD gene mutations with asymmetric atrophy during disease progression. Importantly, the same pattern has been also shown in FTDP-17, indicating more asymmetric atrophy in FTDP-17 with *GRN* mutations than in cases with *MAPT*, who typically have rather symmetric frontotemporal atrophy (Ghetti et al., 2008). Interestingly, our findings do not seem to support these results, since all three patients in this study, despite a variable degree of diffuse neurodegeneration, had the predominance of either left or right hemispheric atrophy, most often in the frontotemporal areas.

The exact nature of the somewhat heterogeneous behavioral profile initially seen in our patients with FTDP-17 with *MAPT* is unknown. Interestingly, in the present study both patients with right-sided asymmetry in neuroimaging (in SPECT in both cases and also in MRI in Case 1) presented with a different behavioral profile at disease onset. Subject no. 2 was mainly disinhibited at onset, while Subject no. 1 was depressed and apathetic. Thus the asymmetric pattern of atrophy does not seem to fully explain the behavioral and personality profile seen in our patients. Also, our observations are only partially consistent with previous reports indicating that disinhibition, hypomania, impaired insight, and indifference are typically associated with right frontal damage, whereas the highest prevalence of depression has been noted following left hemisphere injury, particularly damage to the left frontal lobe (see Heilman et al., 2012; Robinson, 1998). Thus the present study adds to the discussion about the valence hypothesis, as well as the existence of mutually inhibitory interhemispheric processes

in regard to affect and emotion (see Harciarek & Heilman, 2009). Further, our results does not entirely support findings by Mychack et al. (2001), who argued that in FTD the early appearance of socially inappropriate behavior might help differentiate patients with predominantly right-sided from left-sided degeneration, additionally emphasizing the importance of right frontal regions in the mediation of social behavior (see also Harciarek & Cosentino, in press).

FTD is a disorder of paralimbic prefrontal-insular circuitry, with disinhibition, indifference and social cognition deficits being its hallmark clinical features (Caycedo et al., 2009). While an in-depth discussion of the construct of social cognition is beyond the scope of this article, it should be mentioned that social cognitive abilities consist of a number of processes that form the basis of the complex and dynamic set of behaviors and mutually shared expectations that enable individuals to effectively interact with one another across a range of different scenarios and environments (for review see Harciarek & Cosentino, in press). Thus, since FTD is most often associated with early and progressive neurodegeneration of orbitofrontal, anterior temporal as well as insular cortex, which subserves social cognitive abilities (Forbes & Grafman, 2010), atrophy to any of these regions would likely compromise some component abilities of social cognition. In turn, this would modify the way patients with FTD perceive or engage in social interactions, resulting in behavior perceived by an observer to be inappropriate or eccentric, as also took place in our patients with FTDP-17. Also, since right-sided networks appear to be particularly important for social cognition, and these networks have been shown to be specifically vulnerable in bvFTD (see Eslinger et al., 2011), based on early behavioral abnormalities observed in our cases no. 1 and no. 2, it could be hypothesized that the same right-sided anterior networks might be also particularly prone to be affected in FTDP-17. The mechanism accounting for this possible vulnerability of anterior right hemisphere networks in FTDP-17 has never been studied. Nonetheless, it has recently been shown that neurodegeneration in bvFTD may target specific neurons (i.e. von Economo neurons) that are both over-represented in the right anterior cingulate and frontoinsular cortex, as well as specialized for social cognition (Seeley et al., 2005). These morphologically unique and phylogenetically recent neurons offer an explanation as to why highly evolved capacities, such as self-awareness and social cognition, deteriorate early in FTD, and probably also in FTDP-17 with *MAPT* (Seeley et al., 2012). Future studies are warranted, however, to test this explanatory hypothesis.

