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Empathy in multiple sclerosis—Correlates with cognitive, psychological and occupational functioning

K. van der Hiele[a,b,c,*], E.E.A. van Egmond[a,b,c,d], P.J. Jongen[e,f], J.J.L. van der Klink[g,o], E.A.C. Beenakker[h], J.J.J. van Eijk[i], S.T.F.M. Frequin[j], E. Hoitsma[k], J.P. Mostert[l], W.I.M. Verhagen[m], D.A.M. van Gorp[d], H.A.M. Middelkoop[a,n], L.H. Visser[c,d]

[a] Institute of Psychology, Health, Medical and Neuropsychology Unit, Leiden University, PO Box 9555, 2300 RB, Leiden, the Netherlands
[b] National Multiple Sclerosis Foundation, Industrieweg 130C, 3044 AT, Rotterdam, the Netherlands
[c] Department of Neurology, Elisabeth-TweeSteden Hospital, PO Box 90151, 5000 LC, Tilburg, the Netherlands
[d] Department of Care Ethics, University of Humanistic Studies, PO Box 797, 3500 AT, Utrecht, the Netherlands
[e] MS4 Research Institute, Ubbergseweg 34, 6522 KJ, Nijmegen, the Netherlands
[f] Department of Community & Occupational Medicine, University of Groningen, University Medical Centre Groningen, PO Box 30001, 9700 RB, Groningen, the Netherlands
[g] Tilburg School of Social and Behavioural Sciences, Tranzo Scientific Centre for Care and Welfare, Tilburg University, PO Box 90153, 5000 LE, Tilburg, the Netherlands
[h] Department of Neurology, Medical Centre Leeuwarden, PO Box 888, 8901 BR, Leeuwarden, the Netherlands
[i] Department of Neurology, Jeroen Bosch Hospital, PO Box 90153, 2000 ME, 's-Hertogenbosch, the Netherlands
[j] Department of Neurology, St. Antonius Hospital, PO Box 2500, 3430 EM, Nieuwegein, the Netherlands
[k] Department of Neurology, Alrijne Hospital Leiden, PO Box 9650, 2300 RD, Leiden, the Netherlands
[l] Department of Neurology, Rijnstate Hospital, PO Box 9555, 6800 TA, Arnhem, the Netherlands
[m] Department of Neurology, Canisius-Wilhelmina Hospital, PO Box 9015, 6500 GS, Nijmegen, the Netherlands
[n] Department of Neurology, Leiden University Medical Centre, PO Box 9600, 2300 RD, Leiden, the Netherlands
[o] Optentia, North West University of South Africa, PO Box 1174, Vanderbijlpark, South-Africa

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ABSTRACT

Background: Recent studies report deficits in social cognition in individuals with multiple sclerosis (MS). Social cognitive skills such as empathy are important for adequate social and occupational functioning. Our objectives are: (1) to examine whether empathy differs between individuals with MS and healthy controls, (2) to examine relations between empathy and cognitive, psychological and occupational functioning.

Methods: 278 individuals with MS (relapsing-remitting subtype) and 128 healthy controls from the MS@Work study participated in this investigation. The participants completed questionnaires about demographics, cognitive, psychological and occupational functioning, and underwent neurological and neuropsychological examinations. Mann-Whitney U-tests were used to examine group differences in empathy. Pearson and Spearman rank correlation analyses were used to examine relations between empathy and the other measures.

Results: Empathy did not differ between individuals with MS and healthy controls. In individuals with MS, higher empathy was correlated with a higher educational level (X^2(df) = 13.2(2), $p = 0.001$), better verbal learning ($r = 0.20$, $p = 0.001$), less symptoms of depression ($r = -0.21$, $p = 0.001$), higher extraversion ($r = 0.25$, $p \leq 0.001$), agreeableness ($r = 0.55$, $p \leq 0.001$) and conscientiousness ($r = 0.27$, $p \leq 0.001$) and better occupational functioning in terms of work scheduling and output demands ($r = 0.23$, $p = 0.002$) and less cognitive/psychological work barriers ($r = -0.21$, $p = 0.001$). In healthy controls, higher empathy was correlated with less symptoms of depression ($r = -0.34$, $p \leq 0.001$), less fatigue ($r = -0.37$, $p \leq 0.001$), higher agreeableness ($r = 0.59$, $p \leq 0.001$) and better occupational functioning in terms of work ability as compared to lifetime best ($r = 0.28$, $p = 0.001$) and less cognitive/psychological work barriers ($r = -0.34$, $p \leq 0.001$). Empathy did not differ between unemployed and employed individuals with MS or healthy controls.

