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Brief Report

Neurodivergence as a Risk Factor for Post-COVID-19 Syndrome

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Abstract

Objectives: Neurodivergent (ND) individuals (e.g., autistic people) are more likely to experience health problems that are characterised by 'Central Sensitisation' (CS). Recent research suggests that a so-called 'Long-COVID' syndrome might also be explained by a heightened response to internal physiological stimuli, much like in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The primary objective of this study was to establish whether individuals who scored highly on a measure of CS would be more likely to experience long-term symptoms of COVID-19. A secondary aim considered if having a Type D personality was also linked to ongoing COVID-19 symptoms. Method: Using a standardised assessment tool, we examined whether traits associated with autism would predict long-term COVID-19 symptoms in 267 Healthcare Workers (HCWs). We also used a measure of Type D personality to establish if negative affect and social inhibition were related to Long-COVID. Results: A higher number of autistic traits predicted COVID-19 symptoms that lasted more than 12 weeks regardless of formal autism diagnosis. A personality measure also showed that negative affect was associated with experiencing COVID-19 symptoms for 4–12 weeks, though the direction of causality in this case is uncertain. Conclusions: Our main findings were (i) more HCWs scored above threshold for neurodivergence than those who were self-declared as having been diagnosed as neurodivergent; (ii) while there was no association between long-term COVID-19 and self-declared neurodivergent status, scores for the 'sensory reactivity' item of a standardised autism scale was predictive of COVID-19 symptoms lasting beyond 12 weeks post-infection; and (iii) HCWs with Type D Personality were not more likely to experience long-term COVID-19.

Keywords: COVID-19; long-COVID; post-COVID-19 syndrome; autism; neurodivergence; neurotypical

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1. Introduction

Since the onset of the global COVID-19 pandemic in 2020, researchers have sought to understand the long-term consequences of SARS-CoV-2 infection. Guidelines have been published in attempts to define a 'Long-COVID' syndrome, suggesting that the duration of COVID-19 symptoms can be categorised as either acute COVID-19 symptoms (AC), lasting up to 4 weeks post-infection; ongoing symptomatic COVID-19 (OSC), with symptoms up to 12 weeks; or post-COVID-19 syndrome (PCS), when symptoms span beyond 12 weeks—more commonly known as Long-COVID [1]. Long-term symptoms can include physiological sequalae, typically shortness of breath (SOB), cough, headache,

myalgia/arthralgia, fatigue and/or psychological outcomes such as cognitive impairment, memory loss, anxiety and depression [2]. Recent studies suggest that some individuals are more prone to developing long-term symptoms of COVID-19, with females, smokers and those with pre-existing co-morbidities being the most at risk [3–8]. Furthermore, symptoms of Long-COVID have been likened to those that characterise myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)—a chronic multi-system condition that has been found to be triggered by infectious diseases such as Influenza and Coronaviruses [8].

While the mechanisms underlying ME/CFS are not fully understood, a key theory is that of 'Central Sensitization' (CS), whereby the nervous system has an amplified response to certain stimuli. For example, a heightened reaction to nociceptive input may lead to hyperalgesia, and thus, a heightened experience of pain [9]. This theory has been applied to certain groups, where an amplified internal response to external stimuli is commonplace, such as in neurodivergent (ND) people (e.g., autistic people). Accordingly, a recent study found that a large proportion of autistic individuals met the diagnostic criteria for ME/CFS, as well for other conditions characterised by CS, including fibromyalgia and irritable bowel syndrome (IBS). Sixty percent of autistic participants also scored at or above the clinical cut-off on a screening tool for CS [9]. Considering this evidence, we aimed to examine whether autistic individuals, and those with higher self-reported autistic characteristics are also at greater risk of developing long-term symptoms of COVID-19. Our hypothesis was that individuals with high scores on a measure of CS would be more likely to report long-term symptoms of COVID-19. Furthermore, as some evidence suggests that Type D traits, including negative affect and social inhibition, are more common in those with conditions such as ME/CFS and fibromyalgia [10], this measure was included to control for these as a possible confounder. We hypothesised that those with Type D personality traits would also be more likely to have prolonged COVID-19 symptoms. To explore our hypotheses, we surveyed a group of healthcare workers (HCWs) and asked them about their experience with ongoing COVID-19 symptoms. Our main aim was to see whether longer-term COVID-19 symptoms were more common in those who scored higher on a measure of autistic characteristics in ND and Type D Personality (TDP).

2. Method

2.1. Ethics Statement

All participants gave their written informed consent, and the Cambridge East Research Ethics Committee approved this study (Ethics Ref: 20/EE/0161), which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Data was collected between August and November 2022. Authors were blinded to identifiable participant information.