It seems worth mentioning that patient No. 2 developed hypergraphia, which has often been seen in patients with temporal lobe epilepsy (Waxman & Geschwind, 1974). As already mentioned, Denny-Brown and Chambers (1958) proposed a reciprocally balanced and mutually inhibitory relationship between the frontal lobes and more posterior regions of the brain, so that lesions of either area will result in a transcortical release of the behaviors associated with the intact region. Thus it could be hypothesized that the initial neurodegeneration of frontal cortex may have disinhibited temporal regions, which became more ac-

tive, resulting in the development of hypergraphia (Paçhalska, 2012). Moreover, the existence of the mutually inhibitory intrahemispheric relationships may also have accounted for further changes in behavior and personality seen as the neurodegeneration progressed. Specifically, the increasing negative symptoms observed later in the disease course could have been related to the additional involvement of more posterior (temporo-parietal) regions mediating approach behaviors (Paçhalska, 2012).

Some support for this explanatory hypothesis comes from studies investigating patterns of change in social functioning in FTD. It has been demonstrated that as the temporal lobes become affected, there is a significant shift toward severe interpersonal coldness with loss of dominance. Further, increased rigidity and depression appear to be particularly common in patients with temporal atrophy, compared to those with bv-FTD (frontal atrophy), who in contrast tend to present with greater disinhibition (for review see Harciarek & Jodzio, 2005). Moreover, the same mechanism, i.e. gradual loss of the intrahemispheric mutual inhibition between frontal regions mediating avoidance behaviors and posterior regions responsible for approach behaviors, may also have accounted for the compulsive-like and utilization behaviors that appeared in our patients with FTDP-17. That is, the slowly progressing but predominant frontotemporal atrophy could have released approach behaviors, possibly contributing to compulsive touching, hoarding, and utilization behavior.

Alternatively, environmental dependency (ED) symptoms, such as imitation (echopraxia) and utilization behavior in both patients with FTD and those with FTDP-17 may be explained in relation to the mirror neuron system in the human brain. Mirror neurons, firstly identified in macaque monkeys in the ventral premotor cortex (Gentilucci et al., 1989) and then in the inferior parietal lobule (Fogassi et al., 2005), activate when the individual sees another person performing an action, or manipulating an object (Oztop et al., in press; Acharya & Shuckla, 2012). The activation of the mirror neurons system may thus lead to the recognition of an action, as well as facilitate initiation of the same motor program as the one observed. In neurologically intact adults, however, the recognition of an action performed by another individual or the recognition of a specific tool does not spontaneously lead to the imitation of a specific (e.g. tool-related) action itself, possibly due to the inhibitory effect of the prefrontal cortex. By comparison, patients with FTD often present with defective response inhibition attributed to a progressive prefrontal atrophy. Thus it seems likely that this faulty inhibitory mechanism may have accounted, at least partly, for the ED symptoms also observed in our patients with FTDP-17.

This study supports both the interfamilial and intrafamilial heterogeneity of neuropsychiatric presentation in FTDP-17 (Reed et al., 2001). On the one hand, personality changes are not observed in all cases of FTDP-17 (Bird et al., 1999). On the other hand, the specificity of neuropsychiatric symptoms may be mutation-associated. As mentioned, it may differ in patients with *GRN* and *MAPT* mutations. Additionally, the symptomatology may also be heterogenous within the

tau mutation spectrum.

There is little prospective psychometric data about the severity of neuropsychiatric symptoms in FTDP-17 patients. In the prospective study by Boeve et al. (2005), patients with *S305N tau* mutation did not have the psychotic symptoms that were present in our patients with *P301L MAPT* mutation. However, our patients, similarly to those reported by Boeve et al. (2005), showed progression of apathy and negative behaviors over the disease course. The comparison of the neuropsychiatric profile of siblings with *S305N tau* mutation against the profile of our patients with *P301L MAPT* mutation confirms also intrafamilial heterogeneity, frequently reported also in other *tau* mutations (Larner, 2009). In our pair of siblings, one was apathetic and depressive at onset, while the other was mainly disinhibited and even euphoric. Similarly, the proband reported by Boeve et al. (2005) was anxious and agitated and presented with aberrant motor behavior, while those features were absent in her sister during the reported observation period. Of note, the patients described by Boeve et al. (2005) were examined at earlier disease stages than our patients, which may partially explain the observed discrepancies.

