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Neuropsychological phenotype and psychopathology in seven adult patients with Phelan-McDermid syndrome: implications for treatment strategy

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Phelan-McDermid syndrome (PMS) or 22q13.3 deletion syndrome is characterized by a variable degree of intellectual disability, impaired speech and language as well as social communicative skills and mild dysmorphic features. The *SHANK3* gene is thought to be a major contributor to the phenotype. Apart from the syndrome-associated autistic features, symptoms from the bipolar spectrum can be discerned, in particular behavior instability and fluctuating mood culminating in a (hypo)manic state. In case of coincident major somatic events, a deteriorating course may occur. This study comprises seven adult patients (four females and three males; aged 21–44 years) with genetically proven PMS. Data from medical records were collected and extensive assessment of neuropsychological variables was performed to identify cognitive characteristics and their relation with psychopathology and treatment. All patients showed profound communication deficits and their developmental functioning ranged from 1.0 to 6.3 years. In addition, they had slow speed of information processing, impairment of attentional and executive functions and cognitive alexithymia. As to psychopathology, features from the affective and anxiety domains were prominent findings in these seven patients suggesting the presence of a bipolar spectrum disorder that could be effectively moderated with mood-stabilizing agents. Results are discussed in terms of the putative involvement of structural brain abnormalities, in particular cerebellar vermis hypoplasia and corpus callosum thinning and their cognitive and emotional sequelae. It is concluded that the treatment of 22q13.3-associated psychopathology should include prescription of mood-stabilizing agents in combination with individually tailored contextual neuropsychological measures.

Keywords: Atypical bipolar disorder, cerebellum, cognition, contextual neuropsychology, mood-stabilizing treatment, neuropsychological phenotype, Phelan-McDermid syndrome, *SHANK3*

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Phelan-McDermid syndrome (PMS [OMIM: 606232]), also known as 22q13.3 deletion syndrome, was first described in the late 1980s by Phelan and co-workers and is characterized by moderate to profound intellectual impairment and severely restricted speech and expressive language in the absence of major dysmorphic features (Phelan *et al.* 1988, 2001). The behavioral phenotype with severely impaired communicative and social skills essentially presents with symptoms from the autism spectrum (Phelan 2008).

The syndrome is typically caused by loss of the distal long arm of chromosome 22 (Phelan & McDermid 2011). The diagnosis is made by genome-wide array analysis which resulted in a significant increase in the identification of PMS in recent years. The most important gene in the critical deleted region, *SH3 and multiple ankyrin repeat domains 3* (*SHANK3*, also known as *ProSAP2*) gene, is located on 22q13.3 [OMIM: 603230] and implicated in the pathophysiology of the syndrome. The *SHANK3* gene is involved in the functionality of postsynaptic (glutamatergic) structures of the central nervous system (Bonaglia *et al.* 2001; Guilmatre *et al.* 2014; Jamain *et al.* 2003) and is likely to be responsible for the clinical features of the disorder especially for the development of language and social communication (Bonaglia *et al.* 2006; Durand *et al.* 2007). Although *SHANK3* is assumed to be the main gene contributing to the phenotype, the severity of the clinical presentation has been reported to be related to the deletion size, indicating that other genes may also contribute to the phenotype (Kolevson *et al.* 2014).

The neurobehavioral phenotype is characterized by communication deficits, hypotonia, sleep disturbances, repetitive motor activities, attentional problems and increased reactivity to sensory stimuli (Cusmano-Ozog *et al.* 2007; Prasad *et al.* 2000). With respect to the latter, a paradoxical reaction

pattern can be discerned with lack of responsiveness to verbal or pain stimuli but exaggerated reactions to sudden environmental events that frequently manifest as challenging behaviors (Philippe *et al.* 2008). Furthermore, the PMS phenotype may include seizures of different types (Figura *et al.* 2014).

Albeit that autistic features have regularly been identified in the PMS phenotype, in postadolescent patients, psychiatric symptoms from the bipolar spectrum appear to be more prominent (Denayer *et al.* 2012; Pasini *et al.* 2010; Serret *et al.* 2015; Verhoeven *et al.* 2012a,b, 2013; Vucurovic *et al.* 2012). Oscillations of mood and behavior may be related to the cerebellum, commonly associated with the modulation of cognition and emotion (De Smet *et al.* 2013; Hoppenbrouwers *et al.* 2008; Schmahmann 2010; Schmahmann *et al.* 2007; Verhoeven *et al.* 2012a,b; Villanueva 2012). Indeed, apart from a broad range of structural brain abnormalities (Kolevson *et al.* 2014), cerebellar malformations such as vermis hypoplasia are reported in PMS patients (Aldinger *et al.* 2013; Verhoeven *et al.* 2012a). In some patients, deterioration of general functioning may occur, even starting at young age and often following acute medical events such as seizures and infections (Denayer *et al.* 2012; Serret *et al.* 2015; Soorya *et al.* 2013; Willemsen *et al.* 2012).

