Investigating the Perception of Emotion Portrayed Through Body Movements in Motor Neuron Disease.

& Clinical Research Portfolio

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Dedicated to my parents

Christine & Hugh

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Does Motor Neuron Disease Cause an Impairment in Theory of Mind?

A Systematic Review

ABSTRACT

Title: Does Motor Neuron Disease Cause an Impairment in Theory of Mind? A Systematic Review

Objective: Motor neuron disease (MND) disrupts electrical signals between the brain and the muscles resulting in physical disability and for some individuals, additional cognitive deficits. Research suggests that MND may also be associated with deficits in Theory of Mind (ToM), or the ability to interpret other's emotions. The aim of the systematic review is to provide an up to date analysis of the literature investigating ToM in MND.

Methods: The literature search was carried out using Web of Science, PubMed and PsycINFO databases on 14th May 2019. Quantitative studies investigating the performance of individuals with MND, aged eighteen or over, on ToM tasks in comparison to a control group were included in the review. Twenty-five papers were included and were systematically analysed by two researchers.

Results: Twenty-one of the twenty-five studies indicated a significant impairment on ToM tasks in an MND group compared to a control group with effect sizes ranging from small to large. Variable findings are discussed in relation to inconsistently controlled confounding variables and heterogeneity within the MND population.

Conclusions: The literature reviewed suggests that ToM deficits are prevalent in the MND population. Implications for clinical practice are considered.

Keywords: Motor neuron disease, Amyotrophic lateral sclerosis, theory of mind, social cognition.

INTRODUCTION

Motor neuron disease (MND) is caused by degeneration of motor neurons in the cortex, the brain stem and spinal cord (Desai-Joy, 2000). The disease, also known as amyotrophic lateral sclerosis (ALS), disrupts electrical signals between the brain and the muscles resulting in weakness, physical disability and speech difficulties. The average age of onset is 56 years and prognosis typically ranges between two and five years (Talbot, 2009). This fatal disease results in physical disability and speech difficulties (Talbot, 2009).

An estimated 50% of people with MND also develop cognitive impairment and 15% develop frontotemporal dementia (FTD) (Ringholz et al, 2005). FTD is a progressive condition associated with memory difficulties, disinhibition and an impairment in theory of mind (ToM) (Bak, 2010). ToM refers to the ability to understand that others have internal experiences different to one's own and to empathise with others (Baron-Cohen, 1991). Cognitive ToM denotes the ability to comprehend another person's perspective and affective ToM refers to the ability to understand the emotions of others (Shamay-Tsoory et al., 2004). MND and FTD share genetic, clinical and neuropathological features and these two conditions may be best conceptualised as related syndromes (Strong et al., 2017). For individuals presenting with ALS and comorbid FTD, experts have suggested the term "amyotrophic lateral sclerosis frontotemporal spectrum disorder" (ALS-FTSD) (Strong et al., 2017). Due to the shorter life expectancy of people with MND, it is currently unknown whether ALS-FTSD may be the "natural endpoint" of the condition (Strong et al., 2017). Due to shared features between these two conditions, researchers have begun to investigate whether ToM may also be impaired in "pure" MND without dementia.

ToM is associated with a specialised set of "mirror" neurons which are activated both when an individual executes a motor act and when they observe another person performing the same

motor act. It has therefore been suggested that the mirror neuron system (MNS) provides a neural mechanism for ToM and for empathising (Baird et al., 2010). ToM tasks are associated with MNS activity in the amygdala, the inferior frontal gyrus, the right superior temporal sulcus, the right inferior parietal lobule, the medial prefrontal cortex, the orbitofrontal cortex, the precuneus, the somatosensory cortex and the occipital cortex (Rajmohan & Mohandas, 2007). Cognitive and affective ToM tasks recruit intersecting and distinct prefrontal areas (Shamay-Tsoory et al., 2009). Indeed, lesions to the ventromedial prefrontal areas are associated with deficits in cognitive ToM. Conversely, damage to the inferior frontal gyrus is associated with impairments in affective ToM (Shamay-Tsoory et al., 2009). Preliminary research in this area suggests that people with MND may have deficits in ToM and social cognition in terms of recognition of facial expressions, intonation and interpretation of others' intentions (Girardi et al., 2011; Meier et al., 2010; Sedda et al., 2014;). Indeed, poor social awareness can be a cause of distress for relatives caring for people with MND (Merrilees et al., 2010).

A recent meta-analysis of 15 studies reported that MND participants performed significantly poorer than controls on tasks of social cognition and emotion recognition with medium effect sizes (Bora, 2017). The author also found a significant correlation between executive dysfunction and social cognition deficits (Bora, 2017). The meta-analysis used a small number of papers (n=15), did not examine study quality and featured an experiment in which the MND sample included participants with comorbid dementia. This is likely to have affected the results. Further research has since been published and the current review will, therefore, aim to provide an up to date analysis of the literature, ascertain whether "pure" MND causes an impairment in ToM abilities and evaluate the methodological quality of the studies in this area. Due to the variable tasks used in this area of research it was not appropriate to combine the results in a meta-analysis.

METHODS

The literature search was carried out on 14th May 2019, with databases searched from inception. Quantitative studies investigating the performance of individuals with MND, over the age of 18, on ToM tasks in comparison to a control group were included (Appendix B, p81). Qualitative studies, animal studies, research in languages other than English, case studies and studies with children under the age of 18 were excluded. Studies which investigated ToM abilities with individuals who had other conditions other than MND or with individuals who had a diagnosis of MND with comorbid dementia were excluded. Research examining cognitive or behavioural deficits that did not include a measure designed to investigate ToM were also excluded. Studies investigating ToM in different populations, rather than with individuals who had MND, were excluded.

Records of titles of 416 papers were retrieved from Web of Science (n=148), PubMed (n=125) and PsycINFO (n=143). Hand searching of reference lists of included papers did not produce any relevant papers not already captured from database searches. Following removal of duplicates, articles were screened by two researchers against inclusion and exclusion criteria (see Prisma flowchart - Appendix C, p82). The 25 papers included were systematically analysed by two researchers and evaluated for methodological quality using the Quality Assessment Scale for MND Research (QAS-MND) (Appendix D, p83). The QAS-MND was adapted from the Case-control studies Assessment Scale (SIGN, 2012) for the current review. At the screening for inclusion stage there was 77% agreement between the researchers and at the quality rating stage agreement was 85%. Differences of opinion were resolved by discussion, and re-examination of the study against inclusion and exclusion criteria. Effect sizes were reported directly from the studies, where provided. Where effect sizes were not directly reported, these were calculated using Cohen's d (Cohen, 1992) for parametric data or Eta Squared for non-

parametric data (Fritz et al., 2012; Richardson, 2011). For several studies data was not provided to allow calculation of effect size, in which case this is denoted by ESNA.

RESULTS

Four studies did not provide the time since symptom onset. For the 21 studies that did provide this information, the mean time since symptom onset was 29.7 months (range=18.5-47 months). The literature reviewed was of moderate to high quality (mean=10.52; range 7-13) and an overview of the results is provided in Table 1. Given research regarding the distinct neural substrates of cognitive and affective ToM, studies relating to these areas were reviewed separately in the following narrative synthesis (Shamay-Tsoory et al., 2009).

Table 1 Systematic Review Studies Investigating ToM in MND (n=25)											
Study	**Clinical Sample (n)**	**Mean months symptom onset**	**Mean ALSFRS-R**	**Spinal/ Bulbar onset**	**Sporadic / Familial**	**Control Sample (n)**	**ToM**	**Mental Health Screen**	**Background Neuropsychological Assessment**	**ToM test Results**	**QAS-MND**
Papps et al. 2005	18	Diagnosed within 24m	NA	NA	S=19	20✓	EFT	HADS ELQ	Dementia pts excluded. MND pts sig impaired on emotive word memory task on cognitive assess.	No sig group differences on EFT once premorbid IQ controlled. Total EFT (p=0.08, d=0.60, medium ES).	11
Gibbons et al. 2007	16	24	NS	S=13 B=3	S=16	16✓	CST	No pts showed signs of depression no measure noted	Dementia pts excluded using MMSE MND pts sig impaired on Stroop task on cognitive assess. MND pts with bulbar symptoms sig impaired on block design task & picture naming task compared to controls & MND pts with spinal symptoms only.	No sig group diff on CST (p=0.06, ESNA), however, some individual MND pts impaired, particularly those with bulbar signs. CST performance correlated with executive task scores.	8
Zimmerman et al. 2007	13	NA	NA	B=13	NA	12✓	EFT Prosody Test	MND group higher GDS scores	ALS-FTD pts differentiated in analysis. MND pts sig impaired on MMSE	MND pts sig impaired on EFT (p=0.01; d=1.1, large ES). No sig differences on Prosody task (p>0.05, d=0.36, small ES). GDS not correlated with EFT/Prosody task. MMSE correlated EFT & Prosody scores	10
Meier et al. 2010	18	34.56	35.78	NA	NA	18✓	FPT Aprosody Test	HADS scores mild & no group differences	Dementia pts excluded using ACE-R. Cognitive battery.	MND group sig impaired on FPT (p=0.01; d=1.23, large effect size) & Aprosody Test (p=0.04, d=0.65, medium ES). No sig correlation between tests & ALS-FRS-R.	12
Cavallo et al. 2011	15	24.8	31.33	S=14 B=1	NA	21✓	RME SCT	HADS subclinical levels & no group differences	Dementia pts excluded. Pts with bulbar signs performed sig. poorer on cognitive battery.	No sig group differences RME (p>0.05, ESNA), MND group sig impaired on SCT (both pts with & without bulbar signs) (p=0.001, ESNA). No correlation between cognitive tasks & SCT.	12
Girardi et al. 2011	14	38.7	29.7	S=7 B=7	S=14	20✓	JPT EFT RME	No group differences on HADS	Dementia pts excluded. MND pts sig impaired verbal memory task on cognitive battery.	MND group sig impaired JPT (p<0.001) correlated with higher self-rated apathy scores. MND sig impaired RME (p<0.05) & EFT (p<0.05) on all emotions. EFT correlated verbal fluency test. ESNA.	12
Staios et al. 2013	35	32.05	36.4	'mixed'	NA	30✓	TASIT	No group differences on HADS	Dementia pts excluded using ACE-R MND pts sig impaired on BSAT	On TASIT MND group comparable to controls on detection of positive (p>0.05,	12

Study	Clinical Sample (n)	Mean months symptom onset	Mean ALSFRS-R	Spinal/ Bulbar onset	Sporadic / Familial	Control Sample (n)	ToM	Mental Health Screen	Background Neuropsychological Assessment	ToM test Results	QAS-MND
Staios et al. 2013 cont.										η^2=0.01, small ES) & negative emotions (p>0.05, η^2=0.01, small ES) & sincere statements (p>0.05, η^2=0.03, small effect size). Sig impaired compared to controls on TASIT sarcastic (p <0.05, η^2=0.19, large ES) & paradoxical sarcastic conditions (p<0.05, η^2=0.21 large ES) after controlling for poorer BSAT.	
Cerami et al. 2014	20	23.9	36.84	S=16 B=4	S=20	56✓	EAT IAT	Subclinical NPI & HDARS & no group differences	Dementia pts excluded using MMSE Cognitive battery identified 20% pts in MND group =ALSci & 10% ALSbi	No sig group differences in intention attribution (p=0.08, Cliff's delta=0.26, small ES) MND group sig impaired emotion attribution (p =0.03; Cliff's delta=0.33, small ES). No correlation between executive functions & EAIT.	10
Crespi et al. 2014	22 MND 16 ALS-FTD	23	NA	S=18 B=4	S=22	55✓	EFT	Clinical NPI-Q score pts excluded & no group differences	Dementia pts excluded using MMSE. Cognitive battery identified 23% ALSci; 9% ALSbi; 4%ALSci/bi; ALS only 64%	MND group sig impaired EFT anger & disgust (p=0.001; r=0.35, medium ES).	10
Savage et al. 2014	13=MND 25=FTD 16=ALS FTD	NA	MND=37.3 ALSFTD =41.2	S=11 B=2	NA	30✓ (except for years of education)	EFT & TASIT	None	Dementia pts in separate group screened using ACE-R & cognitive battery	No sig differences between MND & control group on TASIT (p>0.05, d=0.08, below threshold for small ES) & EFT (p>0.05, d=0.43, small ES). ALS-FTD pts sig impaired on both.	10
Carluer et al. 2015	23	18.78	38.87	S=18 B=5	NA	23✓	FBT	21 MND pts completed NPI-Q, no group differences	Dementia pts excluded using MDRS. MND pts sig impaired on Hayling test, verbal fluency & TMT on cognitive battery 10 pts=ALSci None ALS=bi	MND group sig impaired on FBT (p < 0.001, η^2=0.23, large ES).Sig correlations with FBT &TMT, verbal fluency & letter & number sequencing task.	8
Niven et al. 2015	40	35.68	38	S=34 B=6	S=38 F=2	40✓	ECAS social cognition	HADS sig higher in MND group	ECAS & cognitive battery identified 13 MND pts =ALSci	11 pts had sig impaired social cognition score (p<0.05, ESNA). Further data not available. Validation study for ECAS.	12
Jelsone-Swain et al. 2015	19 (13 in action)	47	36.84	NA	NA	18✓ (13 only in	RME Hand action task	No group differences &	MoCA & cognitive battery administered	There was no significant difference between the MND & control group on RME,	10