This study has several limitations. First, it represents a retrospective case study approach and, hence, not all participants were tested using the same methods and at the same stage of the disease. Thus, our findings and conclusions need to be confirmed in prospective research with larger groups of FTDP-17 patients, and unified methods of behavioral and personality assessment. Secondly, there is evidence to suggest that the behavioral profile may be different in individuals with FTDP-17 with *MAPT* and those with a *GRN* mutation (see Ghetti et al., 2008); so, since we did not test subjects with mutations in *GRN*, our findings cannot be generalized to the entire population of FTDP-17 patients. Further, to fully understand the possible disturbances of inter- and intrahemispheric inhibitory processes in FTDP-17, future studies should also encompass prospective and more detailed neuroimaging data.

CONCLUSIONS

The results of this report indicate a substantial overlap in regard to behavioral and personality changes between FTDP-17 with *MAPT* and bvFTD. Further, this study suggests that in FTDP-17 with *MAPT* early specific behavioral and personality abnormalities may strongly depend on the initial locus of neurodegeneration (e.g., left vs. right frontal cortex) that is not as symmetric as previously thought. Also, these behavioral and personality changes seem to result from the disease-related dynamic imbalance between the inter- and intrahemispheric mutually inhibitory processes, which may possibly also account for symptom formation/change as the disease progresses, eventually resulting in a rather unified/converged behavioral profile of negative symptoms.

ACKNOWLEDGEMENTS

MH and EJS received scholarships from the Polish Ministry of Science and Higher Education during the preparation of the manuscript.

REFERENCES

- Acharya, S. & Shuckla, S. (2012). Mirror neurons: Enigma of the metaphysical brain. *Journal of Natural Science, Biology and Medicine*, 3, 118-124.
- Babinski, J. (1914). Contribution à l'étude des troubles mentaux dans l'hémiplegie organique cérébrale (anosognosie). *Revue Neurologique*, 27, 845-848.
- Benson, D. F. (1973). Psychiatric aspects of aphasia. *British Journal of Psychiatry*, 123, 555-566.
- Bird, T.D., Nochlin, D., Poorkaj, P., Cherrier, M., Kaye, J., Payami, H., Peskind, E., Lampe, T.H., Nemens, E., Boyer, P.J. & Schellenberg, G.D. (1999). A clinical pathological comparison of three families with frontotemporal dementia and identical mutations in the tau gene (P301L). *Brain*, 122, 741-756.
- Blessed, G., Tomlison, B.E. & Roth, M. (1968). The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *British Journal of Psychiatry*, 114, 797-811