Although over the past decades nearly 300 patients with PMS have been described (Bonaglia *et al.* 2011; Dhar *et al.* 2010; Sarasua *et al.* 2014; Soorya *et al.* 2013), the neuropsychiatric diagnosis and treatment is reported in only 13 patients, however, without any information about the underlying cognitive mechanisms (Table 1). To address this issue, this study aims at the detailed description of neurocognitive functioning in seven adult patients with PMS in order to provide tools for an adequate treatment strategy. For further illustration, a detailed case description is also included.

Methods

All patients were referred to the Vincent van Gogh specialized outpatient Department for Psychopathology and Genetics in Venray, The Netherlands, for extensive examination of recurrent challenging behaviors. Most of them were included in the research project on PMS of the University Medical Centre Groningen.

Apart from standardized neuropsychiatric examination with careful analysis of data from the medical records, detailed evaluation of the major neuropsychological domains was performed by formal assessments, whenever possible. To this end, the level of intellectual disability and adaptive functioning was recorded by means of Vineland Screener (Scholte *et al.* 2008) and Snijders-Oomen Non-Verbal Intelligence Test (Tellegen *et al.* 1998). Memory was tested with two subtests of the Dutch Neuropsychological test battery for elderly patients with mild intellectual disability (Verberne 1998) and visuospatial and motor functioning with the Beery Test (Beery *et al.* 2004). From these tests, also, levels of speed and executive processes were derived.

As to social cognition, assessment was performed with the Theory of Mind Test (Steerneman *et al.* 2003) and proxy versions of the Bermond-Vorst Alexithymia Questionnaire (Vorst & Bermond 2001) and the Toronto Alexithymia Scale (Bagby *et al.* 1994). Alexithymia can be defined as a disturbance in affective information processing and social cognitive functions in which the corpus callosum and the cingulate and insular cortex are involved as well as the amygdala and (orbito) prefrontal cortex (the latter two as mediators of the affective process in general). Typically, two subtypes are distinguished, i.e. *affective alexithymia*, reflecting problems in the conscious experience of arousal that accompanies emotions, and *cognitive alexithymia*, that refers to difficulties in identifying, verbalizing and analyzing emotions (Swart *et al.* 2009; Wingbermühle *et al.* 2012). Finally, interpersonal functioning and psychopathology were investigated by means of the Psychopathology Inventory of Mentally Retarded Adults (Matson *et al.* 1994).

In line with the guidelines of Lezak *et al.* (2004) for persons in whom formal testing with complex tasks is difficult, performance on ineligible domains was assigned through independent clinical judgment by the first and the last author. Actual test results were presented in *z*-scores.

Results

Case example (patient 2 from Table 2)

The patient is a 22-year-old female and has one healthy older brother. Apart from prenatal growth retardation, pregnancy and delivery were undisturbed. From the early months on, hypotonia and feeding problems became apparent. Developmental history was characterized by delayed milestones, global intellectual disability, sleep disturbances, ritualistic/compulsive behaviors and, in particular, delayed development of speech and receptive language. At the age of 4 years, Wechsler Intelligence Scale for Children-Revised developmental assessment showed a verbal and performance IQ of 71 and 55, respectively. An unbalanced translocation 11;22 with derivative chromosome 22 was shown by means of conventional karyotyping. The patient attended special education until the age of 18 years. Since her late adolescence, recurrent mood changes paralleled by an increase of pre-existent autistic behaviors became prominent. Treatment with paroxetine was started 6 months prior to referral to our institute. Shortly thereafter, her behavior further derailed with possibly hallucinatory experiences. On subsequent addition of haloperidol, later replaced by risperidone, she developed symptoms from a serotonin syndrome for which she was hospitalized. Discontinuation of all psychotropics and symptomatic somatic treatment resulted in a rapid remission and the patient was discharged to her parent's home. In retrospect, the initial hallucinatory derailment of behavior could be attributed to a previously unrecognized delirious reaction to a urinary tract infection that was only diagnosed during the hospitalization period. As her general functioning did not reach premorbid levels, she was referred for extensive diagnostic assessment.

