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# ORIGINAL ARTICLE

# Theory of mind and executive dysfunction in chronic inflammatory demyelinating polyneuropathy

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## Abstract

Background and purpose: Although chronic inflammatory demyelinating polyneuropathy (CIDP) is understood as a disease affecting the peripheral nervous system, mild cognitive dysfunction, particularly in the executive domain, has been described to form part of the condition. Here our interest lay in CIDP-related theory of mind (ToM) capacities as an aspect of social cognition relevant for many aspects of everyday life.

Methods: Twenty-nine patients with CIDP and 23 healthy controls participated in this study. They were subjected to overview cognitive testing, different executive function (EF) tasks, as well as to the Faux Pas Recognition Task (FPRT) for assessing cognitive ToM and the Reading the Mind in the Eyes Test (RMET) with respect to affective ToM.

Results: Persons with CIDP and controls did not differ with respect to their overall cognitive state. However, in the German verbal fluency standard, the digit span forward and the digit span backward tests used as EF tasks patients performed significantly worse than controls. Further, performance was abnormally low in the FPRT, whilst the groups did not differ with respect to RMET results. The FPRT and digit span backward results correlated with each other.

Conclusions: Patients with CIDP showed deficits in cognitive ToM performance together with EF dysfunction, whilst affective ToM was preserved. Altogether, the results suggest that low cognitive ToM capacities in patients with CIDP arise as a particular aspect of disease-related executive dysfunction.

#### KEYWORDS CIDP, cognitive dysfunction, executive function, theory of mind

# INTRODUCTION

Peripheral nerve damage is not commonly associated with mental dysfunction. Yet, low performance in cognitive tasks imposing executive processing demands has been reported to prevail in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) [1]. This interesting finding raises further questions,

amongst others, with respect to social cognition, aspects of which are thought to involve executive functioning (EF) [2]. The determination of corresponding task performances could therefore extend the description of CIDP-related mental change with respect to relevant competences needed for everyday life and, at the same time, help to conceptualize the nature of poorly defined cognitive disease sequelae.

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Theory of mind (ToM) is a central aspect of social cognition and can be divided into two major functional domains [3-5]. On the one hand, 'affective' ToM summarizes empathy-related functions, allowing for a relatively immediate understanding of sensory input which the perceiver can relate to own mental states, for example observed facial or bodily expressions. It is typically viewed as the result of automatic processes for the imagery of another person's condition in one's own mind, conceivable as a reenactment of an own emotional state [6, 7]. In contrast to this, 'cognitive' ToM denotes the capacity to interpret social situations and interactions, for example with respect to the delineation of strategies behind a particular conduct. It comprises complex computations in order to attribute meaning to external behaviors and construe them as targeted action plans [8]. For example, when listening to a story in which different protagonists occur, one needs to update the concept of the portrayed social event constantly during the narration, switch between the perspectives of the presented characters, store information and flexibly retrieve it. In so doing, cognitive ToM as the active reasoning about information on social situations and events involves EF-related operations to a higher degree than affective ToM as the decoding of emotional stimulus valence [9]. According to its constitutive character for human behavior, ToM is a research focus in various academic disciplines, taking quite different perspectives, for example, in brain sciences with a key interest in involved neuroanatomical regions or in cognitive psychology often following a more systemic approach. With regard to the latter, embodied cognition (EC) theories hold a particular position, especially with respect to the affective part of ToM. A central EC idea, relevant for both normal and pathological states, is that sensorimotor simulation of observed behaviors serves to generate a mental copy of the agent's condition in the recipient [10-16]. Various clinical findings have been interpreted in this general framework, for example ToM deficits in persons with central motor impairments, such as Parkinson's disease (PD) or Huntington's disease. However, even peripheral muscle denervation was associated with dysfunctions of emotional content processing [17]. Such occasional reports seem to tie in with the strictest EC positions, according to which, failures of sensorimotor integrity contribute to affective ToM deficits, independently from the physical level of the underlying neuronal disorder [18-20]. Of course, if this were true, it would have important implications for peripheral nerve diseases.