2.2. Participants

In this observational survey-based study, HCWs were recruited from three northeast England hospitals and formed an opportunistic sample. HCWs were invited via email to complete an online survey, which was advertised to all HCWs using the weekly communications service. We can approximate that around 12,000 HCWs will have been in receipt of the email invite at the time of sending.

2.3. Materials and Procedure

The anonymous survey explored HCWs' experience of COVID-19 symptoms, including nature, severity and duration. Prior COVID-19 history was defined as previous positive self-reported polymerase chain reaction (PCR), antibody (AB) and/or lateral flow tests (LFT). HCWs indicated which COVID-19 symptoms they experienced from the following

list: chest pain; memory/concentration problems; cough; diarrhoea; fatigue; fever/chills; headache; joint pain; loss taste/sell; muscle pain; nausea/vomiting; SOB; sore throat; swollen lymph nodes. Severity was ranked as 'Mild' (no interference with daily activities); 'Moderate' (some interference); 'Severe' (prevented daily activities); 'Very Severe' (required hospital visit/hospitalisation). Symptom duration was categorised according to previously cited guidelines [1], such as AC, OscS, or PCS. Vaccination history was also recorded. HCWs were invited to self-declare whether they were neurodivergent. Autistic traits were assessed using the Ritvo Autism & Asperger Diagnostic Scale (RAADS-14) [11]. TDP was explored using the DS14, a psychometric tool that captures negative affectivity and social inhibition [12]. Effects of age and gender were also considered within our analyses.

2.4. Statistical Analysis

Statistical analysis was conducted using JASPv0.16.3.0. Categorical outcomes were examined with chi-square tests and multinomial regression. Continuous outcomes were investigated using ANOVA. Effect sizes are given as eta-squared for scale outcomes and Cramer's V for categorical outcomes. An alpha level of 0.05 indicating significance was used throughout. Initial sample size calculation indicated that in order to have 90% power to detect an association between neurodivergence status and Long-COVID outcomes equivalent to a Cramer's V = 0.3, a total sample of at least 141 participants would be needed.

3. Results

Of the 267 respondents (35 M, 226 F, 6 other; mean age 48.3 years), 153 (57%) reported one episode of COVID-19, 100 (37%) reported two episodes, and 14 (5%) recalled three or more, which had been diagnosed on positive PCR (208, 78%), LFT (158, 41%) or AB tests (33, 12%), with 111 positive on both PCR and LFT. A total of 212 (79.5%) received three doses of vaccine, 23 (8.5%) had more than three doses, 24 (9%) had two doses, 3 (1%) had one dose and 3 (1%) had none. Two (1%) declined to give vaccine information. Regarding COVID-19 symptoms, 124 (46%) resolved within 4 weeks (AC), 64 (24%) between 4 and 12 weeks (OSC) and 79 (30%) had symptoms > 12 weeks (PCS). See Table 1 for HCW characteristics.

Thirty-eight (14%) self-declared being ND (16 autistic; 14 attention deficit hyperactivity disorder; 21 others also had dyslexia, dyscalculia, or dyspraxia; 12 had multiple conditions), whilst 7 (3%) declined to answer. There was no significant association between either OSC or PCS and self-declared ND status ($X^2(2) = 2.59$, $p = 0.27$, V = 0.10). Based on the RAADS cut-off of 14, 83 (31%) scored above this threshold and there was a significant association of being above the threshold with a likelihood of experiencing OSC or PCS ($X^2(2) = 10.01$, $p = 0.007$, V = 0.22).

There was a significant association between the number of COVID-19 episodes and symptom duration ($X^2(4) = 13.57$, $p = 0.009$, V = 0.29), with 2 episodes being associated with PCS. An increased number of symptoms during the first episode was reported by people going on to develop either OSC or PSC (7.5 (2.9) or 8.3 (3.0) vs. 5.1 (2.9) symptoms; $F(2, 272) = 34.46$, $p < 0.001$, $\eta^2 = 0.2$), with the increased occurrence of every symptom being associated with OSC or PCS except fever and sore throat. Those reporting PCS also reported greater severity of symptoms during the first episode compared to those with OSC, or those whose symptoms resolved ($X^2(6) = 43.90$, $p < 0.001$, V = 0.29). There was no association of reported first episode symptom severity with ND status ($X^2(6) = 2.58$, $p = 0.86$).

Table 1. Characteristics of the three patient groups (Acute COVID-19 Symptoms, AC; Ongoing Symptomatic COVID-19, OSC; Post-COVID-19 Syndrome. PCS) showing mean (SD) for age, totals and subscale totals for the RAADs and DS14 and median number of symptoms reported during first COVID-19 episode.