At examination, the patient presented with mild intellectual disability, mood instability accompanied by fluctuating obsessive behaviors, attentional and social cognitive dysfunctions (marked cognitive alexithymia) without, however, signs of major affective or psychotic disorder. Motor functioning was undisturbed.

Microarray analysis showed a terminal 11q24.2q25 duplication of 8.77 Mb and a terminal 22q13.33 deletion of 512 kb [arr 11q24.2q25(126.236.301-134.938.471)x3.22q13.33(50.791.826-51.197.839)x1, (Affymetrix, Santa Clara, CA, USA) cytoscan HD array, Human Genome build HG19]. The 22q13.33 deletion encompassed 23 genes including

Table 1: Case reports on neuropsychiatric diagnosis and treatment of adult patients with PMS

Authors	Sex/age (years, months)	Level of ID	Key symptoms	Previous treatment and result	Psychiatric diagnosis	Brain imaging results (MRI unless otherwise stated)	Treatment	Result
Pasini *et al.* (2010) ($n=1$)	F/18	Severe	Periods of mood oscillation and hyperactivity	Resistance to benzodiazepines and haloperidol	—	—	Risperidone up to 6 mg daily	Marked stabilization of mood and behavior, only at the dose of 1 mg risperidone
Vucurovic *et al.* (2012) ($n=1$)	M/18	Severe	Disinhibited behaviors, affective instability and rapid mood swings	No effect of several antipsychotics and antidepressants	Atypical bipolar disorder	No abnormalities	carbamazepine (400–800 mg) and aripiprazole (30 mg)	Stabilization of mood changes
Verhoeven *et al.* (2012a) ($n=2$)	M/29	severe	sleep disturbances, disinhibited behaviors, depressed mood	no effect of selective serotonin reuptake inhibitor (SSRIs) and haloperidol	atypical bipolar disorder	hypoplasia cerebellar vermis	nortriptyline (50 mg) and valproic acid (1200 mg)	stabilization of mood and behavior
	M/31	Severe	Unstable pattern of mood and activity and recurrent depressive episodes	—	Atypical bipolar disorder	Hypoplasia cerebellar vermis	Carbamazepine (400 mg) and paroxetine (30 mg)	Stabilization of mood and behavior
Verhoeven *et al.* (2013) ($n=1$)	F/70	Severe	Episodes with psychomotor agitation and sleep disturbances	No effect of lithium, valproic acid, antipsychotics and antidepressants	Atypical bipolar disorder	No developmental abnormalities	Carbamazepine (600 mg) and pipamperone (120 mg)	Partial stabilization of mood and behavior
Denayer *et al.* (2012) ($n=5$)	M/17.8	Severe	Episodic impulsivity	—	—	Normal (10 months)	Mianserin*	—
	F/24.9	Severe	Psychotic and catatonic symptoms and severe swings of mood and activity	No effect of neuroleptics and benzodiazepines	Rapid cycling bipolar disorder	Normal [computer tomography (CT) at 19 years]	Lithium, valproic acid, carbamazepine*	—
	F/43.10	Severe	—	—	Bipolar disorder	Corticosubcortical atrophy (CT at 41 years)	—	—
	M/46.6	Severe	Unstable pattern of mood and sleep	No effect of haloperidol (neuroleptic malignant syndrome)	Bipolar disorder	Basal ganglia infarctions (CT at 40 years)	Valproic acid*	—
	F/51.11	Severe	—	—	Bipolar disorder	Corticosubcortical atrophy (CT at 43 years)	—	—

Table 1: Continued.

Authors	Sex/age (years, months)	Level of ID	Key symptoms	Previous treatment and result	Psychiatric diagnosis	Brain imaging results (MRI unless otherwise stated)	Treatment	Result
Messias *et al.* (2013) ($n = 1$)	F/38	Moderate	Symptoms of the affective and psychotic spectrum	No response to SSRI or benzodiazepine monotherapy	Adult onset psychosis	—	Quetiapine (600 mg)	Remission of psychosis and persistent depressive symptoms
Serret *et al.* (2015) ($n = 2$)	M/21	Severe	Disinhibited behaviors, confusion, catatonic symptoms, deterioration	No effect of several antipsychotics and antidepressants	Atypical bipolar disorder	—	Lithium (0.8 mmol/l)	Stabilization of mood and behavior
	F/17	Severe	Disinhibited behaviors, confusion, catatonic symptoms, deterioration	Partial effect of benzodiazepines	Atypical bipolar disorder	—	Lithium (0.7 mmol/l)	Stabilization of mood and behavior

*Daily dose not mentioned.