In the initially mentioned study on cognitive functioning of patients with CIDP ToM performances were not tested, and the identified executive deficits were interpreted as a symptom of neuroinflammation, subtly affecting the central nervous system next to its predominant targets at peripheral sites [1]. Against this background, performances in cognitive and affective ToM tasks were assessed in persons with CIDP and healthy controls together with a number of further cognitive capacities. For the outlined interrelatedness of cognitive ToM and EF, it was presumed that, if CIDP was associated with executive dysfunction, it should also impact on cognitive ToM capacities. In contrast to this, a predominant affective ToM deficit without EF and cognitive ToM impairment would be compatible with the theoretical position that sensorimotor dysfunction, independently from its origin, hampers the embodiment of other persons' mental condition.

# PARTICIPANTS

For the patient group, 29 persons diagnosed with CIDP according to the European Federation of Neurological Societies/Peripheral Nerve Society criteria were enrolled from the outpatient clinic for neurology at the Charité, Campus Benjamin Franklin [21]. All patients were on stable treatment with intravenous immunoglobulins. They were free of other neurological and/or psychiatric diseases, including overt or confirmed cognitive dysfunction, at odds with typical CIDP presentation. Twenty-three participants without CIDP and further neurological and/or psychiatric diseases were recruited from the pool of accompanying persons for the control group. To control for potential language-related confounders, only native German speakers were enrolled. Both groups were matched with respect to age, sex and years of education (see Table 1).

# Assessment of sensorimotor dimensions of disease burden

To delineate disease severity in the CIDP group, the Rasch-built overall disability scale (R-ODS) was used [22]. This instrument for measuring the severity of neuropathies focuses on potential restrictions in 24 representative routine activities of everyday life, reflected by point scores between 0 (worst, complete incapacity for all activities) to 48 (best, full capacity in any of the activities). In the CIDP group only, grip strength and pain were additionally determined with a Martin vigorimeter [23] and the visual analog scale (VAS), respectively, in order to relate surrogate markers of sensorimotor affection to parameters of cognitive functioning.

**TABLE 1** Demographic data of the chronic inflammatory demyelinating polyneuropathy (CIDP) and control groups.

	CIDP group N = 29)	Control group (N = 23)
Age in years	65.03 (SD=12.14)	66.22 (SD=9.43)
Gender	17 male, 12 female	12 male, 11 female
Years of education	10.31 (SD=1.58)	10.91 (SD=1.88)
Mean disease duration in years	6.25 (SD = 5.42)	_
R-ODS	36.17 (SD=7.27)	_
Martin vigorimeter	27.89 (SD=11.17)	_
VAS	4.00 (SD=2.90)	_

Abbreviations: R-ODS, Rasch-built overall disability scale; VAS, visual analog scale.

All participants gave written informed consent to the study protocol in accordance with the Declaration of Helsinki and approved by the ethics committee of the Charité (protocol number EA/165/16).

# METHOD

### Theory of mind assessments

Each participant engaged in two standard ToM paradigms, the Reading the Mind in the Eyes Task (RMET) and the Faux Pas Recognition Test (FPRT). In the RMET participants have to determine the emotional states of persons based on photos of the eyes and the periocular area respectively (one photo per person). The choice has to be made from four predefined possibilities per photo. Per participant, 36 trials are run, and the test score is built as the sum of correct determinations. Since the task requires the decoding of visually presented facial expressions, the RMET is thought to primarily involve empathetic processing, that is, it tests affective ToM [24]. In contrast to this, the FPRT is a textbased task. It consists of short descriptions of situations in which protagonists interact and communicate with each other. Five of the 10 stories presented describe normal conduct; the other five stories contain some inappropriateness in the behavior of one protagonist according to commonly accepted social rules. Per story, participants are required to answer (i) whether a misconduct was present (Faux Pas Detection) and, if this was the case, (ii) why it should be deemed as inappropriate (Faux Pas Inappropriateness); (iii) which goal was pursued by the misconduct (Faux Pas Intention): (iv) whether it followed a strategy of the protagonist or occurred accidentally (Faux Pas Belief); and (v) which emotions it could evoke in the protagonists (Empathy). For each correct (incorrect) response, one (no) point is given. If the response to the first answer (Faux Pas Detection) is incorrect, none of the above-mentioned further questions is asked but a general understanding of the story is addressed by two further questions without changing the point score. Scores for each subscale as mentioned above are calculated as arithmetic means across all stories (stories including a Faux Pas and control stories). Although the last question in the FPRT addresses an aspect of affective ToM, the entire task paradigm emphasizes the cognitive aspects of ToM involving strategic reasoning, changing the perspective etc. [25, 26].