Conclusion: Empathy did not differ between individuals with MS and healthy controls. Within both investigated groups, higher empathy was weakly to moderately correlated with less symptoms of depression, higher agreeableness and better occupational functioning. We also found unique correlations for empathy within the

* Corresponding author.
E-mail addresses: hiele@fsw.leidenuniv.nl (K. van der Hiele), elianne@nationaalmsfonds.nl (E.E.A. van Egmond), ms4ri@kpnmail.nl (P.J. Jongen), j.j.l.vdrKlink@uvt.nl (J.J.L. van der Klink), martijn.beenakker@znb.nl (E.A.C. Beenakker), j.eijkvan@jbz.nl (J.J.J. van Eijk), s.frequin@antoniusziekenhuis.nl (S.T.F.M. Frequin), ehoitsma@alrijne.nl (E. Hoitsma), jmostert@rijnstate.nl (J.P. Mostert), w.verhagen@cwz.nl (W.I.M. Verhagen), dennis.vangorp@phd.uvh.nl (D.A.M. van Gorp), h.a.m.middelkoop@lumc.nl (H.A.M. Middelkoop), lh.visser@etz.nl (L.H. Visser).

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investigated groups. Longitudinal studies are needed to further examine social cognition in relation to cognitive, psychological and occupational functioning in both individuals with MS and healthy controls. It would be particularly interesting to concurrently examine changes in the brain network involved with social cognition.

1. Introduction

Many studies have reported the high prevalence (40% to 65%) and impact of cognitive impairment across all stages and clinical courses of multiple sclerosis (MS) (Amato et al., 2006). These studies found evidence for impairments in -among others- information processing speed, memory and executive functioning. In the past decade more attention is being devoted to examining social cognition and how deficits in this area impact individuals with MS.

The term social cognition refers to mental functions that underlie social interactions. It involves constructs such as social perception (the ability to perceive information about the mental state of others based on behavioural signals), empathy (the ability to understand the intentions of others, predict their behaviour and experience an emotion triggered by their emotion) and theory of mind (ToM; the ability to attribute mental states to oneself or others) (Green et al., 2008; Labbe et al., 2018; Baron-Cohen and Wheelwright, 2004). Such functional abilities are vital for developing deep social interactions and may impact employment as well as relationships with friends, family and caregivers. Social cognition relies on a broad network of brain regions involving subcortical and neocortical brain areas, including the medial prefrontal cortex (Labbe et al., 2018; Decety, 2011).

Recent studies provide evidence for reduced empathy and ToM in individuals with MS, even in the early stages of relapsing-remitting MS (Gleichgerrcht et al., 2015; Almeida et al., 2016; Kraemer et al., 2013; Banati et al., 2010; Pottgen et al., 2013). Individuals with MS were specifically impaired in the recognition of negative facial emotional expressions and the ability to infer mental states of others during visual tasks (i.e. images and videos) (Cotter et al., 2016). Impairments in social cognition in MS were generally not found to be related to disease duration, degree of disability, relapse rate or disease course (Gleichgerrcht et al., 2015; Almeida et al., 2016; Kraemer et al., 2013; Dulau et al., 2017). Positive associations have been demonstrated between social cognition and the traditionally investigated cognitive functions (i.e. memory, information processing speed and executive functioning) (Kraemer et al., 2013; Pottgen et al., 2013; Dulau et al., 2017; Chalah et al., 2017). However, reduced social cognition in MS does appear to be independent of general cognitive impairment, meaning that reduced social cognition is not simply a consequence of cognitive impairment (Pottgen et al., 2013). Further research is needed to clarify the association between social cognition on the one hand and MS disease characteristics and cognitive performance on the other hand (Cotter et al., 2016).

Given that social cognitive skills such as empathy are perceived vital for occupational success (Longmire and Harrison, 2018; van der Klink et al., 2016) and considering that work participation is often compromised in MS (Julian et al., 2008), it is of special interest to examine relations between social cognition and occupational functioning in MS. To the best of our knowledge, the relationship between social cognition and occupational functioning in MS has not been previously investigated.

In the current study we will specifically focus on empathy, affective ToM and emotional reactivity as measured with Baron-Cohen's Empathy Quotient (Baron-Cohen and Wheelwright, 2004). Our objectives are (1) to examine whether empathy differs between individuals with MS and controls, (2) to examine relations between empathy and cognitive, psychological and occupational functioning. Based on previous studies, we expect to find reduced empathy in individuals with MS as compared with healthy controls (Gleichgerrcht et al., 2015; Almeida et al., 2016; Kraemer et al., 2013; Banati et al., 2010; Pottgen et al., 2013). Furthermore, we expect to find correlations between higher empathy and better executive functioning (Kraemer et al., 2013; Dulau et al., 2017), information processing speed (Pottgen et al., 2013; Dulau et al., 2017; Chalah et al., 2017) and learning and delayed memory (Pottgen et al., 2013; Dulau et al., 2017), and between higher empathy and better occupational functioning. In accordance with previous studies, we do not expect to find correlations between empathy and disease duration, disability and symptoms of depression (Gleichgerrcht et al., 2015; Almeida et al., 2016; Kraemer et al., 2013; Chalah et al., 2017). These correlations may not be unique to individuals with MS, and we therefore expect similar correlations between empathy and cognitive, psychological and occupational functioning in healthy controls.