SHANK3. Assessment of routine hematological and biochemical parameters as well as genotyping cytochrome P450 1A2, 2C9, 2C19 and 2D6 showed normal values. magnetic resonance imaging (MRI) of the brain with special attention for cerebellar structures disclosed no abnormalities.

In addition to educational and pedagogic recommendations based on her neuropsychological profile (e.g. environmental structuring and low expressed emotion to avoid social-emotional overestimation), treatment with valproic acid was started. After 6 months, a dose of 600 mg/day (plasma concentration: 45 mg/l) had resulted in a notable stabilization of mood and behavior and less prominent behavioral problems albeit that previous performance levels were still not fully attained. Planned addition of quetiapine, for further stabilization through relapse prevention, has not been performed yet. As the patient awaits transfer from her parent's home to a specialized sheltered home facility, addition will be reconsidered when transfer has taken place.

Neuropsychological profiles

For all patients, deletion size, neuropsychological data and proposed treatment regimen with preliminary results, where possible, are specified in Table 2. The level of intellectual disability varied between mild and moderate to profound with a corresponding range of adaptive functioning and developmental ages (1.0–6.3 years). In all, marked impairment of speech and language formed the core dysfunctions. Speed of information processing, attention and executive functioning were in general mildly impaired, whereas memory, visuospatial and visuomotor functioning corresponded with developmental age. As to social cognition, diminished perspective taking, in particular marked cognitive alexithymia, was present. With respect to psychopathology and interpersonal functioning, typical characteristics were from the affective and anxiety domains with, for example, impulsive, irritable and demanding behaviors.

Brain imaging and treatment response

As can be inferred from Table 2, in four patients, MRI brain was performed yielding vermis hypoplasia in three of them. In all, treatment was started with the implementation of contextual measures based on their individual profiles. In five patients, a mood-stabilizing anticonvulsant was prescribed that resulted in marked stabilization of mood and behavior. Three of them were additionally treated with the atypical antipsychotic quetiapine.

Discussion

In this study, the results of extensive assessment of seven adult patients with genetically proven PMS are described, focusing on the treatment utility of the individual cognitive and psychopathological profile.

The phenotype of PMS comprises a moderate to severe cognitive disability with profound communication deficits,

Table 2: Neuropsychological characteristics of patients with PMS

	1	2	3	4	5	6	7
Sex	Male	Female	Female	Female	Male	Male	Female
Age	44	22	33	23	31	30	21
Karyotype	46, XY, del(22)(q13.33; q13.33)	46, XX, der(22)t(11;22) (q24.2;q13.33)	46, XX, del(22)(q13.32; q13.33)	46, XY, der(22)t(8;22) (q24.3;.q13.33) (8qtel+;22gtel−)dn	46, XY, del(22)(q13.32; q13.33)	46, XY, del(22)(q13.32; q13.33)	46, XX, del(22)(q13.33)
Del22q13 size	~63 kb	~515 kb	~1.98 Mb	Unknown	~2.15 Mb	~2.15 Mb	~88 kb
Level of ID	Profound	Mild to moderate (SON IQ = 61)	Mild to moderate (SON-IQ = 55)	Profound	Moderate to severe	Severe	Mild to moderate (SON-IQ = 60)
SON-R6-40	—	−2.90	−2.95	—	—	—	−2.74
Adaptive functioning (years, months)	—	—	—	—	—	—	—
Total	1.2	6.3	3.7	1.0	3.3	2.4	4.8
Communication	1.6	—	3.9	0.8	3.0	1.1	5.0
Social	1.2	—	3.3	0.10	3.1	2.4	4.9
Daily functioning	1.2	—	7.3	1.4	3.8	2.11	4.7
Motor	—	—	7.9	1.7	3.1	3.1	4.0
Attention	—	Marked dysfunction	Mild dysfunction	Marked dysfunction	Mild dysfunction	Mild dysfunction	Mild dysfunction
Speed of information processing	—	Slow	Slow	Very slow	Slow	Slow	Slow
Memory	—	Conform	Perseveration	Perseveration	Conform	Conform	Strong in all modalities
NETOL 8 word test (total correct; *z*-score)	—	−0.37	−2.42	—	—	—	—
NETOL 8 word test (recognition; *z*-score)	—	0.82	−4.89	—	—	—	—
NETOL story (immediate recall; *z*-score)	—	0.72	−1.50	—	−1.22	—	—
NETOL story (delayed recall; *z*-score)	—	1.18	−1.18	—	−0.29	—	—
Visuospatial and visuomotoric functioning	—	Conform	Conform	Conform	Conform	Conform	Impaired
Beery visual-motor integration (*z*-score)	—	−0.8	0.0	—	—	—	<−3.00
Beery visual perception (*z*-score)	—	−0.5	<−2.60	—	—	—	−2.67
Beery motor coordination (*z*-score)	—	0.9	0.3	—	—	—	<−3.00
Speech/spontaneous speech	Virtually absent speech (single words only)	Incomplex sentences	Poor articulation, simple sentences	Absent	Poor articulation, elementary sentences	Virtually absent single words only	Elementary sentences