## Further cognitive assessments

Against the background of previously reported executive dysfunction in CIDP particularly affecting verbal fluency (VF), participants performed the German standard test (Regensburger Wortfluessigkeitstest) [1, 27]. It is composed of four conditions, namely semantic alternating (words denoting animals and furniture alternatingly), semantic non-alternating (words denoting vegetables), phonemic alternating (g-words and r-words alternatingly) and phonemic nonalternating word production (s-words). In each of the four parts, as many words as possible have to be named within 2 min. Proper names and words containing the same word stem are not allowed. The VF score is the sum of correctly produced words over the four conditions, based on the digital recordings of the subjects' performances. Further, our interest was in working memory functions, assessed as the maximum forward and backward digit memory span (DS-F and DS-B), association learning, tested by the short-term and delayed recall of pair associations, and in visuoconstructive capacities, tested by a mental rotation task. The formal assessment tools were taken from the Parkinson Neuropsychomotoric Dementia Assessment (PANDA), a test construct similar to the Montreal Cognitive Assessment. The PANDA was used here since it imposes comparably high executive demands, previously reported to be affected in CIDP, and since the investigation was part of a larger series of studies implying persons with PD. The total score, ranging from 0 (worst) to 30 (best), is provided as an index of the general cognitive status [28]. Further, mood was assessed using the Hamilton Depression Inventory (HAMD) as it might interfere with cognitive performance.

#### **Statistical analyses**

To test for normal distribution of the data, Kolmogorov-Smirnov tests were performed and Q-Q plots and histograms were visually inspected. Results showed that the RMET and VF variables were normally distributed; however, all other variables were not normally distributed. Thus, an independent sample t test was conducted to test for differences in the RMET between groups. To analyze potential differences in the VF test, a mixed model design ANOVA was conducted with the within-subject factor VF subscales (four levels: semantic non-alternating, semantic alternating, phonemic non-alternating, phonemic alternating) and the between-subject factor group (two levels: CIDP group, control group). Significant interactions involving group or VF subscales are reported. Post hoc pairwise comparisons were applied in the case of significant interactions involving group or VF subscales. After Bonferroni corrections, statistical test results had a significance threshold of p < 0.05. In the case of sphericity violation, the Greenhouse-Geisser correction was performed. Non-parametric Mann-Whitney U tests were applied to test for group differences with respect to non-normally distributed variables, for the results from FPRT, DS-F, DS-B, PANDA and HAMD.

To test for associations between variables within the CIDP group, Spearman correlations were conducted for all subscales of the FPRT with the VF subscales, DS-F, DS-B, PANDA, HAMD, VAS, grip strength, disease duration in years and R-ODS.

Finally, five different backwards multivariate linear regressions were carried out within the CIDP group to test for predictive effects of the VF subscales, DS-F and DS-B, PANDA, HAMD, disease duration, grip strength, VAS and R-ODS as independent variables on the different subscales of the FPRT as outcome variables. All statistical analyses were performed with SPSS (IBM SPSS Statistics Version 28.0).