Study	Clinical Sample (n)	Mean months symptom onset	Mean ALSFRS-R	Spinal/ Bulbar onset	Sporadic / Familial	Control Sample (n)	ToM	Mental Health Screen	Background Neuropsychological Assessment	ToM test Results	QAS-MND
Jeslone-Swain et al. 2015 cont.	understanding exp)					action understanding experiemen)		Subclinical GDS scores		although individual MND pts were impaired (p> 0.05; d=0.54, medium ES). MND group sig impaired on action understanding (p<0.05; ESNA).	
Van der Hulst et al. 2015	33	31.3	34.7	S=22 B=11	NA	26✓	JPT IRIQ	No group differences on HADS	Dementia pts excluded using ACE-R & MND group sig poorer verbal fluency, GNT & FrSBe on cognitive battery.	MND group sig impaired empathy IRIQ (p=0.05, ESNA) & impaired on affective aspect of JPT (p=0.01, d=0.74, medium ES), but not cognitive aspect (p=0.10, d=0.59, medium ES). JPT score correlated with poor verbal fluency, higher apathy on FrSBe & poorer GNT.	12
Watermeyer et al. 2015	55	31.8	34.05	S=42 B=13	NA	49✓	RME TASIT IRIQ CST	No group differences on HADS	Dementia pts excluded MND pts sig impaired on DKEFS & verbal fluency of cognitive battery	No sig group differences on RME (p>0.05, d=0.1 below threshold of small ES), TASIT (p>0.05, d=0.2, small ES) or IRIQ (p>0.05, d=0.04, small ES). MND group sig impaired on CST Single Inference sub test(p= 0.001, d =1.01, large ES), Pairs Inference subtest (p = 0.002, d = 0.67, medium ES) & Written Scenarios subtest (p =0.006, d =0.62, medium ES). Social cognition scores correlated with executive function tasks.	11
Aho-Ozhan et al. 2016	30	41	27.9	S=21 B=9	NA	29 ✓	EFT	MND group higher BDI scores	Dementia pts excluded using MMSE	When difference in BDI scores controlled for MND group sig impaired on EFT disgust (p=0.01, d=0.6, medium ES) & fear (p=0.01, d=1.1, large ES).	11
Burke et al. 2016a	106	NA	NA	S=78 B=28	NA	50✓	RME	NA	Dementia pts excluded Cognitive battery administered as part of population based study MND=70 no cognitive deficits; 19 executive impairment; 19 cognitive & executive impairment	MND sig impaired on RME (p< 0.001; η^2=0.19, large ES). MND group with no cognitive deficit performed better than MND group with executive impairment & MND group with cognitive and executive impairments had lowest scores on RME.	9

Study	Clinical Sample (n)	Mean months symptom onset	Mean ALSFRS-R	Spinal/ Bulbar onset	Sporadic / Familial	Control Sample (n)	ToM	Mental Health Screen	Background Neuropsychological Assessment	ToM test Results	QAS-MND
Burke et al. 2016b	59	Bulbar onset =10.8m since diagnosis; Spinal=14.3m since diagnosis	No sig difference between bulbar/spinal onset pts	S=39 B=20	NA	59✓	JPT RME	MND pts higher HADS scores. No sig difference between bulbar spinal onset HADS	Dementia pts excluded Cognitive battery administered as part of population based study. MND pts impaired on working memory, verbal fluency, backward digit span	No sig difference between MND & control pts on RME ($p>0.05$, ESNA) or JPT ($p>0.05$, ESNA). Bulbar sig impaired compared to controls on RME.	9
Trojsi et al. 2016	22	18.73	Pts in stage 1-2 KCSS	S=13 B=9	S=22	15✓	ATOM EAT RME	No group differences on BDI	Dementia pts excluded using ACE-R. MND sig poorer memory prose test cognitive battery	MND group sig impaired EAT ($p=0.001$; $\eta^2=0.38$, large ES) & RME ($p=0.004$; $\eta^2=0.33$, large ES). MND group normal range on ATOM ($p=0.24$, $\eta^2=0.09$, medium ES). Bulbar pts more impaired than spinal onset. EAT & RME correlated with education, memory & quality of life.	13
Keller et al. 2017	65	20.9	39.6	S=50 B=15	F=3 S=62	33✓	ECAS Social cognition	NA	MND pts sig impaired on all aspects of ECAS except memory & social cognition	No sig difference between groups on ECAS social cognition ($p=0.309$, ESNA)	11
Poletti et al. 2017	21	33.62	NA	S=18 B=3	NA	21✓ except gender not matched	RME	MND group STAI & BDI higher than controls	Dementia pts excluded using MoCA. MND pts sig impaired on MoCA, working memory & eye tracking ALSbi=4; ALSci=2	MND sig impaired on RME ($p=0.03$, $d=0.8$, large ES). No correlation between STAI/BDI & RME. MoCA & RME correlated.	8
Radakovic et al. 2017	30	24	39.1	S=25 B=5	NA	29✓	EFT JPT	MND group sig higher GDS score	Dementia pts excluded. MND group impaired verbal fluency & PGMT & higher apathy scores on cognitive battery	MND group impaired on JPT ($p=0.047$, $\eta^2=0.08$, medium ES). no sig group differences on EFT ($p=0.10$, $d=0.6$, medium ES). Social cognition associated with increased apathy. No correlation between GDS and social cognition.	12
Trojsi et al. 2017	21	18.5	41	B=9 S=12	S=21	15✓	ATOM EAT	No group differences on BDI	Dementia pts excluded Using ACE-R. No sig group differences at baseline on cognitive battery	At baseline no sig group differences on ATOM/ EAT ($p>0.05$). After 6 months MND group sig impaired on EAT compared to controls ($p<0.05$, $d=0.36$, small ES) & MND original baseline scores ($p<0.01$, $d=0.60$, medium ES). After 6 months MND group sig impaired on ATOM compared to controls ($p<0.01$, $d=0.86$,	13

Study	Clinical Sample (n)	Mean months symptom onset	Mean ALSFRS -R	Spinal/ Bulbar onset	Sporadic / Familial	Control Sample (n)	ToM	Mental Health Screen	Background Neuropsychological Assessment	ToM test Results	QAS-MND
Trojsi et al. 2017 cont.										large ES) and original MND baseline ($p<0.01$, $d=0.81$, large ES). Bulbar onset impaired EAT & ATOM, spinal onset only impaired EAT.	
Andrews et al 2017	33	35.7	36.4	B=11 L=22	NA	22✓	CATS	No clinical severity on HADS	Individuals with dementia diagnosis excluded & those with cognitive impairment on ACE-R. No sig group difference on ACE-R. MND group sig impaired on BSAT	MND group impaired on complex facial expression ($p = 0.001$, $r = 0.47$, medium ES), and prosody emotion recognition ($p=0.002$, $r = 0.41$, medium ES). Simple facial affect recognition ($p=0.67$, $r=0.06$, below threshold for small effect) and semantic affect comprehension unimpaired ($p=0.13$, $r=0.21$, small ES). Sig correlation between BSAT & CATS.	10
Martins et al. 2019	21	36	NA	S=18 B=3	S=21	25 ✓	FERT	MND significantly higher HADS scores	Dementia pts excluded using MMSE/ No sig group difference on MMSE. MND group only completed verbal fluency test & CBI-R to classify type MND.	MND group sig poorer recognition of sadness on FERT only ($p=0.004$, $r=0.43$, medium ES). No correlation between MMSE & FERT.	7

✓= matched age sex and education; ACE-R=Addenbrookes Cognitive Examination Revised; ALS-FTD=Amyotrophic Lateral Sclerosis Frontotemporal Dementia; ATOM=Advanced ToM Test; BSAT=Brixton Spatial Anticipation test; CATS= Comprehensive Affect Testing System; CBI= Cambridge Behaviour Inventory-Revised; CST= Cartoon and Scenarios Test; EAT= The Emotion Attribution Task; EFT=The Eckman Faces Test; ELQ=Emotional Lability Questionnaire; ES=effect size; ESNA= ES not available; FBT= False Belief Task; FERT= Facial Emotion Recognition Test; FPT=Faux Pas Test; GNT=Graded Naming Test; IRIQ=The Interpersonal Reactivity Index Questionnaire; JPT= The Judgement of Preference Task; KCSS=Kings Clinical Staging System; MDRS= Mattis Dementia Rating Scale; MoCA=Montreal Cognitive Assessment; η^2= Eta Squared; NPI-Q= Neuropsychiatric Inventory Questionnaire; Pts=participants; RME= The Reading the Mind in the Eyes Test; SCT=The Story Completion Task; STAI=State Trait Anxiety Inventory; TASIT=The Awareness of Social Inference Test; TMT=Trail Making Test;ToM-15= Theory of Mind 15 Items.

Cognitive ToM

Seven studies examined cognitive ToM. Three of the seven studies exploring this did not report significant differences between the MND and control groups. MND participants performed comparably to controls on the Intention Attribution Task (IAT) (Happé, 1994), involving suggesting a plausible ending to social stories (Cerami et al., 2014) and on a version of the Judgement of Preference Task (JPT), which entails deciphering which of four pictures in a box a cartoon face in the centre is "thinking of" (Van der Hulst et al., 2015). Trosji et al. (2016) administered the Advanced Theory of Mind Test (ATOM) (Happé, 1994), involving understanding the behaviour of story characters. This study which was rated the highest quality (QAS-MND=13) reported that the control group performed comparably to the MND group (mean months since symptom onset=18.73 months) on the ATOM.

On the contrary several studies reported that MND participants were significantly impaired on a false belief task (TOM-15) (Carluer et al., 2015), a story completion task (SCT) (Ciaramidaro et al., 2007; Cavallo et al., 2011) and an assessment involving deciphering intention based on hand movements (Jelsone-Swain et al., 2015). Trosji et al. (2017) also conducted a follow up study, rated as the highest quality (QAS-MND=13). The authors reported that in accordance with their previous findings MND participants (mean months since symptom onset=18.5) and controls were tested on the ATOM and cognitive tests at baseline and the two groups performed comparably. When retested six months later, however, bulbar and spinal onset MND participants showed a significant decline in ATOM scores compared to controls and a proportion of the MND group had developed ALS with cognitive impairment (ALSci) (n=2) and ALS with behavioural impairment (ALSbi) (n=2) (Trojsi et al., 2017). This may indicate that cognitive ToM deficits become more prevalent as the disease progresses.

With regards to neurological findings, data from positron emission tomography (PET) during the ToM-15 task revealed that the MND group's poorer performance correlated with hypometabolic activity in the supplementary motor area and the dorsomedial and dorsolateral prefrontal cortices (Carluer et al., 2015). Furthermore, functional magnetic resonance imaging (fMRI) scanning during the hand action intention attribution task revealed that poorer performance within the MND group was associated with reduced activity in the prefrontal cortex and middle temporal gyrus (Jelsone-Swain et al., 2015). Finally, Trojsi et al., (2016) reported reduced FMRI activity in frontotemporal areas at baseline and at six months in the MND group compared to controls during the ATOM.

QAS-MND ratings of studies which found a significant impairment in cognitive ToM (mean=10.75; range=8-13) were comparable to quality ratings of the experiments which did not report significant group differences in cognitive ToM (mean =11.66; range=10-13). Inconsistent findings in this area do not appear to be accounted for by differences in overall study quality. Studies that did not find significant group differences on cognitive theory of mind tasks typically reported small to medium effect sizes (Cerami et al., 2014; Trosji et al., 2016; Van der Hulst et al., 2015), whilst the studies finding significant group differences reported large effect sizes (Carluer et al., 2015; Trosji et al., 2017), or the effect size data were not available (Cavallo et al., 2011; Jelsone-Swain et al., 2015). As such it is possible that non-significant results may be attributable to the studies being underpowered, however, larger studies would be required to investigate this further.

Affective ToM

Twenty-four studies investigated affective ToM. Seventeen studies reported that MND groups performed significantly poorer on tasks of Affective ToM than control groups and seven studies did not replicate this finding. Several studies have administered the Reading the Mind in the Eyes Test (RME) (Baron-Cohen et al., 2001) and reported a significant impairment in MND groups (Burke et al., 2016a; Girardi et al., 2011; Trojsi et al., 2016; Poletti et al., 2017). Four studies did not replicate this finding (Burke et al., 2016b; Cavallo et al., 2011; Jelsone-Swain et al., 2015; Watermeyer et al., 2015).

Some studies reported that MND participants performed comparably to controls on The Eckman Faces Test (EFT) (Young et al., 2002), which entails deciphering emotion portrayed by facial expressions (Papps et al., 2005; Radakovic et al., 2017; Savage et al., 2014). On the contrary, other studies have reported that individuals with MND perform significantly poorer on EFT compared to controls (Aho-Ozhan et al., 2016; Crespi et al., 2014; Girardi et al., 2011; Martins et al, 2019; Zimmerman et al., 2007). Andrews et al. (2017) reported that the MND group performed comparably to controls on the basic version of the EFT, but were impaired when asked to identify corresponding prosody or match multiple expressions.

The Awareness of Social Inference Test (TASIT), involves identifying the emotion of actors in social scenes (McDonald et al., 2003). Whilst some studies have suggested individuals with MND are impaired on TASIT compared to neurotypicals (Staios et al., 2013), other studies have not found significant group differences (Savage et al., 2014; Watermeyer et al., 2015).

Meier et al. (2010) found that MND participants were significantly impaired on a faux pas test of affective ToM during which examinees must detect the emotional states of characters and an aprosody task involving discerning emotions from phonetic information. Similar experiments reported that people with MND performed significantly poorer on affective prosody tasks (Andrews et al., 2017; Zimmerman et al., 2007).