Table 2: Continued

	1	2	3	4	5	6	7
Expressive language	Very limited	Limited	Very limited	Extremely limited	Limited	Very limited	Limited
Receptive language	Extremely limited	Very limited	Very limited	Very limited	Very limited	Very limited	Very limited
NETOL sentence completion (*z*-score)	—	0.86	−2.71	—	−1.29	—	0.86
Executive functioning	—	Mild dysfunction	Mildly impaired	Conform	Mildly impaired	Mildly impaired	Mildly impaired
WISC-III Mazes (*z*-score)	—	−3.0	—	—	—	—	−3.0
EFI by proxy (*z*-score)	—	—	—	—	—	—	−1.92
Social cognition including socio-emotional functioning	0.6	Impaired perspective taking	Impaired emotion recognition and perspective taking	Conform	Conform	Conform	Impaired emotion recognition and perspective taking
TOM test revised total score/TOM-related (developmental age in years, months)	—	<−2/4.0	<−2/5.6	—	—	—	−1.75/8.0
BVAQ by proxy (affective alexithymia; *z*-score)	—	0.81	0.81	—	—	—	2.37
BVAQ by proxy (cognitive alexithymia; *z*-score)	—	5.08	5.08	—	—	—	4.64
TAS-20 recognition (*z*-score)	—	0.65	0.37	—	—	—	1.21
TAS-20 description (*z*-score)	—	1.45	2.01	—	—	—	1.78
TAS-20 extern (*z*-score)	—	2.01	1.33	—	—	—	3.60
TAS-20 total score (*z*-score)	—	1.65	1.40	—	—	—	2.64
Interpersonal functioning	Irritability	Anxious and demanding	Anxious, easily disbalanced	Desperation, fiddling, and disquietedness diminish during interpersonal contact	Irritable and disinhibited	Impulsive and challenging	Irritable and episodic disinhibited
Main psychiatric domain (PIMRA total)	Affective (14)	Affective/anxiety (23)	Anxiety (9)	Affective (7)	Affective (10)	Affective (18)	Affective/anxiety (11)
MRI brain	Not possible	No abnormalities	Hypoplasia of cerebellar vermis and mild ventricular enlargements	Not possible	Hypoplasia of cerebellar vermis and mild ventricular enlargements	Hypoplasia of cerebellar vermis and mild ventricular enlargements	Not available

Table 2: Continued

	1	2	3	4	5	6	7
Treatment regimen and response	Profile-based contextual measures augmented with pipamperone (120 mg, 250 μg/l); lamotrigine (350 mg; 4.2 mg/l); levothyroxine (125 μg); marked stabilization of mood and behavior (6 months)	Profile-based contextual measures augmented with valproic acid (600 mg; 45 mg/l); marked improvement of functioning (9 months)	Profile-based contextual measures augmented with valproic acid (600 mg); quetiapine (300 mg); marked improvement of functioning (>1 year)	Profile-based contextual measures augmented with (proposed) valproic acid and quetiapine; treatment advice not implemented	Profile-based contextual measures augmented with valproic acid (900 mg; 69 mg/l); quetipapine (150 mg; 112 μg/l); marked improvement of functioning (3 months)	Profile-based contextual measures augmented with valproic acid (600 mg, 39 mg/l); quetiapine (800 mg, 45/154 μg/l); full stabilization of mood and behavior (>1 year)	Profile-based contextual measures augmented with quetiapine (1000 mg; 455 μg/l at 800 mg);marked improvement of functioning (>1 year)
Remarks on previous pharmacological treatment	Olanzapine tapered off; valproic acid (1650 mg) replaced by lamotrigine (350 mg; 4.2 mg/l)	—	—	—	Long-lasting treatment with paroxetine and carbamazepine gradually tapered off	—	Fluoxetine, lithium and valproic acid tapered off because of side effects