- Boeve, B.F. & Hutton, M. (2008). Refining Frontotemporal Dementia With Parkinsonism Linked to Chromosome 17 Introducing FTDP-17 (MAPT) and FTDP-17 (PGRN). *Archives of Neurology*, 65, 460-464.
- Boeve, B.F., Tremont-Lukats, I.W., Waclawik, A.J., Murrell, J.R., Hermann, B., Jack, C.R., Shiung, M.M., Smith, G.E., Nair, A.R., Lindor, N., Koppikar, V. & Ghetti, B. (2005). Longitudinal characterization of two siblings with frontotemporal dementia and parkinsonism linked to chromosome 17 associated with the S305N tau mutation. *Brain*, 128, 752-772.
- Caycedo, A.M., Miller, B., Kramer, J. & Rascofsky, K. (2009). Early features in frontotemporal dementia. *Current Alzheimer Research*, 6, 337-340.
- Cummings, J. L., Mega, M., Gray K., Rosenberg-Thompson, S., Carusi D. A. & Gorbain, J. (1994). The Neuropsychiatric Inventory: a comprehensive assessment of psychopathology in dementia. *Neurology*, 44, 2308-2314.
- Davidson, R. J. (1984). Affect, cognition and hemispheric specialization. In C. E. Izard, J. Kagan, R. Zajonc (Eds.), *Emotions, cognition, and behavior* (pp. 320-365). New York: Cambridge University Press.
- Davidson, R. J., Ekman, P., Saron, C. D., Senulis, J. A., & Friesen, W. V. (1990). Approach-withdrawal and cerebral asymmetry: Emotional expression and brain physiology: I. *Journal of Personality and Social Psychology*, 58, 330-341.
- Denny-Brown, D., & Chambers, R. A. (1958). The parietal lobe and behavior. *Research Publications—Association for Research in Nervous and Mental Disease*, 36, 35-117.
- Dubois, A., Slachevsky, A., Litvan, I. & Pillon, B. (2000). The FAB -A frontal assessment battery at bedside. *Neurology*, 55, 1621-1626.
- Eslinger, P.J., Moore, P., Anderson, C. & Grossman, M. (2011). Social cognition, executive functioning, and neuroimaging correlates of empathic deficits in frontotemporal dementia. *Journal of Neuropsychiatry and Clinical Neuroscience*, 23, 74-82.
- Fogassi, L., Ferrari, P.F., Gesierich, B., Rozzi, S., Chersi, F. & Rizzolatti, G. (2005). Parietal lobe: from action organization to intention understanding. *Science*, 308, 662-667.
- Folstein, M.F., Folstein, S.E. & McHugh, P.R. (1975). Mini-mental state. *Journal of Psychiatry Research*, 12, 189-198
- Foster, N.L., Wilhelmsen, K., Sima, A.A., Jones, M.Z., D'Amato, C.J. & Gilman, S. (1997). Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. *Annals of Neurology*, 41, 706-715
- Forbes, C.E. & Grafman, J. (2010). The role of the human prefrontal cortex in social cognition and moral judgment. *Annual Review of Neuroscience*, 33, 299-324.
- Fox, N. A., Rubin, K. H., Calkins, S. D., Marshall, T. R., Coplan, R. J., Porges, S. W., et al. (1995). Frontal activation asymmetry and social competence at four years of age. *Child Development*, 66, 1770-1784.