2. Material and methods

2.1. Design and participants

278 individuals with MS (relapsing-remitting subtype) who had participated in the MS@Work study, a prospective longitudinal study on work participation in individuals with relapsing-remitting MS, were included in this investigation (van der Hiele et al., 2015). The individuals with MS were recruited from 16 MS outpatient clinics in the Netherlands. The criteria for inclusion were a diagnosis of relapsing-remitting MS according to the Polman-McDonald criteria 2010 (Polman et al., 2011), at least 18 years old and having a paid job or within three years since the last past job. Individuals with co-morbid psychiatric and neurological disorders, substance abuse, neurological impairment that might interfere with cognitive testing, unable to speak and/or read Dutch, or who did not complete Baron-Cohen's Empathy Quotient were excluded from the study.

We recruited 128 healthy controls via advertisements on social media and in local newspapers. The criteria for inclusion were 18 years or older and having a paid job or within three years since the last paid job. Individuals with a psychiatric, neurological or other chronic disorder, substance abuse, or unable to speak and/or read Dutch were excluded.

The study was approved by the Medical Ethical Committee Brabant (NL43098.008.12 1307) and the Board of Directors of the participating MS outpatient clinics. All participating subjects provided written informed consent. The study is performed in agreement with the declaration of Helsinki (World Medical, 2013). Reporting of this study was performed according to the STROBE guidelines (von Elm et al., 2007).

2.2. Procedure

Individuals with MS underwent yearly neurological and neuropsychological examinations at their MS outpatient clinic for a period of three years. The healthy controls underwent a neuropsychological examination at baseline. All participants were asked to complete yearly online questionnaires on demographic characteristics, occupational functioning, empathy, self-reported cognitive and neuropsychiatric functioning, fatigue and mood for a period of three years. The current study focuses on the baseline phase, which took place between March 2014 and January 2017. For more details about the MS@Work study we refer to the study protocol (van der Hiele et al., 2015)

2.3. Measures

2.3.1. Empathy

Baron-Cohen's Empathy Quotient (Baron-Cohen and Wheelwright, 2004; Lawrence et al., 2004), a self-report questionnaire, was used to assess empathy, affective ToM and emotional reactivity. Higher scores indicate more empathy; low empathy: 0–32; average empathy: 33–52, above average: 53–63; very high empathy: 64–80 (Baron-Cohen, 2012).

2.3.2. Neurological examination

The neurological examination included the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Higher scores indicate more symptoms and disability due to MS. The EDSS was administered by a neurologist.

2.3.3. Cognitive examination

We used the Paced Auditory Serial Addition Test (3 s version) (PASAT) (Gronwall, 1977) (total correct) and the written version of the Symbol Digit Modalities Test (SDMT) (Smith, 1982) (total correct) to examine information processing speed and working memory. Higher scores on the PASAT and SDMT indicate higher information processing speed and better working memory. The Rey Verbal Learning Test (RVLT) (Brand, 1985) (total correct learning trials 1–5 and total correct delayed recall) and Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict et al., 1996) (total correct learning trials 1–3 and total correct delayed recall) were used to examine learning and memory capacities. Higher scores indicate better learning and memory. The Trail Making Test (TMT) (Reitan, 1956) and the Design Fluency (DF) and Colour Word Interference (CWI) subtests of the Delis-Kaplan Executive Function System (Delis et al., 2004) were used to examine executive functioning. Lower TMT (TMT B-A index) and CWI contrast scores (timecard 3 + 4 minus card 1 + 2) and higher DF scores (total correct) indicate better executive functioning.

2.3.4. Neuropsychiatric examination

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) was used to assess symptoms of anxiety and depression. Higher subscale scores indicate more symptoms of anxiety or depression. The Modified Fatigue Impact Scale-20 (MFIS) (Kos et al., 2003) was used to determine the physical, psychosocial and cognitive impact of fatigue. Higher scores indicate a higher impact of fatigue on daily functioning. The NEO Five-Factor Personality Inventory (NEO-FFI) (Hoekstra et al., 1996) was used to assess the extent to which the personality traits of neuroticism, extraversion, openness, agreeableness and conscientiousness are present. Higher scores indicate a higher presence of the respective personality traits.