Conform, performance corresponding developmental age/level of ID. PIMRA, Psychopathology Inventory for Mentally Retarded Adults (maximum total score = 56; Matson *et al.* 1994; Sturmey & Ley 1990). SON-R6-40, Snijders-Oomen Non-Verbal Intelligence Test (Tellegen *et al.* 1998). TOM-test-R, Theory of Mind Test-Revised (Steerneman *et al.* 2003). Beery VMI, Beery-Buktenica Developmental Test for Visual-Motor Integration (Beery *et al.* 2004). EFI, Executive Function Index (Janssen *et al.* 2009). BVAQ, Bermond-Vorst Alexithymia Questionnaire (Vorst & Bermond 2001). TAS-20, Toronto Alexithymia Scale (Bagby *et al.* 1994). NETOL, Neuropsychologische Testset voor Ouderen met Licht verstandelijke handicap (Neuropsychological test battery for elderly patients with mild intellectual disability) (Verberne 1998). WISC-III, Wechsler Intelligence Scale for Children-III (Kort *et al.* 2002).

characterized by dysfunctions in speech/language and executive attention, as well as cognitive alexithymia and emotional instability. This constellation appears to form the core of the observed enhanced sensitivity to environmental stimuli which, in turn, may intensify mood oscillations. In fact, in postadolescents, this specific neuropsychological and psychopathology profile can be best typified as a disorder of affect and cognition, pointing at a PMS-specific atypical bipolar disorder for which a pharmacological treatment strategy with valproic acid and/or quetiapine, like in 'classical' bipolar disorder, would be a rational choice (Chiesa *et al.* 2012; Cipriani *et al.* 2013). Our data are in support of those from the literature as presented in Table 1 suggesting that a treatment regimen with mood-stabilizing agents in combination with tailored contextual measures based on the individual neuropsychological profile appears effective in balancing mood and behavior and in preventing relapses.

Interestingly, similar to the case report presented here, regression in motor and social skills with a slow and possibly incomplete recovery may occur after acute somatic events (Bonaglia *et al.* 2011; Denayer *et al.* 2012; Serret *et al.* 2015; Soorya *et al.* 2013). This phenomenon may be obscured by previously described increase of autistic-like behaviors that may occur in response to sudden environmental events (Philippe *et al.* 2008).

The enhanced susceptibility to mood dysregulations as seen in PMS patients may be associated with structural abnormalities of the cerebellum and corpus callosum. The cerebellum has been shown to significantly contribute to the modulation of behavior, cognition and emotion, maintaining context bound homeostasis, disturbances of which sometimes are referred to as cerebellar cognitive affective syndrome (Schmahmann 2010; Schmahmann *et al.* 2007). In particular, hypoplasia of the cerebellar vermis can be observed in patients with PMS (Aldinger *et al.* 2013; Tabolacci *et al.* 2005, Verhoeven *et al.* 2012b). In addition to the cerebellum, morphological irregularities of the corpus callosum, especially thinning, are reported in PMS (Aldinger *et al.* 2013; Doheny *et al.* 1997; Lindquist *et al.* 2005; Philippe *et al.* 2008) and, because of the involvement in the interhemispheric communication, hypothesized to be implicated in bipolar disorder too (Arnone *et al.* 2008; Bellani *et al.* 2009; Lloyd *et al.* 2014; Serafini *et al.* 2014). Here, in three of the four patients with the available MRI results, hypoplasia of the cerebellar vermis was found, adding to the aforementioned hypothesis. Still, the relationship between cerebellar abnormalities and (susceptibility to) mood dysregulations should be further investigated in larger samples.

To summarize, firstly, based on individual histories showing a fluctuating pattern of mood paralleled by variations in the intensity of autistic-like behaviors, a diagnosis of atypical bipolar disorder is most appropriate and necessitates a mood-stabilizing pharmacotherapy. Secondly, techniques from the neuropsychological and cognitive behavioral domain, such as goal management and perspective taking training, should be applied to compensate for the impaired orchestration of cognition and emotion. Such a combined treatment strategy is meant to reduce the risk for relapse of a bipolar episode and to reduce hyper-reactivity to contextual stimuli.

In conclusion, the emerging neuropsychological profile of PMS with specific attentional, executive and social cognitive deficits, against the background of the regulatory function of the cerebellum, provides vistas for a personalized rehabilitative treatment approach in patients with PMS.

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