The affective ToM version of the Judgement of Preference Task (JPT) consists of asking respondents to identify which of four pictures a cartoon face "likes the best" (Girardi et al., 2011). Three studies found MND participants performed significantly poorer on the JPT compared to control subjects (Girardi et al. , 2011; Radakovic et al. 2017; Van der Hulst et al., 2015) and one study did not (Burke et al., 2016b). Niven et al. (2015) found MND participants were significantly impaired on a JPT subtest of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) compared to control subjects, although other research has failed to replicate this finding (Keller et al., 2017).

Van der Hulst et al. (2015) reported that an MND group rated themselves as significantly less empathetic than controls on The Interpersonal Reactivity Index Questionnaire (IRIQ). Watermeyer et al. (2015) did not identify any group differences on the IRIQ, however, ten of the fifty-five MND participants fell below the cut off score for empathetic concern or perspective taking.

Watermeyer et al. (2015) reported that the MND group performed significantly poorer than controls on the Happé Cartoon and Scenarios Test (CST) which involves identifying the story character's emotions (Happé**,** Brownell & Winner, 1999). In a similar experiment involving

identifying story characters' emotions, the MND group performed significantly poorer than controls (Cerami et al., 2014). Gibbons et al. (2007) did not find significant group differences on the CST.

Trojsi et al. (2016, 2017) also conducted high quality research (QAS-MND=13) using the Emotion Attribution Task (EAT)**,** during which the examinee is asked to identify the emotion of a story character (Happé, 1994). The MND group had a mean of 18.73 months since symptom onset and were significantly impaired on EAT compared to neurotypicals (Troksi et al. 2016). Whilst further research by Trojsi., (2017) with individuals at a similar stage of disease (mean months since symptom onset=18.5) found no significant group differences on the EAT at baselines, after six months the MND group had developed an impairment on EAT (Trojsi et al., 2017).

With regards to neurological findings, voxel-based morphometry during an emotion attribution experiment demonstrated that poorer performance correlated with reduced grey-matter density in the anterior cingulate cortex and right inferior frontal gyrus within the MND group (Cerami et al., 2014). Crespi et al. (2014) found that poor performance on the EFT in an MND group correlated with abnormalities in white matter of the right inferior longitudinal fasciculus and inferior fronto-occipital fasciculus, identified using diffusion tensor imaging. Research using fMRI reported that MND participants showed increased activity in the right inferior frontal gyrus and decreased activity in the hippocampus bilaterally when processing images of sad faces on the EFT (Aho-Ozhan et al., 2016). FMRI analysis during EAT task revealed reduced connectivity in prefrontal areas in the MND group within the posterior cingulate, precuneus and medial prefrontal cortices (Trosji et al., 2017). The authors reported positive correlations between atypical activity in the prefrontal cortex, affective ToM and disease duration.

QAS-MND ratings of seventeen studies which found a significant impairment in affective ToM in the MND group (QAS-MND mean=10.82; range=8-13) were comparable to quality ratings of the seven experiments which did not report significant group differences (QAS-MND mean=10.14; range=8-12). There are, therefore, inconsistent findings in this area that do not appear to be accounted for by differences in overall study quality.

Studies which found a significant affective ToM deficit in the MND group compared to controls reported small (Cerami et al., 2014 & Trosji et al., 2017), medium and large effect sizes (Aho-Ozhan et al., 2016; Andrews et al. 2017; Crespi et al., 2014; Burke et al., 2016a; Martins et al, 2019; Meier et al., 2010; Poletti et al., 2017; Radakovic et al., 2017; Staios et al., 2013; Trojsi et al., 2017; Van der Hulst et al., 2015; Watermeyer et al. (2015); Zimmerman et al., 2007). For two of the studies reporting significant results, effect size data were not available (Girardi et al., 2011 & Niven et al., 2015). The studies which did not find significant group differences reported small (Savage et al., 2014) and medium effect sizes (Jelsone- Swain et al., 2015 & Papps et al., 2005). However these data were not available for the majority of studies which did not report significant group differences (Burke et al., 2016b; Cavallo et al., 2011; Gibbons et al., 2007; Keller et al., 2017).

DISCUSSION

The majority of the studies reviewed reported that MND groups performed significantly poorer on ToM tasks compared to control groups with small to large effect sizes. This finding is accordance with a previous meta-analysis which reported that MND groups demonstrated a significant deficit in ToM compared to controls, with medium effect sizes (d=0.65) (Bora, 2017). Further to Bora's (2017) meta-analysis of fifteen studies, the current paper which

reviewed twenty-five papers suggests that individuals with "pure" MND, without dementia, may develop affective and cognitive ToM deficits. Additionally, the current review suggests that both spinal and bulbar onset variant MND are associated with cognitive and affective ToM deficits (Cavallo et al., 2011; Trojsi et al., 2017) and ToM difficulties appear to become more prevalent as the disease progresses (Trojsi et al., 2017; Van der Hulst et al., 2015). The research suggests that individuals with ALSbi and ALSci may be more vulnerable to developing ToM impairments (Carluer et al., 2015; Cerami et al., 2014). Some studies reported a correlation between executive function and ToM deficits (Gibbons et al., 2007; Watermeyer et al., 2015). The current study highlights that ToM impairments can, however, occur in the absence of wider executive dysfunction (Cavallo et al., 2011; Cerami et al., 2014) and appear to reflect focal neurological atrophy (Aho-Ozhan, 2016; Trosji et al., 2017). Finally, ToM deficits may be more pronounced in bulbar onset MND than in limb onset MND (Burke et al., 2016; Trosji et al., 2016).

The majority of studies reported a significant impairment in ToM in the MND group compared to control participants. A limited number of studies, however, did not replicate these results. Some of the research which did not report significant group differences, reported that individual MND participants in the sample were impaired (Gibbons et al., 2007; Jelsone-Swain et al., 2015). Inconsistent findings in this area therefore may be a reflection of the heterogeneity of the MND population. Furthermore, studies reporting significant impairments in the MND group in terms of cognitive and affective ToM appeared to report larger effect sizes, compared to many of the studies reporting non significant results. Thus some studies may have been underpowered to detect relatively small differences between groups. However, this finding also highlights the heterogeneity in effect sizes observed across studies.

Variable findings were not attributable to significant differences in overall study quality, however, they may be related to inconsistency in controlling for confounding variables. Most experiments controlled for anxiety and depression levels, with the exception of Savage et al. (2014), Burke et al. (2016a) and Keller et al. (2017). Only ten of the experiments took precautions to minimise the effects of fatigue (Cavallo et al., 2011; Cerami et al., 2014; Girardi et al., 2011; Meier et al., 2010; Niven et al., 2015; Papps et al., 2005; Trojsi et al., 2016; Trosji et al., 2017; Van der Hulst et al., 2015; Watermeyer et al., 2015). Three studies excluded participants taking medication which may affect cognitive functioning (Papps et al., 2005; Trojsi et al., 2016; Trojsi et al., 2017). Only two of the studies conducted a power analysis (Burke et al., 2016a; Trojsi et al., 2017) and non-significant effects may also be attributed to inadequate sample sizes. Differences between hereditary and sporadic MND were not analysed by any of the studies and may explain some variance in ToM difficulties. Studies reporting an absence of ToM deficits in the MND population may feature patients in less advanced stages of the disease, or a lower proportion of bulbar onset patients who appear to present with a more pronounced ToM impairment (Trojsi et al., 2016). This is in accordance with the results of a recent review which suggested that bulbar onset MND may be associated with a poorer prognosis (Shellikeri et al., 2017). Finally, the studies used a diverse range of tasks which may be of variable sensitivity to detecting ToM impairments.

The current review is limited by the small sample sizes used in most of the studies. This analysis can only provide a preliminary discussion of the relationship between ToM and different aspects of MND, such as bulbar, spinal, familial or sporadic MND subtypes, as these variables have not been well researched. Although the review focused on “pure” MND, it is possible that the experiments featured MND participants in the early stages of undetected dementia who may not have met the threshold for diagnosis. This review reflects deficits in the early stages of the

disease. Further research is required to investigate how ToM is affected in the later stages of the condition. It is not explicitly stated by any of the authors of the studies included whether MND patients recruited for their studies have also taken part in other research. Trojsi et al. (2016, 2017), however, both recruited from the ALS Center of the First Division of Neurology of the Universita degli Studi della Campania. Consequently there may be some degree of overlap between individuals with MND who took part in these studies. Due to low incidence of MND and rapid progression of the disease, there is likely to be few MND participants able to participate in research and the same people may be taking part in the multiple studies. As such results should be interpreted with caution, as this may reduce the generalizability of findings.

In terms of methodological recommendations, the quality of research would be improved by consistently controlling for confounding variables. More specifically, when conducting research in this area, all participants' medication use should be recorded as this may affect performance on tests. Results may be more accurate when testing is scheduled prior to the time individuals are due to take any sedating medications. Additionally, it is important to minimise the effects of tiredness on cognitive performance by undertaking testing in the morning. The Epworth Sleepiness Scale is most commonly used to compare fatigue levels between MND and control groups (Johns, 1991). Researchers should assess whether MND participants are medically fit to partake in the research, particularly noting any respiratory problems. Larger sample sizes would allow for subgroup analysis. Future research is required to explore the relationship between ToM and disease stage. Due to lengthy assessment processes, time since symptom onset, or King's Clinical Staging System, may provide a more accurate indication of disease stage than time since diagnosis. Studies conducted over several time points would help determine whether ToM deficits become more prevalent as the disease progresses.

Research suggests that carers of MND sufferers are distressed by changes in their relatives' social conduct and ability to empathise (Lillo et al, 2012). With regards to clinical practice, it may be helpful to provide psychoeducation to individuals with MND and their families about the possibility of experiencing difficulties with ToM during the course of their condition. This may encourage more explicit discussion of emotions, improve interpersonal relationships and increase compassion for individuals living with MND.

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CHAPTER TWO: MAJOR RESEARCH PROJECT

Investigating the Perception of Emotion Portrayed Through Body Movements in Motor Neuron Disease.

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MRP Plain English Summary

Investigating the Perception of Emotion Portrayed Through Body Movements in Motor Neuron Disease.

Background

Motor Neuron Disease (MND) is a degenerative condition, which disrupts signals sent from the brain to the muscles resulting in physical disability. Some individuals can also experience difficulties with tasks involving thinking, reasoning and perception. In the advanced stages of the disease, this fatal condition causes difficulties breathing and the heart can stop working. Recent research suggests that people with MND can have difficulties understanding the facial expressions and emotions of other people.

Aims

To date research has not yet explored whether people with MND have difficulties interpreting emotions portrayed by body movements. The current study aims to investigate whether MND causes an impairment in the ability to understand other people's emotions through body language.

Methods

Fifteen people who had a diagnosis of MND were recruited for the study. Fifteen individuals who did not have any neurological or mental health conditions were also recruited. These participants are referred to as the control group. Both groups were asked to complete a test of basic motor skills, a test of reasoning skills and a questionnaire to identify psychological distress. Both groups completed well established tests widely used in clinical practice which involved identifying a person's emotion through life like social interactions (TASIT) or through

basic facial expression (ECAS). Both groups also completed a new test called E-Motion, which asks people to interpret emotions portrayed by body movements without any cues from facial expressions. It was predicted that the MND group would perform significantly poorer than the control group on the E-Motion test.

Results

The MND group's scores were compared to the control group's scores on tests using statistical analysis. The findings suggested that the MND group performed significantly poorer than control participants on the new E-Motion test. However, no firm conclusions can be drawn regarding whether MND is associated with difficulties understanding emotions through body movements. This is because E-Motion is a new assessment tool that requires further testing to ensure it is valid for this use.

The results indicate that the MND group scored lower than the controls on the TASIT, although these differences were not statistically significant. Individuals with MND scored significantly lower than the controls on the ECAS social cognition test. The results of the well-established TASIT and ECAS social cognition tests are consistent with previous research findings and indicate that some individuals with a diagnosis of MND may experience difficulties understanding other people's emotions. The current study is limited by the small number of participants and the use of the E-Motion test which has not yet been validated. Further research is required to investigate the validity of E-Motion. In order to explore whether the results of this study are representative of the wider MND population, future research with higher numbers of participants is required.

Investigating the Perception of Emotion Portrayed Through Body Movements in Motor Neuron Disease.

ABSTRACT

Objectives

Motor Neuron Disease (MND) disrupts signals between the brain and the muscles causing physical disability and speech difficulties. Recent studies suggest that Theory of Mind (ToM), or the ability to interpret facial expressions and empathise with others' emotions, can be impaired by MND. Research has, however, not yet investigated whether MND causes deficits in understanding emotion portrayed by body movements. The current study used a novel computerised assessment tool, E-Motion, which was developed with the aim of assessing the ability to interpret emotions through body movements. The primary hypothesis was that individuals with MND would be impaired compared to control participants on the E-Motion test.

Methods

Fifteen individuals with MND and fifteen neurotypical participants were recruited via an MND patient register and opportunity sampling. Participants completed cognitive and psychological assessments and ToM assessments: a subtest of the Awareness of Social Inference Test (TASIT), the Edinburgh Cognitive and Behavioural ALS Screen social cognition test (ECAS) and the E-Motion assessment.