2.3.5. Occupational functioning

Work status was dichotomized as ‘paid job’ or ‘no paid job’ (irrespective of the number of working hours). A single item of the Work Productivity and Activity Impairment Questionnaire (Reilly et al., 1993) ‘presenteeism’ was used to examine the self-reported influence of MS symptoms on productivity while at work in the past 7 days. Higher scores were considered to indicate a higher negative influence of MS symptoms on work productivity. The Work Role Functioning Questionnaire-2.0 (WRFQ-2.0) (Abma et al., 2012; Abma et al., 2016) was used to examine work role functioning, i.e. the perceived percentage of time that physical and emotional problems impact certain work demands. There are four subscales, i.e. work scheduling and output demands, physical demands, mental and social demands, and flexibility demands, with higher scores indicating better work role functioning. A single item of the Work Ability Index (WAI) (Ahlstrom et al., 2010) was used to examine current work ability as compared to lifetime best. Higher scores indicate better work ability as compared to lifetime best. The shortened version of the Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ-23) (Honan et al., 2014) was used to examine psychological/cognitive, physical and external work difficulties. Higher scores indicate greater work difficulties.

2.4. Statistical analyses

Mann-Whitney U tests and X^2 tests were used to examine differences in demographics, disease characteristics and empathy between individuals with MS and healthy controls.

Spearman rank and Pearson correlation analyses (depending on the data distribution) were performed to examine correlations between empathy and demographic, neurological, cognitive, and neuropsychiatric characteristics in individuals with MS and healthy controls.

To examine relations between empathy and occupational functioning, we first used a Mann-Whitney U test to examine differences in empathy between participants with and without a paid job. Spearman rank correlation analyses were then performed to examine correlations between empathy and presenteeism, work ability, work role functioning and work difficulties in individuals with MS and healthy controls.

As additional explorative analyses, Mann-Whitney U tests and independent t-tests were used to examine differences in cognitive, neuropsychiatric and occupational characteristics between individuals with MS and healthy controls.

p-values ≤ 0.05 were considered statistically significant. To correct for multiple testing, a Bonferroni correction was applied for the multiple correlation analyses within the MS and healthy control subgroups where p-values ≤ 0.002 were considered statistically significant. SPSS for Windows (release 23.0) was used for data analysis.

3. Results

3.1. Sample characteristics

Healthy controls were younger ($U = 15{,}072.5$, $p = 0.03$) and were more highly educated ($X^2(df) = 48.0(2)$, $p < 0.001$) than individuals with MS. The individuals with MS mostly had a low disability level (see Table 1).

3.2. Empathy in individuals with MS as compared with healthy controls

Mann–Whitney U-tests showed that individuals with MS (Median = 46.0) and healthy controls (Median = 49.0) did not differ in empathy scores ($U = 15{,}671.50$, $p = 0.053$). Within the individuals with MS, 9% reported low, 66% average, 21% above average and 4% very high levels of empathy. Within the healthy controls, 9% reported low, 58% average, 27% above average and 6% very high levels of empathy

As educational level and age were higher in healthy controls

Table 1
Demographic and disease characteristics of the individuals with MS and healthy controls (HC).

	MS (N = 278)	HC (N = 128)
Gender (female), N (%)	216 (78%)	94 (73%)
Age (years), median (IQR)	43.0 (14.0)	39.0 (18.0)
Educational level		
High, N (%)	113 (41%)	98 (77%)
Medium, N (%)	118 (42%)	27 (21%)
Low, N (%)	47 (17%)	3 (2%)
EDSS, median (IQR)	2.0 (1.5)	–
Disease duration (years), median (IQR)	5.0 (8.0)	–

IQR: Interquartile Range. Medians (IQR) were noted as the variables had a non-parametric distribution. EDSS: Expanded Disability Status Scale.

(Table 1), we examined whether empathy differed between individuals with MS and healthy controls within low, medium and high educational groups and within low and high age groups (based on a median split). No differences in empathy between individuals with MS and healthy controls were found within either subgroup.

3.3. Relations between empathy and demographic, neurological, cognitive, and neuropsychiatric characteristics of the individuals with MS and healthy controls

Kruskal–Wallis and post-hoc Mann–Whitney tests showed that empathy scores were lower for individuals with MS with a low educational level (Median = 41.0) versus individuals with MS with either a medium (Median = 46.0) or high educational level (Median = 47.0) (X^2(df) = 13.2(2), p = 0.001). Within individuals with MS, we found significant correlations between higher empathy scores and better verbal learning, less symptoms of depression, higher extraversion, agreeableness and conscientiousness (Table 2).

A Kruskal-Wallis test showed no differences in empathy for healthy controls with a low (Median = 51.0), medium (Median = 50.0) or high educational level (Median = 49.0) (X^2(df) = 0.09 (2), p = 0.96). Within healthy controls, we found significant correlations between higher empathy scores and less symptoms of depression, less fatigue and higher agreeableness (Table 2).

3.4. Relations between empathy and occupational functioning in individuals with MS and healthy controls

Mann–Whitney *U*-tests showed that empathy did not differ between employed (Median = 46.0) and unemployed individuals with MS (Median = 45.5) (U = 4007.50, p = 0.23). It should be noted that most individuals with MS (86.3%) were employed. Within the individuals with MS, we found significant correlations between higher empathy scores and better occupational functioning in terms of work scheduling and output demands and less cognitive/psychological work barriers (Table 3).