- Gainotti, G. (1972). Emotional behavior and hemispheric side of lesion. *Cortex*, 8, 41–55.
- Gentilucci, M., Fogassi, L., Luppino, G., Matelli, M., Camarda, R. & Rizzolatti, G. (1989). Somatotopic representation in inferior area 6 of the macaque monkey. *Brain, Behavior & Evolution*, 33, 118-121.
- Ghetti, B., Spina, S., Murrell, J.R., Huey, E.D., Pietrini, P., Sweeney, B., Wassermann, E.M., Keohane, C., Farlow, M.R. & Grafman, J. (2008). In vivo and postmortem clinicoanatomical correlations in frontotemporal dementia and parkinsonism linked to chromosome 17. *Neurodegenerative Diseases*, 5, 215-217.
- Ghosh, A., Dutt, A., Bhargava, P. & Snowden, J. (2013) Environmental dependency behaviors in frontotemporal dementia: have we been underrating them? *Journal of Neurology*, 260, 861-866
- Goldstein, K. (1948). *Language and language disturbances*. New York: Grune and Stratton.
- Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S.F., ... Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology*, 76, 1006-1014.
- Grossman, M. (2010). Primary progressive aphasia: clinicopathological correlations. *Nature Review. Neurology*, 6, 88-97.
- Harciarek, M. & Cosentino, S. (2013). Language, Executive Function and Social Cognition in the Diagnosis of Frontotemporal Dementia Syndromes. *International Review of Psychiatry*, 25, 178-196
- Harciarek M. & Heilman K.M. (2009). The contribution of anterior and posterior regions of the right hemisphere to the recognition of emotional faces. *Journal of Clinical and Experimental Neuropsychology*, 31, 322-330.
- Harciarek M. & Jodzio K. (2005). Neuropsychological differences between frontotemporal dementia and Alzheimer's disease. *Neuropsychology Review*, 3, 131-145.
- Harciarek, M. & Kertesz, A. (2011). Primary progressive aphasias and their contribution to the contemporary knowledge about the brain-language relationship. *Neuropsychology Review*, 21, 271-287.
- Hecaen, H., Ajuriagurra, J., & de Massonnet, J. (1951). Les troubles visuoconstructifs par lesion parietooccipitale droit [Visuo-constructive disorders due to right parieto-occipital lesion]. *Encephale*, 40, 122–179.
- Heilman, K.M., Blonder, L.X., Bowers, D. & Valenstein, E. (2012). Emotional disorders associated with neurological diseases. In: K.M. Heilman, E. Valenstein (eds.), *Clinical Neuropsychology. 5th edition* (pp. 466-503), New York: Oxford University Press.
- Hodges, J.R. (ed.). (2007). *Frontotemporal dementia syndromes*. New York: Cambridge University Press.
- Hutton, M. (2001). Missense and splice site mutations in tau associated with FTDP-17: Multiple pathogenic mechanisms. *Neurology*, 56, S21–S25.
- Jastrowitz, M. (1888). Beitrage zur Localisation im Grosshirn and uber deren praktische Verwerthung [Remarks on cerebral localization and on its practical application]. *Deutsche Medizinische Wochenschrift*, 14, 81.
- Kertesz, A. (2011). Frontotemporal Dementia (FTD) 2011. *Acta Neuropsychologica*, 9, 103-114.
- Kertesz, A., Blair, M., McMonagle, P. & Munoz, D. (2007). The diagnosis and course of frontotemporal dementia. *Alzheimer Disease and Associated Disorders*, 21, 155-163.
- Kertesz, A., Davidson, W. & Fox, H. (1997). Frontal Behavioral Inventory: Diagnostic Criteria for Frontal Lobe Dementia. *The Canadian Journal of Neurological Sciences*, 24, 29-35.
- Kertesz, A., Davidson, W., McCabe, P. & Munoz, D. (2003b). Behavioral quantitation is more sensitive than cognitive testing in frontotemporal dementia. *Alzheimer Disease and Associated Disorders*, 17, 223-239.
- Kertesz, A., Davidson, W., McCabe, P., Takagi, K. & Munoz, D. (2003a). Primary progressive aphasia: diagnosis, varieties, evolution. *Journal of the International Neuropsychological Society*, 9, 710-719.
- Kinsbourne, M. (1982). Hemispheric specialization and the growth of human understanding. *American Psychologist*, 37, 411–420.
- Larner, A.J. (2009). Intrafamilial clinical phenotypic heterogeneity with MAPT gene splice site IVS10+16C>T mutation. *Journal of the Neurological Sciences*, 287, 253-256.
- Mesulam, M.M. (2003). Primary progressive aphasia—a language-based dementia. *New England Journal of Medicine*, 349, 1535-1542.
- Mesulam, M., Wicklund, A., Johnson, N., Rogalski, E., Leger, G.C., Rademaker, A., ... Bigio, E.H. (2008). Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. *Annals of Neurology*, 63, 709-719.