Results

A Mann-Whitney U Test indicated that the MND group performed significantly poorer on the E-Motion test with a large effect size ($p<0.01$, Eta squared=0.35, 90% CI [0.14, 0.59]) and on the ECAS social cognition subtest, with a medium effect size ($p=0.02$, Eta squared=0.19, 90%

CI [0.02, 0.41]) compared to controls. An independent t-test indicated that the MND group attained lower scores on the TASIT subtest compared to controls with a medium effect size, although group differences were not significant (p=0.17, d=0.51, CI[-0.21,1.24]).

Conclusions

Although the E-Motion results suggest possible MND-associated deficits in understanding body language, interpreting data from this task is significantly limited because the E-Motion task has not yet been formally validated. In particular, the E-Motion task requires formal development and validation studies. These studies would be required to quantify its performance across internal, external and content validity metrics to allow firmer conclusions to made. Findings from the E-Motion task should not be over-interpreted, and should be regarded as provisional and exploratory. Further research on tool development and replicating findings will be needed to advance the evidence-base in this area. The results of the validated ECAS social cognition test suggest that some individuals with MND may develop difficulties in understanding the emotions of others. This finding is in accordance with previous research in this area. Further research in larger sample sizes and subtypes of MND are required to ascertain whether ToM deficits are prevalent in the wider MND population.

Keywords: Motor neuron disease, amyotrophic lateral sclerosis, theory of mind, social cognition, body movement.

Investigating the Perception of Emotion Portrayed Through Body Movements in Motor Neuron Disease.

BACKGROUND

Motor Neuron Disease (MND) refers to a group of conditions caused by a progressive degeneration of the upper motor neurons in the cortex and the lower motor neurons located in the brain stem and spinal cord (Talbot, 2009). The most common variant, Amyotrophic Lateral Sclerosis (ALS) affects upper and lower motor neurons resulting in muscle stiffness and weakness. The Progressive Muscular Atrophy (PMA) variant causes a deterioration of the lower motor neurons and is associated with muscle atrophy, weakness and weight loss. The Primary Lateral Sclerosis (PLS) variant, affects upper motor neurons, and is associated with muscle spasticity, particularly in the limbs and a longer life expectancy than other types of MND. The average age of onset for MND is 56 years, with a life expectancy of between two and five years (Talbot, 2009). MND disrupts signals between the brain and the muscles resulting in physical disabilities and speech difficulties (Talbot, 2009).

Approximately 50% of MND patients also develop a cognitive impairment. Furthermore, an estimated 15% of individuals develop comorbid frontotemporal dementia (FTD), a progressive condition associated with memory difficulties, disinhibited behaviour and Theory of Mind (ToM) deficits (Bak, 2010). ToM refers to the ability to empathise and to understand that others have internal experiences different to one's own (Bora, 2017). Interestingly, a review of the literature concluded that individuals with a diagnosis of "pure" MND without FTD may also have deficits in ToM in terms of recognition of facial expressions and interpretation of others' intentions (Bora, 2017). Research has suggested that social communication and understanding can also be impaired in MND, which may be a cause of distress for patients and caregivers (Lillo

et al., 2012). Furthermore, the literature suggests that ToM deficits in MND can occur in the absence of wider executive dysfunction and appear to reflect focal neurological atrophy (Cavallo et al., 2011).

Mirror neurons are a set of specialised neurons activated when an individual performs a particular motor act or observes another person performing the same motor act (Di Pellegrino et al., 1992). It has been suggested that a network of these specialised neurons, the Mirror Neuron System (MNS), enables humans to understand other people's mental states and to empathise. Neuroimaging studies have implicated neurons within the areas of the hippocampus, motor cortex, pars opercularis of the inferior frontal gyrus and the rostral posterior parietal cortex in the MNS (Dapretto et al., 2006; Mukamel et al., 2010; Vigneswaran et al., 2013). It has been proposed that damage to the MNS may underlie deficits in ToM associated with various disorders such as autism (Pickett & London, 2005).

Biological motion perception refers to the human ability to identify and interpret the movement of living organisms and is thought to have evolved for the purposes of survival and social interaction (Atkinson et al., 2007). Experiments have shown that point light displays conveying biological motion provide adequate information for participants to ascertain the action and emotional state of the figure (Brownlow et al., 1997; Johansson, 1973). Lulé et al. (2007) reported that compared to controls, MND patients showed reduced activation in the right middle temporal lobe, an area associated with the understanding of biological motion. Furthermore, individuals with MND appear to be impaired in terms of visualising actions (Fiori et al., 2013) and understanding action words (Bak & Hodges, 2004). The ability to deduce emotion from physical movement has, however, not yet been explored in MND.

Aims and Hypothesis

The current study uses E-Motion, a novel test which aims to assess a specific aspect of ToM; the ability to understand emotions through body gestures. The experiment aims to ascertain whether individuals with MND demonstrate an impairment on E-Motion compared to the neurotypical population. Based on the literature proposing possible ToM and biological motion deficits in MND, the primary hypothesis predicted that the MND group's mean score on the E-Motion task would be significantly poorer than the control group's mean score on the E-Motion task.

METHODS

Participants

With regards to sample size, a related study reported that individuals with MND were impaired at interpreting facial expressions compared to control groups with an effect size of 0.8 (Oh et al., 2016). An a-priori power analysis conducted using G*Power software indicated a sample of 15 MND participants and 15 control participants powered at .80 with an alpha of .05 would enable an effect size of .93 to be detected in the current experiment (Faul et al., 2007). This is a larger effect size than reported by Oh et al. (2016), but E-Motion involves the interpretation of more subtle body movements and may therefore, be more sensitive to detecting ToM impairments. Through discussion with other local researchers working in the field of MND, it was determined that recruiting 15 participants would also be attainable in the time available. An invitation to take part in the study was sent to individuals on the Scottish MND register and their spouses. Additional control participants were also recruited via opportunity sampling.

To meet the inclusion criteria, participants in the MND group had a diagnosis of MND, were fluent in English and were 18 years or older. To be eligible to take part in this study, participants

within the MND group were required to demonstrate capacity to consent as agreed by the treating team at the MND Service. All cases were discussed with the patient's MND nurse. An estimated thirty five percent of individuals with MND develop a cognitive impairment, below the threshold indicative of dementia, whilst fifty percent do not develop any cognitive difficulties (Ringholz et al., 2005). Approximately fifteen percent of individuals with a diagnosis of MND develop comorbid frontotemporal, a syndrome known as ALS-FTD (Ringholz et al., 2005). As cognitive impairment is a common symptom of MND, individuals with MND who demonstrated comorbid cognitive impairment were eligible for inclusion in the study. Participants with ALS-FTD were not eligible to take part, as this is considered a distinct syndrome. Participants with MND with a diagnosis of other dementia subtypes or comorbid neurological conditions were not eligible to take part. Exclusion criteria for the MND group also included a history of substance misuse or diagnosis with another psychological disorder. Neurotypical controls were fluent in English, 18 years or older, with no diagnosis of neurological or psychological conditions or substance misuse.

Sixteen control participants were recruited, however, one control participant was excluded from the analysis, having demonstrated significant cognitive impairment on testing. All participants were provided with a debriefing sheet with details of support organisations and were advised to discuss any concerns regarding mental and physical health with their GP (appendix J, p120). Of those control participants included in the analysis, seven were still working and eight were retired. Two participants in the control group self-reported that they had previously experienced depression, from which they had recovered. Six participants in the control group reported current physical conditions which were well managed at the time of the study and were not considered likely to affect cognitive functioning. Consequently these individuals were retained in the sample.

Fifteen individuals who had a diagnosis of MND were recruited. Five participants had a diagnosis of Primary Lateral Sclerosis and ten had a diagnosis of ALS. Within the MND group, only one individual was working and fourteen had retired. The time since symptom onset ranged from six months to seventeen years (mean= 6.5 years) and the time since diagnosis ranged from six months to twelve years (mean= 2.4 years). The majority of the sample presented with limb onset MND (n=14) and only one participant reported bulbar onset symptoms. Fourteen participants presented with sporadic MND and one participant had a first-degree relative with the condition. One participant in the MND group had a previous physical health condition and one MND participant described experiencing depressive symptoms for which they had received treatment. Four MND participants reported having additional physical health conditions which were not neurological in nature. As these conditions were not deemed likely to affect cognitive performance and were well managed at the time of the experiment, these participants were retained in the study.

Procedure

This study was granted ethical approval by the Nottingham Ethics Research Committee (Appendix E, p87; Appendix F, p107). Data was stored in a secure password protected spreadsheet, in line with data protection regulations. Testing was carried out in a quiet clinic space and within patients' homes. Precautions were taken to mitigate risks to the researcher and participants during this process (Appendix G, p111). Prior to taking part all control participants were informed that individual feedback was not provided regarding the results of testing as the battery is not a complete neuropsychological assessment and does not include a clinical interview required to interpret results. Prior to testing all MND participants consented to the results of the ECAS and HADS-M being shared with their treating MND team and consented to

any clinical concerns being shared with the treating MND team. All MND participants were informed that MND can result in cognitive difficulties for some individuals. All MND participants were informed that they could access their ECAS and HADS-M results through arranging an additional neuropsychological testing session and a clinical interview with a Neuropsychologist by contacting their MND nurse. Prior to taking part participants were provided with an information sheet (Appendix H, p115) before being asked for their consent to participate (appendix I, p118). Following the study participants were provided with a debriefing form (appendix J, p120). The testing session took approximately one hour thirty minutes and participants were offered breaks to minimise the effects of fatigue and pain, issues frequently experienced by people with MND. Research costs were funded by the University of Glasgow (Appendix K, p122).

Background Measures

In order to obtain an estimated premorbid IQ, the Test of Premorbid Functioning (TOPF; Wechsler, 2011) was administered to all participants, with the exception of two MND participants who were unable to complete this test due to dysarthria.

Cognitive Screening

Performance on ToM tests may be impeded by cognitive deficits and executive dysfunction. As such, the sample also completed the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (Niven et al., 2015). The ECAS has been specifically designed to account for dysarthria or agraphia associated with MND. Participants write or verbalise answers depending on preserved motor functions and subtests account for motor speed difficulties in score calculations. The ECAS provides a total score, an ALS specific score, indicating cognitive impairment related to MND neuropathology and an ALS non-specific score, indicating cognitive impairments

unrelated to ALS neuropathology. An additional informant-rated ECAS questionnaire, which provides information about behavioural and cognitive symptoms, was not completed for six MND participants as an informant was unavailable.

Psychological Assessment

Affective disturbance may also influence participants' performance on tests of cognitive abilities. Consequently, all control subjects completed the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). All MND participants completed a version of the HADS specifically adapted for this population (HADS-M; Gibbons et al., 2011). For example, items likely to reflect motor difficulties rather than mood for people with MND, such as "I feel as if I am slowed down", are removed from the HADS-M.

Baseline Motor Skills

All participants completed the praxis subtest of the Kaplan Baycrest Neurocognitive Assessment (Leach et al., 2000). Participants were asked to replicate a range of transitive and intransitive pantomime actions as a measure of the ability to interpret basic movements in the absence of emotional cues.

Test of Social Awareness

All participants completed a subtest of the Awareness of Social Inference Test (TASIT; McDonald et al., 2003). This subtest requires participants to identify happiness, sadness, anger, anxiety and neutral emotion from videotaped social scenes.

Test of the Perception of Emotional Body Movements

Both groups completed the E-Motion test, a novel assessment tool created for the study with the aim of assessing the ability to interpret emotions through body language. The E-Motion stimuli were developed from data in a motion capture library (Ma, Paterson & Pollick, 2006). In-depth descriptions of the E-Motion instrument can be found in a previous publication Ma, Paterson & Pollick (2006). The motion capture library stores data obtained from paid actors portraying emotions through body movements whilst wearing body movement sensors. Professor Pollick, Professor of Psychology and Hyuga Tanimoto, Computer Programmer, accessed the data in the library to develop the animations of figures. A combination of software including Character Studio (plug-ins for 3D Studio Max, AutoDesk Inc.) and Matlab (The Mathworks) was used to develop the stimuli. The figures did not feature facial expressions to ensure that the task is reliant on recognising emotions through the body movements alone. E-Motion can be administered on a computer using a Microsoft Powerpoint presentation with embedded videos presenting stimuli of different emotions. E-Motion is exclusively a visual assessment and there are no verbal cues. The assessment consists of 16 consecutive stimuli showing a figure in every possible combination of the four emotions (happy, angry, sad, afraid) and four actions (walking, knocking, lifting, throwing). These 16 stimuli are repeated in three sequential phases with progressively less information. During phase one, participants are presented with the 16 stimuli as full figure animations (Figure 1); in phase two, the 16 stimuli are presented as lines (Figure 2) and in phase three, the 16 stimuli are presented as a point light display (Figure 3). We predicted that this design may make it increasingly difficult to interpret as less cues will be available to participants as the phases progress. In total, each participant was presented 48 video stimuli (16 from phase one, 16 from phase two, 16 from phase three).

The stimuli within each phase were randomised before the start of the study by the lead researcher using an online randomiser number generator. The same order of 48 stimuli was presented consistently to all participants. Each emotional stimuli video lasted thirty seconds and participants were given 10 seconds following the end of the video to answer from a multiple choice format of four emotions (happy, sad, afraid, or angry) placed on a card in front of them. Participants were also asked to rate their confidence in each answer from 0-100%.

The 48 confidence ratings were added together and the total divided by 48 to provide a measure of average confidence for each participant. An actual accuracy score was also calculated as a % of items correct out of 48 for each participant. The actual accuracy score was deducted from the perceived confidence score to produce an "insight" score (either a positive or negative value depending on whether the individual overestimated or underestimated their actual accuracy). This score was designed to provide a measure of the individual's insight into their ability on E-Motion. Further details of the development process of E-Motion are available in appendix L (p124).