Mann–Whitney *U*-tests showed that empathy did not differ between employed (Median = 49.0) and unemployed healthy controls (Median = 35.5) (U = 63.5, p = 0.26). Most healthy controls (98.4%) were employed. Within the healthy controls, we found significant correlations between higher empathy scores and better occupational functioning in terms of work ability as compared to lifetime best and less cognitive/psychological work barriers (Table 3).

3.5. Additional explorative analyses: differences in cognitive, neuropsychiatric and occupational functioning between individuals with MS and healthy controls

The cognitive, neuropsychiatric and occupational characteristics of the individuals with MS and healthy controls are reported in Table 4.

In terms of cognitive functioning, individuals with MS scored worse on the PASAT 3.0 (U = 12,798.5, p < 0.001), SDMT (U = 10,393.5, p < 0.001), RVLT learning (U = 11,802.0, p < 0.001), RVLT delayed recall (U = 13,306.0, p = 0.001), BVMT-R learning (U = 14,024.5, p = 0.03), BVMT-R delayed recall (U = 13,604.5, p = 0.007) and TMT trails B-A (U = 14,541.5, p = 0.04) than healthy controls.

In terms of neuropsychiatric functioning, individuals with MS reported more symptoms of depression (U = 8132.0, p < 0.001) and anxiety (U = 11,900.0, p < 0.001), were more fatigued (t(df) = −11,9(300), p < 0.001) and scored higher on the personality trait neuroticism (U = 13,917.0, p < 0.001) and lower on the personality traits extraversion (U = 12,053.0, p < 0.001) openness (U = 12,200.0, p < 0.001) and conscientiousness (U = 14,258.5, p = 0.002) than healthy controls.

In terms of occupational functioning, individuals with MS reported more presenteeism (U = 7882.0, p < 0.001), decreased work functioning in terms of physical demands (U = 4582.00, p = 0.05), decreased work ability as compared to lifetime best (U = 6400.5, p < 0.001), and more physical (U = 6887.0, p < 0.001), cognitive/psychological (U = 11,723.0, p < 0.001) and external work barriers (U = 10,017.0, p < 0.001) than healthy controls.

4. Discussion

Recent studies reported decreased social cognitive skills in individuals with MS (Gleichgerrcht et al., 2015; Almeida et al., 2016; Kraemer et al., 2013; Banati et al., 2010; Pottgen et al., 2013; Cotter et al., 2016) which may have important implications for their social and occupational functioning. The current study examined differences in empathy between individuals with MS and healthy controls. We further examined correlations between empathy and cognitive, psychological and occupational functioning in both individuals with MS and healthy controls.

4.1. 3.6. Empathy in individuals with MS as compared with healthy controls

Our study revealed no differences in empathy between individuals with MS and healthy controls, as assessed with Baron-Cohen's Empathy Quotient. This is in contrast with previous research in relapsing-remitting MS, which showed *lower* empathy in individuals with (early stage) relapsing-remitting MS as compared with healthy controls (Almeida et al., 2016; Kraemer et al., 2013). Our finding is also in contrast with the study by Banati et al. who found that individuals with MS with less than 7 years of disease duration reported *higher* empathy than healthy controls (Banati et al., 2010). They suggested that empathy might either be overrated due to impaired ToM performance in their sample (and associated brain damage), or that empathy might be higher in the early disease stages due to a more focused emotional processing. This finding could however not be replicated in the current study when examining a subgroup of recently diagnosed individuals

Table 2
Correlations between empathy and demographic, neurological, cognitive, and neuropsychiatric characteristics of the individuals with MS and healthy controls (HC).

	MS	HC
Age	−0.03	0.06
EDSS	−0.01	n.a.
Disease duration in years	−0.05	n.a.
PASAT 3.0 s version	0.0	0.06
SDMT correct	0.14	0.03
RVLT learning	0.20*	0.11
RVLT delayed recall	0.14	0.13
BVMT-R learning	0.02	0.05
BVMT-R delayed recall	0.04	−0.03
TMT trails B-A	−0.04	0.02
DF total correct	0.09	−0.08
CWI card 3 + 4 minus card 1 + 2	−0.09	−0.11
HADS depression	−0.21*	−0.34*
HADS anxiety	−0.18	−0.22
MFIS	−0.06	−0.37*
NEO-FFI neuroticism	−0.17	−0.12
NEO-FFI extraversion	0.25*	0.23
NEO-FFI openness	0.17	0.16
NEO-FFI agreeableness	0.55*	0.59*
NEO-FFI conscientiousness	0.27*	0.24

Pearson's or Spearman's correlation coefficients are noted. EDSS: Expanded Disability Status Scale, PASAT: Paced Auditory Serial Addition Test, SDMT: Symbol Digit Modalities Test, RVLT: Rey Verbal Learning Test, BVMT-R: Brief Visuospatial Memory Test-Revised, TMT: Trail Making Test, DF: Design Fluency Test, CWI: Colour Word Interference Test, HADS: Hospital Anxiety and Depression Scale, MFIS: Modified Fatigue Impact Scale, NEO-FFI: NEO Five-Factor Personality Inventory.

