Psychopathology in premanifest C9orf72 repeat expansion carriers

The clinical phenotype of behavioural variant frontotemporal dementia (bvFTD) is characterised by neuropsychiatric symptoms, including loss of empathy, compulsive behaviour, behavioural disinhibition and apathy. An expansion of a hexanucleotide (GGGGCC) repeat in the chromosome 9 open reading frame 72 gene (c9orf72^{RE}) is the most common genetic cause of bvFTD. Neurobiological and behavioural changes have been evidenced in carriers of c9orf72^{RE}, decades before the estimated onset of symptoms. Recently, Gossink and colleagues investigated the hypothesis that the c9orf72^{RE} genotype phenotypically could encompass a neuropsychiatric hypervulnerability, emerging during early childhood. They used clinical case-record data and performed semi-structured biographical interviews with spouses, first-degree relatives and patients with bvFTD with (N=20) and without (N=23) c9orf72^{RE}. The results revealed limited empathic behaviour early in life and increased rates of compulsive personality traits in c9orf72^{RE} carriers.[1]

Notably, the c9orf72^{RE} does not only cause bvFTD but may also result in amyotrophic lateral sclerosis (ALS), in which it is more frequently associated with neuropsychiatric symptoms, compared with non-c9orf72^{RE} ALS variants. In addition, socioemotional deficits consistent with empathic impairment have been reported in c9orf72^{RE}-carriers with only very mild cognitive and/or functional impairments.[2] Also, increased hazard ratios for psychiatric disorders have been reported in kindreds of c9orf72^{RE} carriers.[3] These combined findings give rise to the hypothesis that, compared with the general population, the prevalence of psychopathological characteristics is increased in c9orf72^{RE} carriers who do not (yet) fulfil the clinical diagnostic criteria for bvFTD or ALS, which we term premanifest carriers in accordance with other genetic disorders.

Inspired by the study of Gossink and colleagues, we tested this hypothesis in 21 c9orf72^{RE} carriers. The number of c9orf72 repeats exceeded 30 in all participants and none of the participants met the clinical diagnostic criteria for ALS or FTD. We conducted a comprehensive psychopathological assessment and compared this with control samples in the literature[4–9] that covered the age range of our sample and that were of the same linguocultural region, if available. We focused on subjective complaints as well as on clinical observations and presence of psychiatric syndromes. All data were collected by trained clinical psychologists or psychiatrists in training, who regularly screened subjects for psychiatric assessment and who were unaware of the genetic status of the present participants. Student's t-tests and χ^2 tests were used to compare means and proportions, respectively.

First, we assessed psychological and somatic complaints by means of the Symptom Checklist, a 90-item multidimensional self-report questionnaire in which participants indicate the subjective severity of 90 psychological (eg, feelings of anxiety) and somatic (eg, palpitations) phenomena on a 5-point Likert scale. The subscales are listed in table 1 and the scores were compared with a sample of healthy control subjects (N=2368).[4] There were no significant differences in psychological and somatic functioning (table 1).

Second, the Comprehensive Psychopathological Rating Scale (CPRS) was used to rate the severity of psychiatric symptoms and psychiatric behaviour. The CPRS is a semistructured interview, in which 40 self-report and 25 observational items are rated on a 7-point Likert scale. As scores above 2 are considered clinically relevant, we listed the symptoms and score frequencies of the items on which at least one participant obtained a rating of 3 or more (table 1). Most commonly, participants reported clinically relevant complaints of inertia (n=5, 23.81%), aches and pains (n=4, 19.05%), reduced sleep, fatigability and failing memory (n=3, 14.29%) (table 1).

The CPRS further encompasses scales for depression and anxiety (ie, the Montgomery and Åsberg Depression Rating Scale and the Brief Anxiety Scale (BAS)) on which we compared our cohort to healthy reference samples (N=1291),[5 6] which did not reveal any significant results (table 1). To the best of our knowledge, no suitable reference data are available in the literature for the other measures, so no additional statistical comparisons were performed. The scores are provided for descriptive purposes.

Third, to estimate the point prevalence of psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders 4thedition (DSM-IV),[10] we used the short structured Mini International Neuropsychiatric Interview. We compared the proportion in our cohort fulfilling the DSM-IV criteria for each disorder to the equivalent proportion in a general population sample (N=1117).[7] This comparison revealed a significantly increased prevalence in our sample for three disorders: eight c9orf72^{RE}-carriers (38%) met the clinical criteria for depressive disorder, seven (33%) for post-traumatic stress disorder and six (29%) for substance abuse or dependence. Four out of eight participants with depressive disorder also met the criteria for post-traumatic stress disorder. One participant met the diagnostic criteria for both depressive disorder and substance abuse/dependence.

We also assessed general cognition with the MMSE. All participants scored above the clinical cut-off (mean (range), 29.43 (27–30)). We calculated Spearman correlations with the psychopathology measures, which did not reveal any significant results (all p's>0.05).

Finally, to converge with the findings of Gossink *et al*,[1] we assessed empathic abilities by means of the Revised Self-Monitoring Scale (RSMS) and the empathic concern scale of the Interpersonal Reactivity Index (IRI), measuring sensitivity to socioemotional cues and allocentric feelings of sympathy for unfortunate others, respectively. Comparisons to healthy reference samples[8 9] revealed significantly reduced scores for both variables (RSMS: $t(84)=379.21$; $p<0.001$; IRI: $t(670)=45.10$, $p<0.001$; see also table 1), replicating other recent findings.[2] Interestingly, there was a positive association between MMSE score and empathic concern score of the IRI ($\rho=0.52$, $p=0.03$), suggesting that worse global cognitive function impedes affective empathic abilities in premanifest c9orf72^{RE}-carriers.