Figure 1: Phase 1 Full Figure Anger Throwing Condition

Figure 2: Phase 2 Line Figure Sad Walking Condition

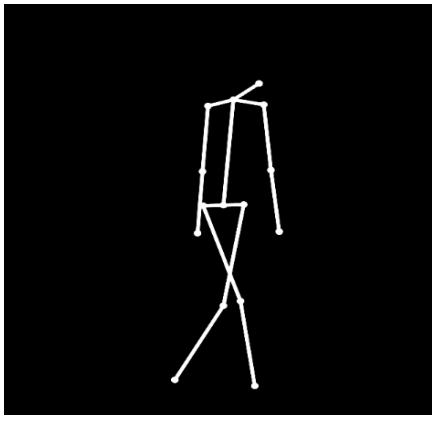
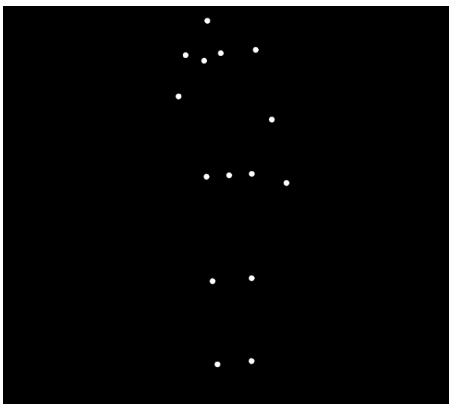


Figure 3: Phase 3 Point Light Dot

Afraid Knock Condition



Data Analysis

Normality testing for each variable was carried out using the Shapiro-Wilk test in combination with inspection of box plots and histograms in order to select the appropriate parametric or non-parametric statistical test. Firstly demographic differences between the two groups were explored. Differences in age, education and IQ of the two groups were investigated using an independent samples t-test. A Mann-Whitney U test was used to explore differences in HADS scores between the two groups and a Chi-Square Test of Independence was used to analyse gender differences between the two groups.

Between group differences on neuropsychological tests were analysed using independent t-tests for normally distributed variables and Mann-Whitney U tests for non-normally distributed variables. Due to the directional hypothesis regarding E-Motion, one-tailed independent t-tests and one-tailed Mann-Whitney U tests were used to investigate group differences on this test. Two-tailed independent t-tests and Mann-Whitney U tests were used to explore group differences regarding performance on all other measures. In accordance with research recommendations Cohen's d effect sizes were calculated for independent t-test results (Field,

2013) and eta-squared effect sizes were calculated for Mann-Whitney U results (Fritz et al., 2012) using an online calculator (Lenhard & Lenhard, 2016). For Cohen's d effect sizes 95% confidence intervals were calculated (Lenhard & Lenhard, 2016). However, in accordance with recent guidelines (Kelley, 2007; Smithson, 2003), 90% confidence intervals were calculated for Eta squared effect sizes, using an online calculator (Uanhoro, 2017).

Exploratory subgroup analyses were then carried out examining within group gender differences and subtypes of MND. Due to the small sample sizes involved in these analyses, the Mann-Whitney U test was used. Associations between the years since symptom onset and performance on the TASIT, E-Motion and the ECAS social cognition, were explored using two-tailed non parametric spearman's rho correlations, due to abnormally distributed data. The relationships between E-Motion and other tests of social cognition were also analysed using two-tailed spearman's rho correlations, due to abnormally distributed data. 95% Confidence intervals for Spearman's rho correlations were calculated using an online calculator for Spearman's rho (Evans, 2019). Finally the internal consistency of E-Motion was explored using Cronbach's alpha.

RESULTS

Sample Characteristics

There were no significant differences between groups with regards to age, years of education, TOPF, HADS-A or HADS-D scores (Table 1.1 & 1.2). Two participants in the MND group were unable to complete the TOPF due to severe dysarthria. Years of education may, therefore, provide a more accurate indication of prior intellectual functioning for the sample. There were no significant differences in gender distribution between the MND and control group (Table 1.3).

Table 1.1 Sample Characteristics									
Independent Samples t-test									
Variable	**MND (n=15)**		**Control (n=15)**		**t (df)**	**p**	**d**	**95 % CI for d**	
	mean	**SD**	**mean**	**SD**				**Lower**	**Upper**
Age (yrs)	64.70	7.05	61.89	6.34	1.15 (28)	0.26	0.42 small	-0.30	1.14
Education (yrs)	13.23	2.91	14.53	2.75	-1.26(28)	0.22	0.46 small	-0.27	1.18
TOPF (IQ)	99.69	12.82	107.13	11.92	-1.59(26)	0.93	0.50 Medium	-0.13	1.33
Levene's test >0.05=equality of variances assumed for age, years of education & TOPF									

* Cohen's d effect sizes= 0.20 small; 0.50 medium and 0.80 large (Cohen, 1998).
*Abbreviations: CI=confidence intervals; d=Cohen's d; df=degrees of freedom; p=significance value; SD=standard deviation; TOPF test of Premorbid functioning

Table 1.2 Sample Characteristics									
Mann-Whitney U test									
Variable	**MND Group**		**Control Group**		**U**	**p-value**	**Eta Squared**	**90% CI for Eta Squared**	
	Mdn	**IQR**	**Mdn**	**IQR**					
HADS-A	5.00	5.00	6.00	9.00	70.0	0.08	0.01 small	0.00	0.14
HADS-D	2.00	3.00	2.00	5.00	109.0	0.88	0.001 no effect	0.00	0.07

* Eta squared effect sizes: 0.01 small, 0.06 medium, 0.14 large (Adams & Conway, 2014).Eta Squared values & CI are given to the nearest two decimal places and values 0.00 are >0.
*Abbreviations: CI=confidence intervals; HADS-A=Hospital Anxiety and Depression Scale Anxiety subscale; HADS-D=Hospital Anxiety and Depression Scale Depression subscale; IQR=Interquartile range; Mdn=Median; p=significance value.

Table 1.3 Sample Characteristics							
Chi-Square Test of Independence							
Variable	**MND (n=15)**		**Control (n=15)**		**χ2 (df)**	**p**	**Cramer's V**
	M	**F**	**M**	**F**			0.27
Gender	11	4	7	8	2.22(1)	0.13	small

*Cramers V effect sizes: 0.10 small; 0.30 medium; 0.5 large. (Kim, 2017).
*Abbreviations: Df=degrees of freedom; p=significance value; χ2 = Chi Squared Value.

Between Group Differences on Neuropsychological Tests

The analysis revealed that MND participants were significantly impaired compared to controls with regards to the total ECAS score and all ECAS subtests with medium to large effect sizes (Table 2). The results of the ECAS questionnaire suggested that the MND group reported significantly more behavioural difficulties compared to the neurotypical group. This result should, however, be interpreted with caution due to missing data for six MND participants, for whom informants were unavailable. The MND group also performed significantly poorer than the control group on the ECAS social cognition subtest with a large effect sizes (Table 2). The MND group scored on average lower than the control group on the TASIT with a medium effect size, although group differences did not reach significance. The analysis showed that individuals with MND also scored significantly lower than control participants on the praxis test with a large effect size (Table 2). It should be noted that confidence intervals shown in table 2 indicate that effect size are broad and indicate that the true effect size for significant results may range from small to large in magnitude.

In comparison to controls, MND participants attained significantly lower scores on the full figure, line, lifting and knocking and throwing conditions of the E-Motion test with large effect sizes (Table 3). The MND group's mean overall E-Motion total score was also significantly lower than the control group's mean score. Confidence intervals suggest that the true difference between groups was within the large range (Table 3). The MND group also significantly overestimated their accuracy on the E-Motion test compared to controls, as indicated by the E-Motion insight score (with a large effect size). However, as shown in table 3 the results indicate that there are significant group differences on E-Motion total and some subscales, however, the confidence intervals indicate that we cannot be certain whether these effects are small or large

in magnitude. These results support the primary hypothesis that the MND group would perform significantly poorer than the control group on the E-Motion test. Control participant's mean scores were higher than the MND participant's mean scores in terms of discerning the emotion from point light, walking, sad, happy, afraid and angry stimuli with small to medium effect sizes (table 3). However, differences on these subscores did not reach statistical significance ($p>0.05$) (Table 3).

Table 2
Between Group Analysis ECAS, TASIT & Praxis Tests

2-tailed Independent t-test	MND		Control		t (df)	p	d	95% CI for d	
	mean	SD	mean	SD				lower	upper
TASIT Total	22.73	3.52	24.20	2.01	-1.40* (22.25)	0.17	0.51 medium	-0.21	1.24
ECAS Total	103.60	20.42	118.73	7.07	-2.71* (17.31)	0.02	0.99 large	0.23	1.75
ECAS ALS non-specific	27.53	4.90	30.13	2.64	-1.81 (28.00)	0.81	0.66 medium	-0.07	1.40
ECAS ALS specific	76.07	17.02	88.60	7.09	-2.63* (18.72)	0.02	0.96 large	0.20	1.67
ECAS exec function	34.13	8.82	41.27	4.48	-2.79* (20.77)	0.01	1.02 large	0.26	1.78
*Levene's Test <0.05 =Equal variances not assumed Levene's Test >0.05=Equal variances assumed (for ECAS ALS non-specific subscale)									
2-tailed Mann Whitney U test	**MND**		**Control**		**U**	**P**	**Eta squared**	**90% CI for Eta Squared**	
	Mdn	**IQR**	**Mdn**	**IQR**				**Lower**	**Upper**
ECAS social cognition	12.00	3.50	12.00	0	75.00	0.02	0.19 large	0.02	0.41
ECAS Questionnaire	1.00	4.00	0.00	0	27.00	<0.01	0.38 large	0.14	0.59
Praxis	40.00	17.00	40.00	0	67.50	0.02	0.23 large	0.08	0.47

* Cohen's d effect sizes= 0.20 small; 0.50 medium and 0.80 large (Cohen, 1998).
* Eta squared effect sizes: 0.01 small, 0.06 medium, 0.14 large (Adams & Conway, 2014). Eta Squared values & CI are given to the nearest two decimal places and values 0.00 are >0.
*Abbreviations CI=confidence intervals; d=Cohen's d; df=degrees of freedom; SD=standard deviation; ECAS=The Edinburgh Cognitive and Behavioural ALS Screen; TASIT=The Awareness of Social Inference Test.

Table 3 Between Group Analysis E-Motion Test									
1-tailed Independent t-test	**MND**		**Control**		**t (df)**	**p**	**d**	**95% CI for d**	
	mean	**SD**	**mean**	**SD**				**lower**	**upper**
E-Motion Lines	9.00	1.51	10.40	1.40	-2.63 (28.00)	0.01	0.96 large	0.21	1.72
E-Motion Point Light	9.80	1.78	10.93	1.53	-1.87 (28.00)	0.36	0.68 medium	-0.04	1.44
E-Motion Walk	10.13	1.06	10.20	1.37	-0.15 (28.00)	0.44	0.05 small	-0.66	0.77
E-Motion Lift	3.80	1.32	5.60	1.30	-3.77 (28.00)	<0.01	1.37 large	0.59	2.17
E-Motion throw	7.93	1.44	8.93	1.39	-1.94 (28.00)	0.03	0.70 large	-0.03	1.44
E-Motion sad	7.60	2.06	8.60	1.50	-1.52 (28.00)	0.07	0.55 medium	-0.17	1.28
E-Motion happy	7.80	1.57	8.67	1.59	-1.50 (28.00)	0.07	0.55 medium	-0.18	1.28
E-Motion afraid	7.60	2.06	7.67	1.59	-0.10 (28.00)	0.46	0.38 small	-0.68	0.75
E-Motion Insight	20.05	14.55	7.93	9.93	2.66 (28.00)	<0.01	1.01 large	0.25	1.77
Levene's test >0.05=equality of variances assumed for all t-test data above									

Table 3 continued.

1 tailed Mann-Whitney U	**MND**		**Control**		**U**	**P**	**Eta squared**	**90% CI for Eta Squared**	
	Mdn	**IQR**	**Mdn**	**IQR**				lower	Upper
E-Motion Total	29.00	3.00	34.00	3.00	34.0	<0.01	0.35 Large	0.14	0.59
E-Motion Figure	10.00	2.00	11.00	3.00	51.5	<0.01	0.22 Large	0.03	0.45
E-Motion angry	8.00	2.00	9.00	3.00	85.5	0.13	0.04 Small	0.00	0.22
E-Motion knock	7.00	2.00	8.00	2.00	65	0.02	0.13 Large	0.00	0.35

* Cohen's d effect sizes= 0.20 small; 0.50 medium and 0.80 large (Cohen, 1998).
* Eta squared effect sizes: 0.01 small, 0.06 medium, 0.14 large (Adams & Conway, 2014). Eta Squared values & CI are given to the nearest two decimal places and values 0.00 are >0.
*Abbreviations: CI=confidence intervals; d=Cohen's d; df=degrees of freedom; Mdn=median; IQR=interquartile range; SD=standard deviation.