* $p \leq 0.002$, n.a.: not applicable.

Table 3
Correlations between empathy and occupational functioning in individuals with MS and healthy controls (HC).

	MS	HC
Presenteeism	0.01	−0.04
Work role functioning		
Work scheduling and output demands	0.23*	0.02
Physical demands	−0.01	−0.06
Mental and social demands	0.12	0.10
Flexibility demands	0.20	0.08
Work ability as compared to lifetime best	0.05	0.28*
Work difficulties		
Physical barriers	−0.09	−0.22
Cognitive/psychological barriers	−0.21*	−0.34*
External barriers	−0.11	−0.17

Spearman's correlation coefficients are noted.
* $p \leq 0.002$.

with MS (data not reported). In fact, empathy was not related to disease duration in our study sample. The median Empathy Quotient for individuals with MS in the current study (46.0) was higher than the median Empathy Quotients of respectively 37.4 and 40.0 reported in the studies by Kraemer et al. (2013) (German population) and Chalah et al. (2017) (French population), and lower than the Empathy Quotient found in the study by Banati et al. (2010) (Hungarian population), which was above 56.0. These differing empathy scores measured using the same instrument may indicate possible cultural differences in self-ratings of empathy. Another explanation for our contrasting findings may be that the sample sizes in the aforementioned studies were relatively small (Almeida et al., 2016; Kraemer et al., 2013; Banati et al., 2010).

The conflicting results on whether empathy is different in individuals with MS as compared with healthy controls indicate the need for further study. As noted by Kraemer et al. (2013) it would be of great interest to examine intra-individual changes in empathy and ToM during the course of MS in a larger sample.

4.2. 3 7. Relations between empathy and demographics, cognitive and psychological functioning

In the current study we found that higher empathy was weakly to moderately correlated with a higher educational level, better verbal learning, less symptoms of depression, and higher extraversion, agreeableness and conscientiousness in individuals with MS. In healthy controls, higher empathy was weakly to moderately correlated with less symptoms of depression, less fatigue and higher agreeableness.

The relationship between social cognition and educational level in individuals with MS has been reported in some studies (Chalah et al., 2017; Prochnow et al., 2011), but not in others (Batista et al., 2017; Batista et al., 2017) depending on the age, disability and MS subtype distribution of the sample involved. To be more specific, the

Table 4
Cognitive, neuropsychiatric and occupational characteristics of the individuals with MS and healthy controls (HC).

	MS (*N* = 278)		HC (*N* = 128)	
	Median (IQR), Mean (SD)	**Min-Max**	**Median (IQR), Mean (SD)**	**Min-Max**
Cognitive functioning				
PASAT 3.0 s version[a]	49.0 (12.0)	6–60	53.0 (8.0)***	21–60
SDMT correct[a]	54.0 (11.0)	27–90	60.0 (11.0)***	31–87
RVLT learning[a]	50.0 (15.0)	23–68	55.5 (13.0)***	29–72
RVLT delayed recall[a]	10.0 (5.0)	2–15	12.0 (4.0)***	3–15
BVMT-R learning[a]	28.0 (7.0)	7–36	29.0 (7.0)*	8–36
BVMT-R delayed recall[a]	11.0 (2.0)	2–12	11.0 (2.0)**	5–12
TMT trails B-A[a]	26.0 (17.6)	–5–132	24.2 (13.5)*	2–111
DF total correct[b]	34.6 (6.0)	19–51	35.7 (6.3)	21–53
CWI card 3 + 4 minus card 1 + 2[a]	52.8 (18.6)	–21–173	51.1 (19.1)	19–123
Neuropsychiatric functioning				
HADS depression[a]	3.0 (5.0)	0–15	1.0 (2.0)***	0–10
HADS anxiety[a]	5.0 (4.0)	0–21	4.0 (2.0)***	0–12
MFIS[b]	37.4 (15.7)	0–80	20.0 (12.7)***	0–66
NEO-FFI neuroticism[a]	29.0 (11.0)	13–49	26.0 (9.0)***	13–52
NEO-FFI extraversion[a]	41.0 (10.0)	22–58	44.0 (8.0)***	23–55
NEO-FFI openness[a]	36.0 (9.0)	22–56	39.5 (8.0)***	26–54
NEO-FFI agreeableness[a]	45.0 (6.0)	31–55	46.0 (7.0)	28–54
NEO-FFI conscientiousness[a]	46.0 (7.0)	28–60	47.0 (8.0)**	30–60
Occupational functioning				
Presenteeism[a]	2.0 (3.0)	1–10	1.0 (1.0)***	1–8
Work role functioning				
Work scheduling and output demands[a]	82.5 (44.0)	0–100	90.0 (36.0)	0–100
Physical demands[a]	90.0 (35.0)	0–100	100.0 (53.0)*	0–100
Mental and social demands[a]	82.1 (36.0)	0–100	89.3 (45.0)	0–100
Flexibility demands[a]	85.0 (35.0)	0–100	90.0 (39.0)	0–100
Work ability as compared to lifetime best[a]	7.0 (2.0)	0–10	9.0 (1.0)***	0–10
Work difficulties[a]				
Physical barriers	18.8 (19.0)	0–84	3.1 (9.0)***	0–50
Cognitive/psychological barriers	22.7 (25.0)	0–80	11.4 (16.0)***	0–43
External barriers	25.0 (34.0)	0–100	6.3 (19.0)***	0–94