Our study has the following limitation. Given the lack of suitable reference data for the CPRS, we were unable to perform any additional statistical analyses, apart from the performance on the Montgomery Asberg Depression Rating Scale and the BAS. We, thus, reported on the prevalence of clinically relevant scores in our cohort, for descriptive purposes.

To conclude, we observed a notably increased point prevalence of psychiatric syndromes in our cohort of 21 premanifest c9orf72^{RE} carriers. Interestingly, this was not reflected in participants' self-reports of psychiatric symptoms, potentially aligning with FTD-typical anosognosia. The present findings converge with those of Gossink *et al*,[1] underscoring the psychiatric hypervulnerability associated with c9orf72^{RE}. Our results also add to previously documented empathic deficits[2] by revealing increased rates of depressive

Table 1 Neuropsychological and psychiatric measurements

	Premanifest C9orf72^{RE}	Reference sample	Statistical results	
	Mean (SD)	Mean (SD)	Test statistic	P value
The Symptom Checklist-90				
Agoraphobia	7.67 (1.46)	7.86 (2.34)	t(2385)=0.14	0.71
Anxiety	12.24 (3.13)	12.76 (4.41)	t(2385)=0.29	0.59
Depression	22.24 (7.89)	21.58 (7.56)	t(2386)=0.16	0.69
Somatization	16.33 (4.90)	16.68 (5.34)	t(2386)=0.09	0.77
Insufficiency of thinking and acting	13.71 (4.69)	12.63 (4.25)	t(2380)=1.34	0.25
Sensitivity	22.95 (8.11)	24.05 (7.64)	t(2385)=0.43	0.51
Hostility	7.00 (1.22)	7.22 (2.10)	t(2385)=0.23	0.63
Sleep disturbance	5.29 (1.82)	4.46 (2.20)	t(2380)=2.97	0.09
Psycho-neuroticism	118.67 (32.48)	118.28 (32.38)	t(2387)=0.00	0.96
The Comprehensive Psychopathological Rating Scale (CPRS)				
Montgomery and Asberg Depression Rating Scale	2.43 (2.77)	2.7 (3.2)	t(1310)=0.18	0.67
Brief Anxiety Scale	2.95 (3.84)	3.91 (3.92)	t(1310)=1.24	0.27
	3	4	5	6
	N(%)	N(%)	N(%)	N(%)
CPRS*				
Sadness	1 (4.76)	0	0	0
Elation	0	1 (4.76)	0	0
Hostile feelings	2 (9.52)	0	0	0
Inability to feel	0	1 (4.76)	1 (4.76)	0
Worrying over trifles	0	2 (9.52)	0	0
Indecision	2 (9.52)	0	0	0
Inertia	5 (23.81)	0	0	0
Fatigability	2 (9.52)	1 (4.76)	0	0
Concentration difficulties	1 (4.76)	0	0	0
Failing memory	3 (14.29)	0	0	0
Reduced appetite	1 (4.76)	0	0	0
Reduced sleep	1 (4.76)	2 (9.52)	0	0
Aches and pains	2 (9.52)	2 (9.52)	0	0
	N (%)	N (%)	Test statistic	P value
The MINI-International Neuropsychiatric Interview				
Depressive disorder	8 (38.10)	12 (1.07)	$\chi^2(1,1117)=163.62$	<0.001
Panic disorder	0 (0)	4 (.36)	NA	
Agoraphobia	0 (0)	27 (2.42)	NA	
Social phobia	0 (0)	10 (.09)	NA	
Specific phobia	0 (0)	9 (.81)	NA	
Generalised anxiety disorder	0 (0)	13 (1.16)	NA	
Posttraumatic stress disorder	7 (33.33)	5 (.45)	$\chi^2(1,1117)=213.65$	<0.001
Obsessive compulsive disorder	0 (0)	6 (.54)	NA	
Alcohol abuse or dependence	6 (28.57)	51 (4.57)	$\chi^2(1,1117)=24.97$	<0.001
	Mean (SD)	Mean (SD)	Test statistic	P value
Revised Self-Monitoring Scale				
Total score	41.30 (6.40)	58.20 (1.70)	t(84)=379.21	<0.001
Interpersonal reactivity index				
Empathic concern	11.78 (3.56)	18.05 (4.23)	t(670)=45.09	<0.001

Values indicate: count (percentage) or mean (SD).
*CPRS rating: 3=*symptom is clinically relevant, but not always present*, 4=*symptom is almost continuously present*, 5=*symptom is continuously present* and 6=*dominant symptom*.

disorder, post-traumatic stress disorder and substance abuse/dependence, with high comorbidity rates. Whether these are c9orf72^{RE} generic or relate to the environmental stressors that are associated with an ontogeny in an affected family[3], remains an open question. Longitudinal studies in early life c9orf72^{RE} and non-carrier siblings may reveal further insights into the interplay between environmental, genetic, neurobiological and psychopathological factors, and the relation of subjective complaints to pheno-conversion.

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