Exploratory Subgroup Analysis

Mann-Whitney U tests were used to explore gender differences within groups and Eta squared effect sizes were calculated (η^2) In the control group there were no significant differences regarding E-Motion scores of males (n=7, Mdn=33) and females (n=8, Mdn=34) (U=21.5, p=0.45, η^2=0.03, 90% CI [0.00, 0.45]). On the TASIT, however, male control participants (n=7, Mdn=23) performed significantly poorer than female controls with a large effect size (n=8, Mdn=25) (U=6, p=0.01, η^2=0.45, 90% CI [0.12, 0.74]). Male control participants (Mdn=12) and female control participants (Mdn=12) performed comparably on the ECAS social cognition test (U=28, p=1.00, η^2=0.00, 90% CI not available due to no variance).There were no significant differences in terms of the performance of male MND participants (n=11, Mdn=29) and female MND participants (n=4, Mdn=28) on the E-Motion test (U=21.5, p=0.947, η^2=0.00, 90% CI not available due to low variance), the TASIT test (M Mdn= 22, F Mdn=25; U=9.5, p=0.10, η^2=0.04, 90% CI [0.00, 0.30]) or the ECAS social cognition test (M Mdn=12, F Mdn=12, U=19.5, p=0.70, η^2=0.01, 90% CI [0.00, 0.19]).

Within the MND group, a Spearman's correlation analysis indicated that there were no significant associations between years since symptom onset or diagnosis and severity of difficulties on the TASIT, E-Motion or any sub conditions of E-Motion or the ECAS (p=>0.05; *rs*=-0.12 to 0.4). Fourteen participants had limb onset and one participant reported bulbar onset MND. Fourteen MND participants presented with sporadic variant and one reported a family history of this condition. With the limited sample size, it was not possible to undertake any meaningful sub analysis of these variables. The scores of the individual with bulbar onset MND were comparable to other MND participants within this group and did not represent outliers on any assessments. The individual with familial MND performed within the lower range of the

MND group on E-Motion and attained the lowest score on praxis, the TASIT, ECAS total, ALS specific and ALS non-specific aspects of the ECAS. Mann-Whitney U tests did not reveal any significant differences between individuals with PLS (n=5) and MND (n=10) with regards to performance on the ECAS social cognition (PLS Mdn=12, MND Mdn=12, U=19.5, p=0.42, η^2=0.03, 90% CI [0.00, 0.29]), TASIT (PLS Mdn=25, MND Mdn=23, U=22.5, p=0.77, η^2=0.01, 90% CI [0.00, 0.19]), or E-Motion tests (PLS Mdn=30, MND Mdn=28.5, U=11, p=0.08, η^2=0.01, 90% CI [0.00, 0.22]).

Within the MND group, seven of the participants' ECAS total scores and ALS-specific scores fell below the threshold indicative of cognitive impairment relating to MND. Two of these participants also showed signs of ALS non-specific cognitive deficits. The group of MND participants who had a comorbid cognitive impairment (MNDci) (n=7, mean time since symptom onset= 5.87 years) was comparable to the group of "pure" MND participants who did not have any cognitive impairments (MNDp) (n=8, mean time since symptom onset= 7 years) in terms of disease stage.

Mann-Whitney U tests were used to explore differences between individuals with "pure" MND referring to individuals who did not display a cognitive deficit (MNDp), individuals with MND and a comorbid cognitive impairment (MNDci) and control participants, as data were not normally distributed. Individuals with MNDci performed poorest across all three social cognition tests. Regarding the E-Motion test, individuals with MNDci attained lower scores compared to the MNDp group with a medium effect size, however, the difference did not reach significance (U=16.5; p=0.18; η^2=0.07, 90% CI [0.00, 0.37]). When analysed separately, both the MNDp group and MNDci group performed significantly poorer on E-Motion compared to

controls with large effect sizes (MNDp: U=24, p=0.02, η^2=0.24, 90% CI [0.03, 0.62]; MNDci: U=10, p<0.01, η^2=0.41, 90% CI [0.15, 0.71]).

Table 4 Social Cognition Tests						
Assessment	**Control (n=15)**		**MNDp (n=8)**		**MNDci (n=7)**	
	Mdn	**IQR**	**Mdn**	**IQR**	**Mdn**	**IQR**
E-Motion total	34.00	3.00	29.00	3.00	28.00	5.00
TASIT	25.00	2.00	25.50	4.00	20.00	5.00
ECAS social cognition	12.00	0.00	12.00	0.00	9.00	7.00

*Abbreviations: Mdn=median; MNDci: MND with cognitive impairment; MNDp= "pure" MND without cognitive impairment; IQR=interquartile range.

The MNDci group performed significantly poorer than the MNDp group on the TASIT (U=3.5, p=0.004, η^2=0.54, 90% CI [0.17, 0.72]) with a large effect size. The MNDci group also performed significantly poorer than the MNDp group on the ECAS social cognition test with a large effect size, however, confidence intervals indicate that the true magnitude of the effect may have been within the small to large range (U=13.5, p=0.05, η^2=0.27, 90% CI [0.01,0.70]). MNDci participants attained significantly lower scores than the control group on the TASIT (U=13.5, p<0.01, η^2=0.35, 90% CI [0.05,0.65]) with a large effect size, although confidence intervals indicate that the true effect may have been within the small to large range. MNDci participants performed significantly poorer than the controls on the ECAS social cognition test with a large effect size (U=22.5, p<0.01, η^2=0.45, 90% CI [0.15, 0.90]). Individuals in the MND group who did not demonstrate a cognitive impairment performed comparably to the control group on the TASIT (U=43.5, p=0.28, η^2=0.05, 90% CI [0.00, 0.38]) and ECAS social cognition test (U=52.5, p=0.17, η^2=0.01, 90% CI [0.00, 0.17]).

Exploring the Relationships Between E-Motion and Other Variables

The relationships between the three social cognition tests; E-Motion, TASIT and ECAS social cognition, in addition to the relationship between ToM abilities, cognitive impairment and executive function were explored. As these variables were not normally distributed and the sample sizes between groups were small, Spearman's correlation was used for this analysis.

Within the MND group, analysis revealed positive correlations between ECAS social cognition and ECAS executive function scores (rs=0.69, p<0.01, 95% CI [0.27, 0.89]) and between ECAS social cognition and ECAS total (rs= 0.88, p<0.01, 95%CI [0.66, 0.96]) with large effect sizes. The TASIT positively correlated with ECAS executive function scores (rs= 0.70, p<0.01, 95% CI [0.29, 0.89]) and the ECAS total (rs=0.57, p=0.03, 95%CI [0.07, 0.84]) with results indicating large effect sizes. ECAS social cognition was also positively associated with the TASIT with a large effect size (rs= 0.701, p<0.01, 95% CI [0.29, 0.89]). Within the MND group, the E-Motion total was not correlated with years of education or the ECAS total score or executive function scores. Within the MND group there were no significant correlations between E-Motion test and the TASIT and effect sizes were below the threshold for a small effect (rs=0.02, p=0.93, 95% CI [-0.5, 0.53]) or ECAS social cognition test (rs=-0.03, p=0, 95% CI [-0.53, 0.49]). Within the control group there were no significant correlations regarding the three social cognition tests and any other variables examined. Within the control group there were no significant correlations between the E-Motion test and the TASIT (rs=0.36, p=00.18, 95% CI [-0.19, 0.74]) or ECAS social cognition test (rs=0.00, p=0, 95% CI not available due to no variance). The correlation between the TASIT and E-Motion test within the control group met the threshold for a small effect size. Spearman's Rho correlational analysis of the combined MND and control groups (n=30) identified a positive association between E-Motion and executive function (rs= 0.42, p=0.02, 95% CI [0.07, 0.68]), praxis (rs=0.399, p=0.03, 95% CI

[0.04, 0.66] and ECAS total (*rs*= 0.48, p=0.01, 95% CI [0.15, 0.72]) with effect sizes within the medium range. Within the whole sample there was no significant relationships between E-Motion and the TASIT and effect sizes were within the small range (*rs*=0.25, p=0.13, 95% CI [-0.12, 0.56]) or ECAS social cognition test (*rs*=0.29, p=0.11, 95% CI [-0.08, 0.59]). The sample's TASIT scores positively correlated with ECAS executive function scores and indicated a medium association (*rs*= 0.38, p=0.04, 95% CI [0.24, 0.76]). The results indicated a large positive association between ECAS social cognition and ECAS executive function (*rs*=0.55, p<0.01, 95% CI [0.2, 0.74]) and a medium positive correlation between ECAS social cognition and praxis (*rs*= 0.39, p=0.04, 95% CI [0.03, 0.66]). The sample's ECAS social cognition scores positively correlated with their performance on the TASIT with a medium effect size (*rs*= 0.43, p=0.02, 95% CI [0.08,0.68]). Interestingly, individual participants within the MND group attained high scores on the ECAS social cognition, TASIT, ECAS executive function or ECAS total, but demonstrated an impairment on E-Motion.

Internal Consistency Analysis of the E-Motion Test

In order to assess internal consistency of the E-Motion test, a post hoc Cronbach's alpha test was used to analyse the whole sample's responses (n=30) to the E-Motion stimuli (Cronbach, 1951). Guidelines vary, however, Hinton et al. (2004) suggest that a Cronbach's alpha of below 0.5 indicates poor reliability, an alpha of 0.5 to 0.7 is indicative of moderate reliability and an alpha value of above 0.7 suggests high reliability. The total E-Motion scale consists of 48 items. Each stimuli number, phase, emotion and movement type is provided in Appendix L, table L.2 (page 122). All respondents (n=30) achieved 100% accuracy on items 29, 33, 41 and 45 and as such these items were excluded by the Cronbach's alpha analysis. The full E-Motion test (excluding items 29, 33, 41 and 45) had low internal consistency (α=0.38, 95% CI [0.02, 0.66]). The Cronbach's alpha analysis indicated that removal of item numbers 3, 6, 7, 9, 11,

13, 17, 18, 22, 28, 30, 34, 39, 46 and 48 would improve Cronbach's alpha for the total E-Motion scale (α=0.67, 95% CI [0.47, 0.82]).

The internal consistency of each emotion subscale; happiness, sadness, anger and fear were also explored. The happy subscale consists of 12 items. Following the removal of items 29 and 33 from the analysis due to having no variance, the reliability of the happy subscale was calculated as poor (α=0.23, 95% CI [-0.26, 0.58]). Further removal of items 6 and 27 from the happy subscale improves the internal consistency somewhat, however, the alpha remains within the poor range (α=0.44, 95% CI [0.08, 0.70]). The anger subscale consisted of 12 items, however only 11 items were analysed due to item 45 being discounted, due to having no variance in the sample. The removal of item number seven would improve the original moderate internal consistency of the anger subscale from an alpha of 0.55 (95% CI [0.27, 0.76]) to 0.58 (95% CI [0.31, 0.77]). The internal consistency of the afraid subscale, consisting of 12 items (α=0.51, CI [0.2, 0.73]) was within the moderate range. The analysis indicated that the internal consistency of the afraid subscale would be improved by the removal of items 17, 31 and 43 (α=0.56, CI [0.28, 0.76]). The sad subscale consisted of 12 items, however, item 41 was not included in the analysis due to there being no variance. The remaining 11 items of the sad subscale indicated poor internal consistency (α =0.46, 95% CI [0.12, 0.71]). The Cronbach's alpha analysis suggested that removal of items 3, 39 and 48 would improve the internal consistency of this subscale to within the moderate range (α=0.61, 95%CI [0.36, 0.79]).

DISCUSSION

ToM Impairments in MND

The results of the current study support the primary hypothesis that the MND group would demonstrate a significant impairment on E-Motion compared to controls. The findings regarding E-Motion indicated a large effect size. However, it is important to note that the test has not yet been formally validated and as such firm conclusions regarding whether MND is associated with difficulties understanding emotional body language cannot be made. The MND group, however, did perform poorer across all three social cognition tests compared to the control group and differences between groups on the validated ECAS social cognition subtest were significant. These findings are in accordance with previous research which has highlighted ToM deficits in the MND population (Bora, 2017). The results of the current study suggest that some individuals with this condition, may develop ToM deficits. Indeed carers of MND sufferers can experience distress related to changes in their loved one's social conduct (Lillo et al., 2012). With regards to clinical practice, it may be helpful to provide psychoeducation to patients and their families about the possibility of experiencing difficulties with ToM during the course of their condition. This may increase understanding and improve interpersonal relationships.

Exploratory Subgroup Analysis

The ECAS total scores indicated that seven MND participants (46%) presented with cognitive impairment. This proportion is consistent with previous estimates that 50% of individuals with MND develop a cognitive impairment (Ringholz et al., 2005). The MND group as a whole and the MNDp and MNDci groups performed significantly poorer than the control participants on the E-Motion test with large effect sizes. Confidence intervals indicated that the true effect size was indeed within the large range for differences between the MNDci and control group on E-Motion. However, confidence intervals indicate that true effect sizes may have ranged between

small to large regarding group differences between the MNDp group and control group on E-Motion.

Only the MNDci group demonstrated a significant impairment on TASIT compared to controls with a large effect size. This result is in accordance with findings of a previous study, which reported that individuals with MND and comorbid cognitive deficits showed a significant impairment on the TASIT compared to controls (Savage et al., 2014). Individuals with "pure" MND, however, scored within the normal range on this test (Savage et al., 2014). Findings are, however, mixed and a another study reported that individuals with "pure" MND were impaired compared to controls on the TASIT (Staios et al., 2013). Inconsistent findings regarding social cognition deficits and individuals with MNDci and MNDp may be attributable to considerable heterogeneity of this population in terms of clinical symptomology and time since symptom onset. Indeed, research suggests that ToM difficulties appear to become more prevalent as the disease progresses (Trojsi et al., 2017).