IQR: Interquartile Range. PASAT: Paced Auditory Serial Addition Test, SDMT: Symbol Digit Modalities Test, RVLT: Rey Verbal Learning Test, BVMT-R: Brief Visuospatial Memory Test-Revised, TMT: Trail Making Test, DF: Design Fluency Test, CWI: Colour Word Interference Test, HADS: Hospital Anxiety and Depression Scale, MFIS: Modified Fatigue Impact Scale, NEO-FFI: NEO Five-Factor Personality Inventory. Significant group differences;
* $p \leq 0.05$,
** $p \leq 0.01$,
*** $p \leq 0.001$.
[a] median (IQR).
[b] mean (SD).

relationship between social cognition and education is often *not* found in samples with younger, less disabled and less progressive individuals with MS. Chalah et al. (2017) refer to the 'cognitive reserve hypothesis' to understand the relationship between social cognition and education, where a higher educational level is considered one of the protective factors against cognitive decline, including social cognition, in spite of MS-related brain damage. This is consistent with the fact that we did not find a relationship between empathy and educational level in our healthy control sample.

The identified association between better verbal learning and social cognition in individuals with MS was observed previously in a study that used a ToM task, i.e. the Movie for the Assessment of Social Cognition (Pottgen et al., 2013). It is unclear why we only found a correlation between empathy and verbal learning, and not with executive functioning (Kraemer et al., 2013; Raimo et al., 2017) or information processing speed (Pottgen et al., 2013; Chalah et al., 2017) as was reported in previous studies. Differences may be explained by the fact that we only used a self-report measure of empathy and did not include ToM tasks. Using both a ToM task and Baron-Cohen's Empathy Quotient, Kraemer et al. only established associations between the ToM task and executive functioning (Kraemer et al., 2013). Consequently, our positive correlation between self-reported empathy and verbal learning is a novel one, suggesting an interaction between empathy and new learning in individuals with MS, possibly reflecting the role of the hippocampus in both empathy and declarative memory (Beadle et al., 2013).

While previous studies did not establish associations between social cognition (mostly ToM) and symptoms of depression (Kraemer et al., 2013; Pottgen et al., 2013; Chalah et al., 2017; Raimo et al., 2017), the current study illuminated a negative correlation between empathy and symptoms of depression in both individuals with MS and healthy controls. A recent study in the general Dutch population reported a similar negative correlation between cognitive empathy and depression (Bennik et al., 2019). In contrast, another study reported *higher* self-reported dispositional empathy in patients suffering from depression, mainly driven by increased personal distress (Thoma et al., 2011). As only 10.1% of the individuals with MS and 1.6% of the healthy controls in the current sample had depression scores indicative of a clinical depression (HADS $\geq$ 8), the identified correlation may better be explained by depressive feelings hindering a person's ability to focus on others and experience emotions based on their emotions.

In healthy controls, an additional correlation was identified between higher empathy and a lower impact of fatigue. We did not find this correlation in individuals with MS, and a previous study also did not find an association between ToM performance and fatigue in MS (Chalah et al., 2017). Studies have shown that empathy sometimes leads to compassion fatigue and sometimes to compassion satisfaction (Hansen et al., 2018). The healthy controls in our sample seem to experience more positive feelings (compassion satisfaction) in relation to their empathy, including less fatigue and less depressive feelings. We suspect that the type of fatigue experienced by individuals with MS may be a different type of fatigue (MS-related fatigue) caused by a combination of MS-related pathophysiological and psychological factors (Bol et al., 2009), which is unrelated to empathy.

Furthermore, empathy was weakly to moderately correlated with several personality traits, i.e. higher extraversion, agreeableness and conscientiousness. The personality trait 'agreeableness' was most strongly correlated with increased empathy, which is not surprising as persons scoring high on agreeableness are considered kind, empathetic and cooperative, indicating an overlap in constructs. The observed correlation between empathy and agreeableness in healthy controls confirms this hypothesis.