# RESULTS

The CIDP and control groups did not differ from each other with respect to RMET performance (CIDP group M=22.72 [SD=3.305] vs. control group M=23.48 [SD=3.953], t(50)=0.75, p=0.46).

Concerning VF, the ANOVA showed a significant main effect of group (F(1, 50)=8.42, p=0.005,  $\eta^2$ =0.14) with lower scores in the CIDP group compared to the control group. The mean numbers of correct words produced per subtask were 20.36 (SE=0.951) in controls and 16.66 (SE=0.847) in participants with CIDP (see Figure 1).

Further, a significant effect of VF subscale (F(2.35, 117.33) = 29.78,  $p \le 0.001$ ,  $\eta^2 = 0.37$ ) was found with lower scores across both groups in the semantic non-alternating subscale (M = 13.60) compared to the semantic alternating subscale (M = 20.52,  $p \le 0.001$ ), the phonemic non-alternating subscale (M = 20.46,  $p \le 0.001$ ) and the phonemic alternating subscale (M = 18.62,  $p \le 0.001$ ). The Greenhouse–Geisser correction method was applied for violation of the sphericity assumption. There were no interactions between group and subscale (F(2.35, 117.33) = 1.16, p = 0.321,  $\eta^2 = 0.023$ ), indicating that the lower VF scores in CIDP patients than in controls were unrelated to the particular subtask demand.

Mann–Whitney *U* tests showed significant differences between CIDP and control groups for all FPRT subscales (see Table 2). Further, results showed significant differences between groups for the DS-F, DS-B and HAMD scores. No differences were seen in the PANDA score (see Table 3).

The Spearman analyses showed that the results in all FPRT subcategories significantly correlated with the DS-B test in the CIDP group (see Table 4). Further, singular correlations of the FP Intention subscale were identified with the DS-F (r=0.538 p=0.003, 95%CI 0.202, 0.760) and with the PANDA (r=0.405 p=0.029, 95% CI 0.034, 0.678).

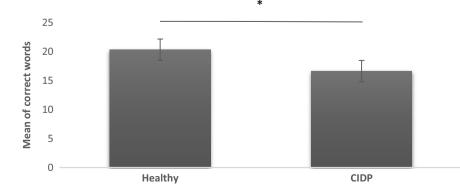
The results of the regression analyses showed that DS-B performance significantly predicted FP Detection (b = 0.034, p = 0.047) and FP Belief performance (b = 0.075, p = 0.004). The regression model with FP Detection performance as outcome variable reached significance with p = 0.047 and  $R^2 = 0.110$ , whereas the model with FP Belief performance as outcome variable was significant with p=0.029 and  $R^2=0.223$ . Further, performance in the DS-B (b=0.079, p=0.011), PANDA (b=0.024, p=0.005) and HAMD (b=0.014, p=0.018) were significant predictors for FP Intention performance ( $R^2=0.390$ , p=0.004). For FP Empathy performance, the significant predictors DS-B (b=0.078, p<0.001), HAMD (b=0.011, p=0.007), R-ODS (b=0.007, p=0.027) and disease duration (b=0.015, p=0.003) were found ( $R^2=0.420$ , p=0.002). The regression model with FP Inappropriateness performance as the outcome variable did not reach significance ( $R^2=0.102$ , p=0.054).

# DISCUSSION

The main result of this study is an impairment of cognitive ToM and further executive task performances in persons with CIDP. Concerning the different tests used, DS-B performance turned out as most related to the results in the five subscales of the FPRT. Further, affective ToM performance as measured by the RMET was not found different in CIDP compared to controls.

The exact impact of EF on social cognitive capacities has been evaluated somewhat heterogeneously in studies implying different neurological and psychiatric conditions as well as healthy persons [29-32]. However, most researchers agree on the notion that ToM involves a number of basic EF operations [30, 32, 33] such as the transition between tasks (shifting), replacement of outdated by new information in working memory (updating), suppression of impulses unsuited for the realization of ongoing behavioral plans (inhibition) and the retrieval of memory information (access) [34-36]. Social cognitive demands involving these processes prevail in cognitive rather than in affective ToM, for example if one has to change the perspectives of different persons on a given situation, if premature responses have to be suppressed, and whenever particular informational details need to be kept available for later access [37, 38]. In line with this, associations between EF and cognitive rather than affective ToM performance have been reported, particularly in the context of the age-related decline of mental functions [39-42].