In comparison to the control group, the whole MND group and MNDci sub-group demonstrated impairment on the ECAS social cognition test, a version of the Judgement of Preference Task with large effect sizes (JPT). Interestingly, individuals with MNDp were not significantly impaired on this test although results indicated a small effect size. These findings suggest that this subtest may only be sensitive to relatively pronounced ToM difficulties, likely to be present in the context of broader cognitive impairment. Indeed, Niven et al. (2015) reported that 30% (n=12) of participants in their MND group demonstrated an impairment on the ECAS social cognition test. Eleven of the individuals impaired on the ECAS social cognition test had comorbid cognitive impairments and only one had an isolated ToM impairment.

Exploratory use of E-Motion Tool

This experiment provides the first exploratory use of E-Motion as a proposed ToM test. Performance on the ECAS social cognition test was positively associated with performance on the TASIT with medium to large effect sizes. The E-Motion test, was not significantly associated with the other social cognition tests, although the results showed a weak association between E-Motion and TASIT within the small range. It is therefore, possible that E-Motion does measure ToM constructs related to those measured by the TASIT and that within a larger sample size, further significant correlations between E-Motion and other ToM tests would be detected.

Another possible explanation for the dearth of correlations between E-Motion and other tests is that the three social cognition tests may be measuring different aspects of ToM. Indeed MND participants attained lower scores than controls on the TASIT, although group differences did not reach significance. The MND group was significantly impaired on ECAS social cognition test with a medium effect size and on E-Motion with a large effect size. It is therefore also possible that all three tests detect different aspects of ToM with variable sensitivity.

The variation in sensitivity of the three social cognition tests may be understood in the context of the functional organisation of the MNS. Imaging studies have demonstrated that the premotor area of the MNS, involved in understanding motor acts, is somatotopically arranged (Fabbri-Destro & Rizzolatti, 2008). Accordingly, when an individual observes another person performing movements with different parts of the body, distinct cortical areas of the premotor MNS are activated. Similarly, there is emerging evidence that neurological mirroring occurs in the processing of auditory information. This auditory mirroring is associated with distinct and

overlapping areas of the MNS such as the insula, auditory cortex, superior temporal gyrus, angular gyrus, Wernicke's area and Broca's area (Stephens et al., 2010).

It is possible that in situations where there are more cues available (i.e. auditory and visual, facial and body movements), individuals who have sustained damage to an area of the MNS during the course of MND may be able to compensate using other intact areas of their MNS. During the TASIT, the examinee is asked to ascertain the emotion of an actor through auditory and visual cues in naturalistic social situations. The ECAS social cognition subtest examines ToM through direction of eye gaze of a cartoon face and as such provides fewer cues in comparison to the TASIT. The E-Motion test requires examinees to deduce the emotion of a figure from subtle body movements alone. Tasks such as the TASIT feature auditory, visual, facial and body movement cues. It is possible that individuals who have an MND and a comorbid impairment in ToM related to a focal MNS region may have been more able to mask the deficit by using alternative cues on the TASIT.

Analysis revealed that all three ToM tests were positively associated with executive function and general cognitive abilities with medium to large effect sizes. Interestingly, when examining the performance of MNDci and MNDp participants separately, only participants with MNDci exhibited deficits on the TASIT and ECAS social cognition subtest with large effect sizes. In contrast, both individuals with MNDci and MNDp demonstrated significantly poorer performance on the E-Motion test compared to controls with large effect sizes. Furthermore, results demonstrated that individual MND participants were impaired on E-Motion despite normal TASIT, ECAS total, social cognition and executive function scores. An impairment on the E-Motion test does not appear to reflect lower levels of education, global cognitive impairment or broader executive dysfunction. Results of the E-Motion test must be interpreted

with caution, as the assessment has not yet been validated. However the current study suggests that E-Motion appears to be detecting an impairment distinct from global cognitive deficits. This is in accordance with previous findings that the ToM deficits associated with MND appear to be "over and above" wider executive dysfunction or cognitive impairment (Cavallo et al., 2011; p2).

With regards to the internal consistency data, results indicate sub-optimal and highly variable reliability for the overall scale and subscales. In the format used in the study the E-Motion total scale as a whole (α=0.38), the happy subscale (α=0.23) and sad subscale (α=0.46) demonstrated poor internal consistency (Hinton et al., 2004). However, analysis of anger subscale as used in the study (minus item 45 which was excluded due to having no variance) indicated moderate internal consistency (α=0.55) (Hinton et al., 2004). The afraid (α=0.51) subscale as used in the study, prior to removal of any items also appears to demonstrate moderate internal consistency (Hinton et al., 2004). It is important to note that confidence intervals provided for alpha values relating to the angry and afraid subscales indicated that the true range of internal consistency for these scales may range from low to high. The broad confidence intervals are likely a result of low sample sizes and a low number of items involved in the Cronbach's analyses (Bujang et al., 2018). It is possible that the discriminatory power of E-Motion, to differentiate between MND and control groups is based on the anger and afraid subscales, rather than the test as a whole. The wide variation in subscale reliability suggests that there is a need for comprehensive optimization to ensure all scales yield high internal consistency, before further use.

Limitations and Suggestions for Future Research

The results of the validated ECAS social cognition test suggest that some individuals with MND develop ToM deficits. The exploration of any differences in social cognition deficits between

bulbar and limb onset MND and familial and sporadic presentations is beyond the scope of the current study due to the small sample size. It was not possible to explore the relationship between behavioural impairments and social cognition due to missing informant questionnaire data. There is a dearth of research regarding these aspects of MND in relation to ToM and further investigation is required.

The current study provides preliminary data for the E-Motion assessment tool. However it is important to note that the validity and reliability of the test has not been established. The MND group were significantly impaired on E-Motion compared to the control group which may indicate that some individuals with MND may have a difficulty with a particular aspect of ToM, specifically understanding emotional body language. However, E-Motion did not significantly correlate with other ToM tests in the current study. This suggests that either E-Motion is not measuring ToM, or as discussed it may be that it is sensitive to a different aspect of ToM than is captured by the TASIT and ECAS social cognition tests. Further research in a large neurotypical population comparing E-Motion to a broader range of ToM tests and informant measures of ToM would be required to investigate convergent validity.

It is a significant limitation of the study that the internal consistency analysis was run post hoc, rather than in the initial development phase of the tool. The Cronbach's alpha results are also limited by the use of a mixed sample of individuals with MND and control participants. Research suggests that a sample size of 30 is required for Cronbach's analysis and as such it was not appropriate to analyse the MND (n=15) and control groups (n=15) scores separately (Bujang et al., 2018). The Cronbach's alpha results demonstrated that the internal consistency of E-Motion and E-Motion subscales was variable and may be improved by removal of specific items. Research suggests that for smaller scales of less than ten items, Cronbach's alpha may

underestimate the internal consistency of scales (Taber, 2018). These results should, therefore, be interpreted with caution as the subscales analysed had a low number of items. Further testing of E-Motion with a larger sample of neurotypical participants, more representative of the wider population, should be carried out before removal of items from the scale. This would ensure the Cronbach's alpha analysis is more accurate and that subsequent removal of items results in the most internally consistent version of the E-Motion test. A formal pilot study with a large sample would enable further investigation of the internal consistency of E-Motion by emotion subscales (happiness, sadness, anger, fear), movement subscales (walking, lifting, knocking, throwing) and phase subscales (full figure, line figure and point light conditions).

Another limitation of this study is that the increase in familywise error rate across the statistical analyses was not controlled for using Bonferroni correction or a false discovery rate controlling procedure (Cabin & Mitchell, 2000). Effect sizes and confidence intervals were, however, calculated to provide indicators of the magnitude of our findings. The difference between groups on E-Motion ($p=0.001$) remains significant when considering a more conservative significance level ($p=<0.01$). The results of this study are, however, preliminary and future research must be undertaken before concluding that individuals with MND may have any deficts in understanding emotional body language.

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APPENDICES

Appendix A Instruction for Authors

Journal of Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

All authors should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (ICMJE).

Structure

Your paper should be compiled in the following order: title page; abstract; keywords; main text introduction, methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

Word Limits

Please include a word count for your paper.

A typical paper for this journal should be approximately 3000 words. Illustrations are welcomed (please see instructions below).

Style Guidelines

Please refer to these quick style guidelines when preparing your paper, rather than any published articles or a sample copy.

Please use British (-ise) spelling style consistently throughout your manuscript.

Please use single quotation marks, except where 'a quotation is "within" a quotation'. Please note that long quotations should be indented without quotation marks.

Formatting and Templates

Papers may be submitted in Word format. Figures should be saved separately from the text

References:

Please use this reference guide when preparing your paper.

Checklist: What to Include

1. Author details. Please ensure everyone meeting the International Committee of Medical Journal Editors (ICMJE) requirements for authorship is included as an author of your paper. All authors of a manuscript should include their full name and affiliation on the cover page of the manuscript. Where available, please also include ORCiDs and social media handles (Facebook, Twitter or LinkedIn). One author will need to be identified as the corresponding author, with their email address normally displayed in the article PDF (depending on the journal) and the online article. Authors' affiliations are the affiliations where the research was conducted. If any of the named co-authors moves affiliation during the peer-review process, the new affiliation can be given as a footnote. Please note that no changes to affiliation can be made after your paper is accepted. Read more on authorship.
2. Should contain a structured abstract of 250 words. A structured abstract should cover (in the following order): Objective, Methods, Results and Conclusions. Short Reports, Non-systematic Reviews, Commentaries and Case Reports require a maximum 150-word "block" style, non-structured abstract.
3. Graphical abstract (optional). This is an image to give readers a clear idea of the content of your article. It should be a maximum width of 525 pixels. If your image is narrower than 525 pixels, please place it on a white background 525 pixels wide to ensure the dimensions are maintained. Save the graphical abstract as a .jpg, .png, or .gif. Please do not embed it in the manuscript file but save it as a separate file, labelled GraphicalAbstract1.
4. You can opt to include a video abstract with your article. Find out how these can help your work reach a wider audience, and what to think about when filming.
5. Between 3 and 5 keywords. Read making your article more discoverable, including information on choosing a title and search engine optimization.

6. Funding details. Please supply all details required by your funding and grant-awarding bodies.
7. Disclosure statement. This is to acknowledge any financial interest or benefit that has arisen from the direct applications of your research. Further guidance on what is a conflict of interest and how to disclose it.
8. Biographical note. Please supply a short biographical note for each author. This could be adapted from your departmental website or academic networking profile and should be relatively brief (e.g. no more than 200 words).
9. Data availability statement. If there is a data set associated with the paper, please provide information about where the data supporting the results or analyses presented in the paper can be found. Where applicable, this should include the hyperlink, DOI or other persistent identifier associated with the data set(s). Templates are also available to support authors.
10. Data deposition. If you choose to share or make the data underlying the study open, please deposit your data in a recognized data repository prior to or at the time of submission. You will be asked to provide the DOI, pre-reserved DOI, or other persistent identifier for the data set.

11. Supplemental online material. Supplemental material can be a video, dataset, fileset, sound file or anything which supports (and is pertinent to) your paper. We publish supplemental material online via Figshare. Find out more about supplemental material and how to submit it with your article.
12. Figures. Figures should be high quality (1200 dpi for line art, 600 dpi for grayscale and 300 dpi for colour, at the correct size). Figures should be supplied in one of our preferred file formats: EPS, PS, JPEG, GIF, or Microsoft Word (DOC or DOCX). For information relating to other file types, please consult our Submission of electronic artwork document.
13. Tables. Tables should present new information rather than duplicating what is in the text. Readers should be able to interpret the table without reference to the text. Please supply editable files.
14. Equations. If you are submitting your manuscript as a Word document, please ensure that equations are editable. More information about mathematical symbols and equations.
15. Units. Please use SI units (non-italicized).

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Clinical Trials Registry

In order to be published in a Taylor & Francis journal, all clinical trials must have been registered in a public repository at the beginning of the research process (prior to patient enrolment). Trial registration numbers should be included in the abstract, with full details in the methods section. The registry should be publicly accessible (at no charge), open to all prospective registrants, and managed by a not-for-profit organization. For a list of registries that meet these requirements, please visit the WHO International Clinical Trials Registry Platform (ICTRP). The registration of all clinical trials facilitates the sharing of information among clinicians, researchers, and patients, enhances public confidence in research, and is in accordance with the ICMJE guidelines.

legislation requires. Authors who do not have formal ethics review committees should include a statement that their study follows the principles of the Declaration of Helsinki.