	AC ***n* = 124**	**OSC** ***n* = 64**	**PCS** ***n* = 79**
Age (years)	47.1 (11.6)	49.2 (10.0)	49.4 (10.8)
Sex M:F (%M)	24:100 (19.2%)	7:57 (10.9%)	7:79 (8.9%)
Mdn first episode symptoms	5	8	8
RAADS total	8.40 (9.71)	11.77 (9.40)	10.92 (10.0)
RAADS Mentalising	4.33 (5.25)	6.00 (5.36)	4.95 (5.63)
RAADS Social Anxiety	2.45 (3.15)	3.38 (3.27)	3.17 (3.26)
RAADS Sensory Reactivity	1.62 (2.61)	2.39 (2.49)	2.81 (3.02)
DS14 Total	23.34 (11.46)	27.06 (10.33)	25.09 (10.55)
DS14 Negative Affectivity	11.59 (6.94)	14.33 (6.20)	12.54 (6.29)
DS14 Social Inhibition	11.65 (5.84)	12.73 (5.40)	12.54 (5.90)

Examining the subscales of the RAADS, there was no difference between COVID-19 duration groups on mentalising ($F(2, 259) = 2.37$, $p = 0.10$, $\eta^2 = 0.02$) or social anxiety ($F(2, 259) = 2.5$, $p = 0.08$, $\eta^2 = 0.007$), but there was a significant difference in sensory reactivity ($F(2, 259) = 4.85$, $p = 0.009$, $\eta^2 = 0.04$), with post hoc testing showing that there was a significant difference between the AC and PCS (1.62 (2.49) vs. 3.81 (3.02)). There was no overall difference in DS14 between the COVID-19 duration groups ($F(2, 259) = 2.41$, $p = 0.09$, $\eta^2 = 0.02$). Negative affectivity was significantly higher in those experiencing OSC ($F(2, 272) = 3.72$, $p = 0.03$, $\eta^2 = 0.03$), but not those with PCS.

A multinomial logistic model was constructed with three levels of outcomes, related to symptom duration. Age and gender were included in the model at step one, and the two TDP subscales and three RAADs subscales were entered at a second step. The second step resulted in a significant improvement in model fit ($X^2(10) = 22.75$, $p = 0.012$, R^2(McFadden) = 0.064, R^2(Cox & Snell) = 0.044, R^2(Nagelkerke) = 0.087). Only the DS14 subscale for negative affectivity was a significant predictor of OSC versus AC. PCS was significantly predicted by the RAADS sensory reactivity subscale as well as by increasing age and being female. Coefficients are given in Table 2. Repeating the analysis with OSC symptoms as the baseline revealed that none of the factors significantly differentiated that from the PCS group.

Table 2. Coefficients from multinomial logistic regression predicting the occurrence of Ongoing Symptomatic COVD-19 (OSC) or Post-COVID-19 Syndrome (PCS) against baseline AC from the three RAADS and two DS14 subscales.

	Estimate (S.E.)	**Odds Ratio (95% C.I.)**	***p***
OSC v AC			
Intercept	−2.99 (1.03)		
Age	0.03 (0.02)	1.03 (0.99–1.06)	0.07
Sex	M: −0.37 (1.34)	0.69 (0.05–9.63)	0.79
	F-M 0.62 (0.51)	1.86 (0.68–5.08)	0.23
DS14 Negative Affectivity	0.07 (0.03)	1.07 (1.01–1.15)	0.04
DS14 Social Inhibition	−0.08 (0.05)	0.92 (0.84–1.01)	0.92
RAADs Mentalising	−0.003 (0.05)	1.00 (0.91–1.10)	0.95
RAADS Social Anxiety	0.13 (0.08)	1.14 (9.98–1.33)	0.09
RAADS Sensory Reactivity	0.09 (0.08)	1.10 (0.93–1.29)	0.27

Table 2. *Cont.*

	Estimate (S.E.)	Odds Ratio (95% C.I.)	*p*
PCS v AC			
Intercept	−3.10 (1.02)		
Age	0.03 (0.02)	1.03 (1.00–1.06)	0.04
Sex	M: −0.05 (1.31)	0.96 (0.07–12.50)	0.97
	F-M: 1.13 (0.54)	3.09 (1.07–8.88)	0.04
DS14 Negative Affectivity	0.01 (0.03)	1.01 (0.95–1.08)	0.70
DS14 Social Inhibition	−0.04 (0.05)	0.0.96 (0.88–1.05)	0.40
RAADs Mentalising	−0.07 (0.05)	0.93 (0.85–1.02)	0.12
RAADS Social Anxiety	0.13 (0.08)	1.14 (0.98–1.32)	0.09
RAADS Sensory reactivity	0.22 (0.08)	1.25 (1.07–1.46)	0.004