With respect to the tasks used in the current study, the FPRT entails cognitive ToM demands such as the maintenance of the story contents in short-term memory and their selective recall to reconfigure them as a function of the characters' interactions,



**FIGURE 1** Mean of correct words over all verbal fluency subscales. Error bars  $\pm 2$ standard errors; \*indicates p < 0.05. Boxes show means for both groups (healthy M = 20.36, SE = 0.951; CIDP M = 16.66, SE = 0.847). Mixed ANOVA shows a significant difference for the mean of correct words over all subscales between the groups. CIDP, chronic inflammatory demyelinating polyneuropathy.

**TABLE 2** Mean scores and statistical results of the FauxPas (FP) subscales for the chronic inflammatory demyelinatingpolyneuropathy (CIDP) and control groups.

		Control	Statistics
	CIDP	group	р
FP Detection	0.892 (0.110)	0.965 (0.060)	0.005**
FP Inappropriateness	0.889 (0.115)	0.965 (0.065)	0.007**
FP Intention	0.829 (0.192)	0.951 (0.081)	0.003**
FP Belief	0.853 (0.145)	0.947 (0.085)	0.004**
FP Empathy	0.850 (0.141)	0.941 (0.094)	0.010*

*Note*: Standard deviations are presented in parentheses. \**p*<0.05; \*\**p*<0.01.

 TABLE 3
 Mean scores and statistical results of the cognitive assessment for the chronic inflammatory demyelinating polyneuropathy (CIDP) and control groups.

			Statistics
	CIDP	Control group	p
DS-F	6.31 (1.365)	7.39 (1.559)	0.011*
DS-B	4.83 (1.197)	5.74 (1.322)	0.008**
PANDA	24.34 (4.220)	26.30 (4.332)	0.054
HAMD	5.66 (6.241)	2.17 (2.249)	0.049*

Note: Standard deviations are presented in parentheses.

Abbreviations: DS-B, digit span backwards; DS-F, digit span forwards; HAMD, Hamilton Depression Inventory; PANDA, Parkinson Neuropsychomotoric Dementia Assessment. \*p < 0.05; \*\*p < 0.01.

**TABLE 4**Spearman rank order correlations for the chronicinflammatory demyelinating polyneuropathy (CIDP) group.

	DS-B		
	r <sub>s</sub>	CI	р
FP Detection	0.395	0.022, 0.672	0.034*
FP Inappropriateness	0.377	0.001, 0.660	0.044*
FP Intention	0.489	0.138, 0.731	0.007**
FP Belief	0.392	0.018, 0.669	0.036*
FP Empathy	0.390	0.016, 0.668	0.036*

Abbreviations: CI, confidence interval; DS-B, digit span backwards;  $r_{\rm s},$  Spearman rank correlation coefficient.

p < 0.05; p < 0.01.

concepts, intentions and empathy [30]. Interestingly, FPRT performances in all subcategories were weakly yet significantly correlated with the DS-B results. This may be explained by overlapping requirements in the FPRT and the DS-B, where number sequences have to be stored and afterwards manipulated within working memory, inverting the original digit order. This also fits in with the weakly predictive value of DS-B results for performances in the different FPRT dimensions, for some of which additional measures were identified as predictive cofactors. Specifically, this held true for the scores of mood and global cognition with respect to the FPRT dimension Intention, as well as for the scores of mood, disease severity and disease duration with respect to the FPRT dimension Empathy. Thus, next to the presumed interaction between cognitive ToM and EF decline, the data suggest an association of the social cognitive deficit with sensorimotor as well as some non-sensorimotor disease burden.