- Mukamel, R., Ekstrom, A.D., Kaplan, J., Iacoboni, M. & Fried, I. (2010). Single-neuron responses in humans during execution and observation of action. *Current Biology*, 20, 750-756.
- Mychack, P., Kramer, J. H., Boone, K. B. & Miller, B. L. (2001). The influence of right frontotemporal dysfunction on social behavior in frontotemporal dementia. *Neurology*, 56 (Suppl 4), 11–15.
- Narożańska, E., Jasińska-Myga, B., Sitek, E.J., Robowski, P., Brockhuis, B., Lass, P., Dubaniewicz, M., Wieczorek, D., Baker, M., Rademakers, R., Wszolek, Z.K. & Stawek, J. (2010). Frontotemporal dementia and parkinsonism linked to chromosome 17 - the first Polish family. *European Journal of Neurology*, 18, 535–537.
- Narożańska, E., Sitek E. & Stawek J. (2012). Otepienie czolowo-skroniowe z parkinsonizmem sprzezone z chromosomem 17 (FTDP-17) - z perspektywy neurologicznej i neuropsychologicznej. In: M. Pączalska & L. Bidzan (eds.), *Otepienie czolowo-skroniowe* (pp. 209-239). Kraków: Krakowska Akademia im. Andrzeja Frycza Modrzewskiego.
- Ongür, D., An, X. & Price, J.L. (1998). Prefrontal cortical projections to the hypothalamus in macaque monkeys. *Journal of Comparative Neurology*, 401, 480-505.
- Oztop, E., Kawato, M. & Arbib, M.A. (in press) Mirror neurons: functions, mechanisms and models. *Neuroscience Letters*. doi: 10.1016/j.neulet.2012.10.005.
- Pączalska, M. & MacQueen, B.D. (2000). Kwestionariusz Zachowań Osoby z Zespołem Czołowym. Authorized translation of the "Frontal Behavioral Inventory". Kraków: Fundacja na rzecz Osób z Dysfunkcjami Mózgu.
- Pączalska, M. (2007). *Neuropsychologia kliniczna-urazy mózgu*. Vol 2. Warsaw: Wydawnictwo Naukowe PWN.
- Pączalska, M. (2008). *Rehabilitacja neuropsychologiczna*. Lublin: Wydawnictwo UMCS.
- Pączalska, M., Bidzan, L., Lukowicz, M., Bidzan, M., Markiewicz, K., Jastrzebowska, G. & Talar, J. (2011). Differential diagnosis of behavioral variant of Fronto-Temporal Dementia (bvFTD). *Medical Science Monitor*, 17(6), CS 311-321.
- Pączalska, M. (2012). Behawioralny wariant otepienia czolowo-skroniowego (bvFTD) In: M. Pączalska & L. Bidzan (eds.), *Otepienie czolowo-skroniowe: Ujecie interdyscyplinarne* (pp. 113-143). Kraków: Wydawnictwo AFM.
- Paulson, H.L., & Stern, M.B. (1997). Clinical manifestations of Parkinson's disease. In R.L. Watts & W. C. Koller (eds.), *Movement Disorders - Neurologic Principles and Practice* (pp. 183-199). New York: Mc Graw-Hill Companies.
- Peplowska, B. & Wszolek, Z. K. (2005) Molekularne podloze FTDP-17. In: P.P. Liberski & Z. K. Wszolek (eds.), *Otepienia czolowo-skroniowe* (pp. 15-51). Lublin: Wyd. Czelej.
- Rabinovici, G. D., Jagusi, W. J., Furst, A. J., Ogar, J. M., Racine, C. A., Mormino, E. C. et al. (2008). Abeta amyloid and glucose metabolism in three variants of primary progressive aphasia. *Annals of Neurology*, 64, 388–401.
- Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J., van Swieten, J.C., Seele, H., Dopper, E.G., Onyike, C.U., Hillis, A.E., Josephs, K.A., Boeve, B.F., Kertesz, A., Seeley, W.W., Rankin, K.P., Johnson, J.K., Gorno-Tempini, M.L., Rosen, H., Prigleau-Latham, C.E., Lee, A., Kipps, C.M., Lillo, P., Piguet, O., Rohrer, J.D., Rossor, M.N., Warren, J.D., Fox, N.C., Galasko, D., Salmon, D.P., Black, S.E., Mesulam, M., Weintraub, S., Dickerson, B.C., Diehl-Schmid, J., Pasquier, F., Deramecourt, V., Lebert, F., Pijnenburg, Y., Chow, T.W., Manes, F., Grafman, J., Cappa, S.F., Freedman, M., Grossman, M. & Miller, B.L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*, 134, 2456-2477.
- Reed, L.A., Wszolek, Z.K. & Hutton M. (2001). Phenotypic correlations in FTDP-17. *Neurobiology of Aging*, 22, 89-107.
- Reuter-Lorenz, P., & Davidson, R. J. (1981). Differential contributions of the two cerebral hemispheres to the perception of happy and sad faces. *Neuropsychologia*, 19, 609–613.
- Robinson, R. (1998). *The clinical neuropsychiatry of stroke: cognitive, behavioral and emotional disorders following vascular brain injury*. New York: Cambridge University Press.
- Rohrer, J.D., Clarkson, M.J., Kittus, R., Rossor, M.N., Ourselin, S., Warren, J.D. & Fox, N.C. (2012). Rates of hemispheric and lobar atrophy in the language variants of frontotemporal lobar degeneration. *Journal of Alzheimers Disease*, 30, 407-411.
- Rohrer, J.D., Lashley, T., Schott, J.M., Warren, J.E., Mead, S., Isaacs, A.M., ...Warren, J.D. (2011) Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. *Brain*, 134, 2565-2581.