A similar model revealed that after controlling for age, gender, RAADs sensory reactivity and TDP negative reactivity, OSC was significantly predicted by the presence of SOB (O.R. 6.14 [2.64–14.29], $p < 0.001$). PCS was predicted by the occurrence of concentration or memory problems (O.R. 5.59 [2.28–13.72], $p < 0.001$) during the first episode. Fever during the first episode was associated with a lower likelihood of OSC (O.R. 0.37 [0.15–0.90], $p = 0.03$ or LC O.R. 0.21 [0.08–0.56], $p = 0.002$). Please see Table 2 for more details.

4. Discussion

Conditions characterised by CS, such as ME/CFS, are more common in those with ASD [10]. PCS, where symptoms of SARS-CoV-2 infection last beyond 12 weeks [1], have been likened to ME/CFS [8]. We explored whether neurodivergent HCWs were more likely to experience prolonged symptoms of COVID-19 and whether TDP traits are a risk factor for PCS.

In our sample, 30% described having COVID-19 symptoms beyond 12 weeks post-infection. This is alarmingly high, given the extent to which ongoing COVID-19 symptoms can impact daily life. Loss of earnings, dependency on caregivers, and an inability to perform everyday activities are just a few of the consequences of PCS cited in the recent literature [13]. Some of the previously highlighted risk factors for prolonged COVID-19 symptoms were replicated in the present study, with females and older individuals being more at risk of PCS. Having had multiple episodes of COVID-19 was also associated with longer length of symptoms, and increased symptom number in the first episode was associated with OSC/PCS.

Regarding Type D Personality, TDP traits overall were not different across the AC/OSC/PCS groups. Importantly, the confounder of negative affect was only marginally associated with OSC, and not at all with PCS. The direction of causality in this finding must be carefully considered, as it is unclear as to whether the presence of OSC might have led to a greater negative affect, or if those with naturally greater negative affectivity were more likely to have had symptoms for longer because they perhaps did not take the actions necessary to accelerate their recovery (e.g., returning to regular activities).

Interestingly, only 13% of HCW self-declared that they were neurodivergent, whereas 31% of the group scored above threshold on the RAADS. This is consistent with the evidence that suggests that people with fewer stereotypical characteristics frequently go undiagnosed [14]. Analyses also revealed that PCS was predicted by the 'sensory reactivity' subscale of the RAADS, suggesting that HCWs who scored highly on this element were more likely to have prolonged symptoms. This finding fits with the theory that a CS mechanism may underlie conditions such as ME/CFS [8]. To be clear, our present findings do not suggest that neurodivergent individuals are more likely to experience 'Long-COVID',

but rather that the CS phenomenon common in this clinical group likely has a place in the pathophysiology of long-term COVID sequalae.

The limitations of the present study are (1) the likelihood of self-selection bias, given that 30% of HWCs had experienced PCS; (2) we relied on HCWs to recall symptoms of COVID-19 retrospectively, (3) the sample was largely made up of female participants (85%), (4) we did not consider whether the HCWs were clinical or non-clinical, nor did we control for workload, which may have contributed to the latency of COVID-19 symptoms, and 5) due to the self-reported nature of the questionnaires used in our study, there is always the possibility that participants may not have answered honestly, especially given that the term 'neurodivergent' has been previously stigmatised. Despite such limitations, our work does provide preliminary evidence to support the sensory reactivity element of neurodivergence as a risk factor for developing Long-COVID. Importantly, this finding has implications for the provision of treatment services in at-risk groups, particularly psychological interventions, which autistic individuals often find difficult to access [15].

5. Conclusions

Our key findings are, firstly, that more HCWs scored above threshold for neurodivergence than those who self-declared as having been diagnosed as neurodivergent; second, there was no association between OSC/PCS and HCWs self-declared neurodivergent status; third, TDP did not differ or predict OSC/PCS, but the negative affectivity subscale was a relatively weak predictor of being in the OSC group; and finally, scoring above or below the RAADS threshold was predictive of PCS, with the sensory reactivity subscale (in addition to age and female sex) predicting COVID-19 symptoms lasting >12 weeks.

Author Contributions: R.K.R., J.R., D.R.C. and A.P. conceived the study and D.R.C. is chief investigator of the CHOIS study. R.K.R. acted as the principal site investigator. R.K.R., J.R. and D.R.C. contributed to the study protocol, design, and data collection. J.R. did the statistical analysis. R.K.R., J.R. and D.R.C. prepared the manuscript. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

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