The absence of a performance deficit in the RMET task in CIDP patients is of interest under different aspects. Clinically, it specifies the profile of social cognitive dysfunction in CIDP patients, suggesting affective ToM be spared from the pathological process, in contrast to the described affection of cognitive ToM. This particular result is of note, since knowledge about non-physical consequences of CIDP is altogether scarce. In particular, studies on CIDP-related quality of life changes raised the question of whether also nonphysical factors contribute to reduced quality of life [43-46]. Mostly, this research showed increased pain, depressiveness, anxiety or fatigue as clinical problems, whereas cognitive dysfunction has only consistently been shown in one previous trial to our knowledge [1, 43-46]. Against this background, a comprehensive assessment of a potential cognitive impact of CIDP seems worthwhile for pragmatic reasons. Conceptually, the results give rise to two short remarks. First, the observed CIDP-related EF decline together with low FPRT, but not RMET performance, supports the assumption that executive operations are important for cognitive rather than affective ToM capacities. Second, the data imply reference to strict EC claims. In this theoretical framework, affective ToM processing eventually involves the different levels of the sensorimotor system and, accordingly, should be hampered by systemic damage of mixed nerves [11, 47, 48]. This assumption was not confirmed using the example of CIDP. However, according to the fluid spectrum of EC positions, the result does not exclude EC effects in general or other interactions between body state and mental condition in the particular case of CIDP [49].

Of course, our study has several limitations. The conducted ToM tests are standard paradigms, but if and to what degree they reflect real-world behaviors remains unclear, which calls for studies on CIDP-related social cognition in natural environments. For example, it would be interesting to systematically assess how attachment figures evaluate the interaction (and its potential disease-related change) with CIDP-affected relatives, spouses, partners or friends. Further, it is important to note that EC concepts comprise a fluid spectrum of ideas, but here reference is only made to the most extreme EC concept, which entails the remote theoretical possibility that even peripheral nerve dysfunction impacts on the sensorimotor copying of perceived information [50]. However, moderate EC views were not put to the test, claiming some subtle involvement of central sensorimotor networks in cognitive processing [49]. A critical point refers to the affective state of persons with CIDP and controls. The former had higher HAMD scores than the latter, the difference being just significant. Although the scores were not indicative of relevant depressiveness, they indicate certain mood differences between

the participants in the different groups. This, being unsurprising in view of the chronic disease burden in CIDP, implies that mood change could have contributed to the cognitive symptoms of the patients. Thus, although it is probably difficult to reach equivalent HAMD scores between persons with and without CIDP, this point should be taken into account in further studies, possibly enrolling cohorts large enough for subanalyses of mood-matched patients and controls. Finally, insight into the nature of cognitive affection in CIDP would certainly profit from the implementation of, for example, functional imaging techniques, a challenge for future trials.

In conclusion, persons with CIDP show deficits of cognitive ToM. They probably arise as a result of executive dysfunction, evident as low performances in further EF tasks. The findings extend previous reports on subtle cognitive deficits associated with the disease and raise some principal questions, for example whether non-peripheral CIDP sequelae are neglected and how important such symptoms may be in the everyday life of affected persons. In a condition in which the focus is naturally on the most evident sensorimotor consequences of the polyneuropathy, this calls for particular attention to a broader spectrum of symptoms and for further research in this field.

#### AUTHOR CONTRIBUTIONS

Hannah Lochmann: Data assessment, statistics, writing (original draft), revision, editing, tables and figures. Michelle Wyrobnik: Data evaluation, statistics, revision and editing. Christin Kupper: Data assessment. Charlotte Rewitzer: Concept, methods. Fabian Klostermann: Concept, methods, project administration, supervision, data evaluation, writing, revision, editing.

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#### CONFLICT OF INTEREST STATEMENT

Fabian Klostermann received honoraria for lecturing and advisory activities, unrelated to the presented research, from Abbvie, Stadapharm, Esteve and CSL Behring.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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