- Rohrer, J.D. & Warren, J.D. (2011). Phenotypic signatures of genetic frontotemporal dementia. *Current Opinion in Neurology*, 24, 542-549.
- Seeley, W.W., Bauer, A.M., Miller, B.L., Gorno-Tempini, M.L., Kramer, J.H., Weiner, M. & Rosen, H.J. (2005). The natural history of temporal variant frontotemporal dementia. *Neurology*, 64, 1384-1390.
- Seeley, W.W., Merkle, F.T., Gaus, S.E., Craig, A.D., Allman, J.M., Hof, P.R. & Economo, C.V. (2012). Distinctive neurons of the anterior cingulate and frontoinsula cortex: a historical perspective. *Cerebral Cortex*, 22, 245-250.
- Sitek, E., Narożańska, E., Sławek, J., Wieczorek, D., Brockhuis, B., Lass, P., Dubaniewicz, M., Jasińska-Myga, B., Baker, M., Rademakers, R. & Wszolek, Z.K. (2009). Unilateral neglect in a patient diagnosed with frontotemporal dementia and parkinsonism linked to chromosome 17. *Acta Neuropsychiatrica*, 21, 209-210.
- Sitek, E.J., Narożańska, E., Barczak, A., Jasińska-Myga, B., Harciarek, M., Chodakowska-Żebrowska, M., Kubiak, M., Wieczorek, D., Konieczna, S., Rademakers, R., Baker, M., Berdyński, M., Brockhuis, B., Barcikowska, M., Żekanowski, C., Heilman, K.M., Wszolek Z.K. & Sławek, J. (in press) Agraphia in patients with frontotemporal dementia and parkinsonism linked to chromosome 17 with P301L MAPT mutation: dysexecutive, aphasic, apraxic or spatial phenomenon? *Neurocase*. doi: 10.1080/13554794.2012.732087
- Sitek, E.J., Narożańska, E., Sławek, J., Wójcik, J., Wieczorek, D., Robowski, P., Schinwelski, M., Jasińska-Myga, B., Baker, M., Rademakers, R. & Wszolek, Z.K. (2010). Psychometric evaluation of personality in a patient with FTDP-17. *Psychiatry and Clinical Neurosciences*, 64, 211-212.
- Sitek, E.J., Barczak, A., Narożańska, E., Chodakowska-Żebrowska, M., Jasińska-Myga, B., Brockhuis, B., Berdyński, M., Wieczorek, D., Żekanowski, C., Konieczna, S., Barcikowska, M., Wszolek, Z.K. & Sławek, J. (2011). The role of neuropsychological assessment in the detection of early symptoms in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). *Acta Neuropsychologica*, 9, 209-226.
- Stuss, D.T., Alexander, M.P., Shallice, T., Picton, T.W. et al. (2005). Multiple frontal systems controlling response speed. *Neuropsychologia*, 43, 396-417.
- Stuss, D.T., Gow, C.A. & Hetherington, C.R. (1992). „No longer Gage”: frontal lobe dysfunction and emotional changes. *Journal of Consulting and Clinical Psychology*, 60, 349-359.
- Stuss, D.T. & Knight, R. (eds.). (2002). *Principles of frontal lobe function*. New York. Oxford University Press.
- Waxman, S.G. & Geschwind, N. (1974). Hypergraphia in temporal lobe epilepsy. *Neurology*, 24, 629-636.
- Whitwell, J.L., Xu, J., Mandrekar, J., Boeve, B.F., Knopman, D.S., Parisi, J.E., Senjem, M.L., Dickson, D.W., Petersen, R.C., Rademakers, R., Jack, C.R. Jr, Josephs, K.A. (2013). Frontal asymmetry in behavioral variant frontotemporal dementia: clinicoimaging and pathogenetic correlates. *Neurobiology and Aging*, 34, 636-639
- Wszolek Z.K., Krygowska-Wajs A. & Barcikowska M. (2003) Ołębienie czołowo-skroniowe z zespołem parkinsonowskim sprzężone z chromosomem 17 (FTDP-17): kryteria kliniczne. *Neurologia i Neurochirurgia Polska*, 37, 173-184.

Address for correspondence:

Michał Harciarek

Department of Clinical Psychology and Neuropsychology,

Institute of Psychology, University of Gdańsk,

Bażyńskiego 4,

80-952 Gdańsk, Poland

e-mail: psymh@univ.gda.pl