4.3. Relations between empathy and occupational functioning

Empathy did not differ between employed and unemployed individuals with MS and healthy controls. This may be explained by an unequal group distribution as most individuals with MS and healthy controls in the current study were employed (respectively 86.3% and 98.4%). Furthermore, those who were unemployed lost their jobs only recently.

In individuals with MS, higher empathy was specifically (weakly) correlated with better occupational functioning in terms of being able to finish work in time, with an acceptable speed and without errors (WRFQ-2.0- work scheduling and output demands). This relationship seems consistent with the previously reported relationship between empathy and executive abilities at work (Kraemer et al., 2013; Raimo et al., 2017). In both individuals with MS and healthy controls, higher empathy was weakly to moderately associated with experiencing less cognitive and psychological barriers at work (MSWDQ-23) including less difficulties in communicating with colleagues, interacting with other people and planning. This relationship seems to reflect the link between empathy and communicating and interacting with others. In healthy controls, higher empathy was also weakly correlated with better work ability as compared to lifetime best, which is a more general measure of work ability.

There is a general lack of evidence in previous studies supporting these specific findings, as most investigations seem to focus on the relationship between empathy and burnout in healthcare professionals or medical students. However, such investigations do indicate that higher empathy in healthcare professionals is associated with less emotional exhaustion and depersonalization, and higher personal accomplishment, confirming a link between empathy and better occupational functioning (Williams et al., 2017).

4.4. Strengths and limitations

Strengths of the current study include the large sample of 287 individuals with MS and 128 healthy controls. We included a detailed examination of neuropsychological and neurological functioning. Furthermore, within the MS@Work study we had the opportunity to examine relations between empathy and occupational functioning in individuals with MS, which has not been previously done. A limitation is that our findings are not representative of the entire MS population, as the MS@Work study specifically recruited individuals with relapsing-remitting MS with a current or recent paid job, who coincidentally had mild disability (Median EDSS of 2.0). A final limitation is that we only included a self-report measure of empathy, i.e. Baron-Cohen's Empathy Quotient. It would be very interesting to further examine the relationship between ToM tasks and cognitive, psychological and occupational functioning, and to also include individuals with more severe MS symptoms.

5. Conclusions

The current study revealed no differences in empathy between individuals with MS and healthy controls. Higher empathy was weakly to moderately correlated with less symptoms of depression, higher agreeableness and better occupational functioning in both individuals with MS and healthy controls.

In individuals with MS, higher empathy was additionally correlated with a higher educational level, better verbal learning, higher extraversion, higher conscientiousness and better occupational functioning in terms of work scheduling and output demands. These might be MS-specific correlations that become apparent with increased brain damage and associated decreases in cognitive functioning, increased use of cognitive reserve capacities and changes in personality.

In healthy controls, higher empathy was additionally correlated with less fatigue and better work ability as compared to lifetime best. These may represent more general correlations between constructs representing aspects of well-being that disappear in individuals with MS. It remains unclear in this observational, cross-sectional study whether

the observed correlations reflect empathy as a cause or an effect of better cognitive, psychological and occupational functioning, or whether brain functioning (either healthy or pathological) is the common denominator affecting all aforementioned factors.

Future studies ought to consider examining changes in social cognition longitudinally in both healthy controls and individuals with MS of differing disease severity and see whether these changes precede, follow or co-occur with changes in cognitive, psychological and occupational functioning. It would be particularly interesting to concurrently examine changes in the brain network involved with social cognition.

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Authors statement

EvE, JvdK, EB, JM, HM declare no conflicts of interest.

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CRediT authorship contribution statement

K. van der Hiele: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **E.E.A. van Egmond:** Data curation, Investigation, Methodology, Project administration, Validation, Writing - original draft, Writing - review & editing. **P.J. Jongen:** Conceptualization, Funding acquisition, Writing - review & editing. **J.J.L. van der Klink:** Conceptualization, Funding acquisition, Writing - review & editing. **E.A.C. Beenakker:** Investigation, Resources, Writing - review & editing. **J.J.J. van Eijk:** Investigation, Resources, Writing - review & editing. **S.T.F.M. Frequin:** Investigation, Resources, Writing - review & editing. **E. Hoitsma:** Investigation, Resources, Writing - review & editing. **J.P. Mostert:** Investigation, Resources, Writing - review & editing. **W.I.M. Verhagen:** Investigation, Resources, Writing - review & editing. **D.A.M. van Gorp:** Data curation, Funding acquisition, Investigation, Project administration, Validation, Writing - review & editing. **H.A.M. Middelkoop:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **L.H. Visser:** Conceptualization, Funding acquisition, Investigation, Resources, Project administration, Validation, Supervision, Writing - review & editing.

Declaration of Competing Interest

All authors declare no conflicts of interest.

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