Complying With Ethics of Experimentation

Please ensure that all research reported in submitted papers has been conducted in an ethical and responsible manner, and is in full compliance with all relevant codes of experimentation and legislation. All papers which report in vivo experiments or clinical trials on humans or animals must include a written statement in the Methods section. This should explain that all work was conducted with the formal approval of the local human subject or animal care committees (institutional and national), and that clinical trials have been registered as

Consent

All authors are required to follow the ICMJE requirements on privacy and informed consent from patients and study participants. Please confirm that any patient, service user, or participant (or that person's parent or legal guardian) in any research, experiment, or clinical trial described

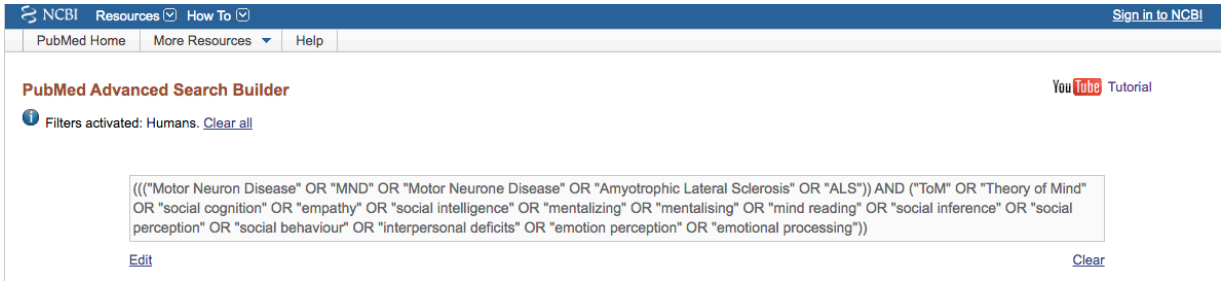
in your paper has given written consent to the inclusion of material pertaining to themselves, that they acknowledge that they cannot be identified via the paper; and that you have fully anonymized them. Where someone is deceased, please ensure you have written consent from the family or estate. Authors may use this Patient Consent Form, which should be completed, saved, and sent to the journal if requested.

Health and Safety

Please confirm that all mandatory laboratory health and safety procedures have been complied with in the course of conducting any experimental work reported in your paper. Please ensure your paper contains all appropriate warnings on any hazards that may be involved in carrying out the experiments or procedures you have described, or that may be involved in instructions, materials, or formulae.

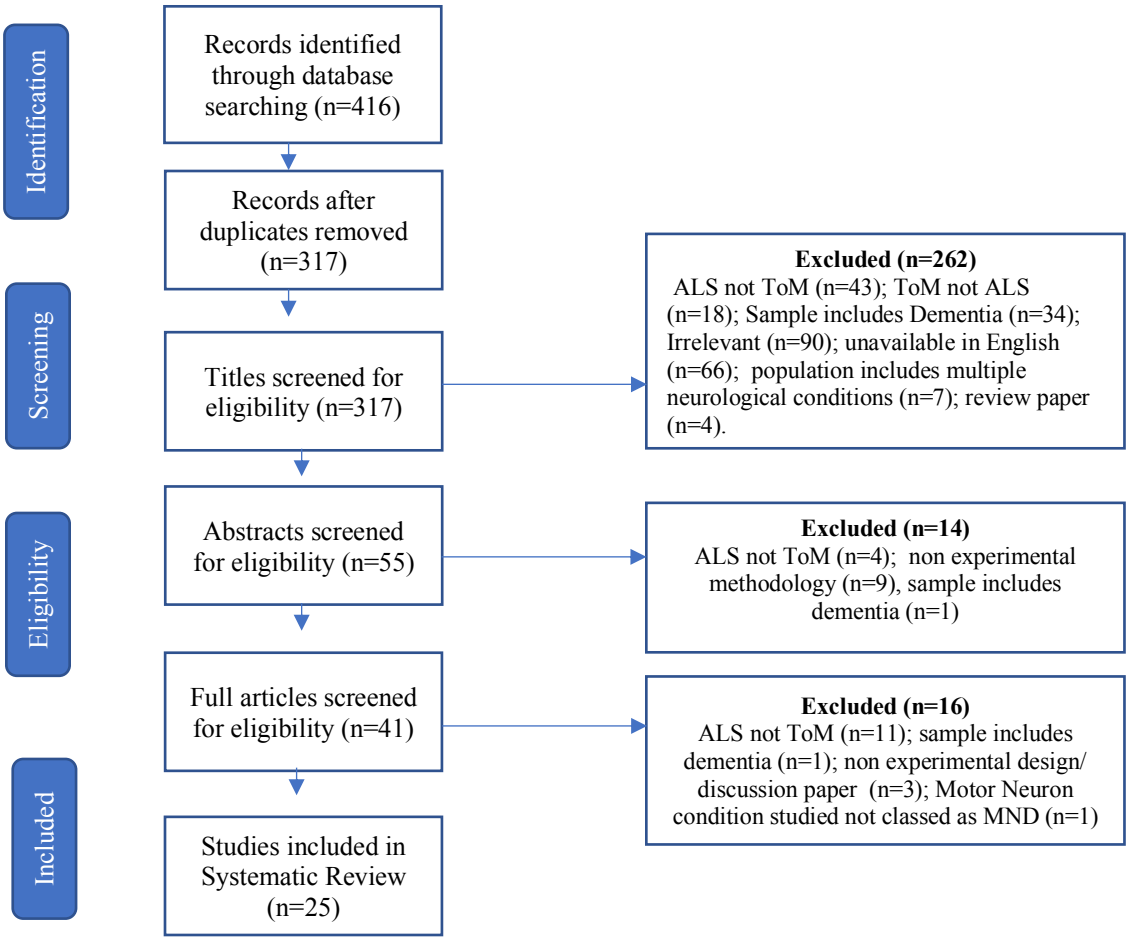
Appendix B Systematic Review Search Strategy

PubMedSearch



Population	Phenomenon of Interest	Design	Measures
Motor Neuron Disease	theory of mind	Controlled study Quantitative research Cohort studies Experiments RCTs Standardization studies	Assessment Tool Survey Measure Questionnaire Task Method
MND	ToM		
Motor Neurone Disease	social cognition		
Amyotrophic Lateral Sclerosis	empathy		
ALS	social intelligence		
	metalizing		
	mentalising		
	mind reading		
	social inference		
	social perception		
	social behaviour		
	interpersonal deficits		
	emotion perception		
	emotional processing		

Appendix C Systematic Review PRISMA Flow Chart



Appendix D Systematic Review Quality Rating Scale

QAS-MND (Adapted from SIGN Case-Control Studies Assessment Scale)

QAS-MND Quality Assessment Scale for review of MND studies			
Insert Study Citation under review			
Criteria	**Yes (1)**	**No (0)**	**Not stated (0)**
Aims			
1. The study addresses an appropriate and clearly focused question (Aims, hypothesis, null hypothesis are clear).			
Sample			
2. The sample size is justified through power calculation			
3. The cases and controls are taken from a comparable population in terms of: *age range (range & no significant difference between mean of groups) performance in MND due to fatigue) *geographical area (as this may effect socioeconomic status & performance on tests) *Years of education (as this may effect cognitive Performance)			
4. Control group inclusion and exclusion criteria are well defined and appropriate (community controls with no history of neurological/ psychiatric conditions)			

5. For the MND group, inclusion and exclusion criteria are well defined and appropriate. * Ensure no comorbid dementia diagnosis, no presence of other neurological/ psychiatric condition. *The MND cases are clearly defined and differentiated from The control group (i.e. through independent validation of diagnosis/ case records to confirm MND diagnosis)			
6. The study provided details of attrition from both groups and this was less than 10% of the original sample.			
Method & Outcome Measures			
7. Both groups completed the assessment under the same conditions.			
8. The same assessment was undertaken by MND and control group. (This may have involved reasonable adjustments- i.e. for Hospital Anxiety & Depression Scale /HADS, for controls and HADS-M for MND group)			
9. The primary outcome measure is valid and reliable.			
10. Tests used are appropriate for people with MND (not affected by motor difficulties such as requiring written responses).			

Insert Study Citation under review			
Criteria	**Yes (1)**	**No (0)**	**Not stated (0)**
11. Groups were tested in the morning or early afternoon (testing later in the day associated with higher levels of fatigue in the MND population which may affect testing).			
Statistical Analysis			
12. Study controls for the main potential confounders in the design and analysis. Specifically, the study has measured anxiety and depression and accounted for this in the analysis.			
13. The researchers have administered a minimal cognitive assessment to screen for dementia (e.g. ECAS) to enable exclusion of any participants meeting criteria for dementia from analysis.			
14. The study provided analysis of possible moderating variables such as stage of MND and type of onset (limb/ bulbar) .			
15. Confidence intervals are provided.			
16. Were the authors' discussions and conclusions justified by the results?			
Notes (authors conclusions, any areas of uncertainty):			

Quality Rating (High, Intermediate, or low)
Study Rating: /16 High 11+ Intermediate 7+ Low: 6 or less
Rater #1 Initials:
Rater #2 Initials:
Additional Comments (If low, please state why):

Appendix E MRP proposal

Title: Major Research Project Proposal

Investigating the Perception of Emotion Portrayed Through Body Movements in Motor Neuron Disease

Abbreviated Title of Project: E-Motion

Base: Institute of Neurological Sciences, Queen Elizabeth University Hospital

Principal Investigator Name: Iona Walker, Trainee Clinical Psychologist

Academic Supervisor: Professor Jon Evans, Professor, University of Glasgow

Field Supervisor: Dr Steven Meldrum, Clinical Neuropsychologist

Version: 2 **Date:** 26th May 2018

BACKGROUND

Motor Neuron Disease

Motor Neuron Disease (MND) refers to a group of disorders caused by a degeneration of the upper motor neurons in the cortex and or involving the lower motor neurons located in the brain stem and spinal cord (Desai Joy, 2000; Talbot, 2009).The disease disrupts signals between the brain and the muscles causing progressive weakness, physical disability and speech difficulties. The average age of onset for MND is 56 years, with a typical prognosis of between two and five

years (Talbot, 2009). The disease is fatal, most commonly due to progressive failure of the respiratory and cardiovascular systems (Talbot, 2009).

Theory of Mind and the Mirror Neuron System

Theory of Mind (TOM) refers to the ability to empathise and to understand that others have internal experiences different to one's own (Baron-Cohen, 1991). Mirror neurons are a proposed set of specialised neurons activated either when an individual performs a particular motor act or observes another person performing a motor act (Di Pellegrino et al, 1992). It has therefore, been suggested that a hypothesised Mirror Neuron System (MNS) enables people to learn how to infer other people's mental states, through imitation and observation of facial expressions and body movements (Dapretto et al, 2006).

In a recent study, experimenters gained consent to observe MNS activity in a group of epilepsy patients via intracranial depth electrodes which had been implanted to identify affected tissue prior to surgery (Mukamel et al, 2010). This pioneering research is the first to directly record activity of these neurons and has provided the most compelling evidence to date for the existence of the human MNS. The study demonstrated areas of the hippocampus and motor cortex showed excitation during the execution and observation of action and emotional expressions. Neuroimaging studies have also implicated neurons within the pars opercularis of the inferior frontal gyrus (inside Broca's area) and the rostral posterior parietal cortex (Vigneswaran et al, 2013; Dapretto et al, 2006). It has been proposed that damage to the MNS may underlie deficits in TOM associated with various disorders, including Autism (Pickett & London, 2005).

Social Cognition in MND

Approximately 50% of MND patients develop cognitive impairment with an estimated 15% of individuals meeting the criteria for Frontotemporal dementia (FTD) (Bak, 2010). FTD is a progressive condition associated with memory difficulties, disinhibited behaviour and TOM deficits. A review of the literature concluded that people with MND may have deficits in TOM in terms of recognition of facial expressions, understanding of verbal expressions and interpretation of others intentions (Sedda et al, 2014). More specifically research suggests MND patients show impairments on the Judgement of Preference Task (Girardi et al, 2011), the Reading the Mind in the Eyes test and the Faux Pas test (Meier et al, 2010). Further research has also suggested that social communication and understanding can be impaired in MND (Cavallo et al, 2011; Cerami et al, 2014; Watermeyer et al, 2015). Indeed, poor social awareness is a significant cause of distress for family members caring for MND patients (Merrilees et al, 2010). It has been argued that MND patient's poor performance on TOM tests is related to underlying executive dysfunction, rather than a specific deficit in social cognition. Evidence suggests that TOM deficits correlate with impaired executive function tasks and as such may be caused by more general executive dysfunction (Gibbons et al, 2007; Burke et al, 2016). A recent study by Girardi et al (2011), however, demonstrated patients with MND showed social cognition deficits on the Judgment of Preference Task, in the absence of executive dysfunction. It is therefore likely that MND causes a TOM deficit "over and above a deficit in executive functions" (Cavallo et al, 2011).

Motion Perception and Social Cognition in MND

Humans have evolved to deduce the internal states and emotions of others from facial expressions and body movements (Gelder, 2006). Biological motion perception refers to the human ability to identify and interpret the movement of living organisms and is thought to have

evolved for the purposes of survival and social interaction (Atkinson et al, 2007). Experiments have shown that point light displays conveying biological motion provide adequate information for participants to ascertain the action, gender and emotional state of the figure (Johansson 1973, Cutting & Kozlowski 1977; Mather & Murdoch, 1994, Brownlow et al, 1997). Lule et al (2007) reported that compared to controls, MND patients show reduced activation in the right middle temporal lobe, an area associated with the understanding of biological motion. Furthermore, individuals with MND appear to be impaired in terms of visualizing actions (Fiori et al, 2013) and understanding verbs and action words (Bak and Hodges, 2004; Grossman et al., 2008). A recent experiment used point light movies to depict an actor walking and conveying five different emotional states: happiness, sadness, neutral, anger, and fear (Chouchourelou et al, 2006). A similar paradigm could be used to ascertain whether MND patients' abilities to deduce emotion from physical movement are impaired.

METHODS

Aims & Hypothesis

The current study aims to ascertain whether the perception of emotion portrayed through body movements is impaired in MND compared to the neurotypical population. The primary hypothesis predicts that the MND group's mean score on the E-Motion, test, will be significantly different to the control group's scores. The null hypothesis predicts that there is no significant difference between mean scores on the E-Motion test for the MND group and the control group.

Power Analysis

An a-priori power analysis was conducted using G*Power software (Faul & Erdfelder, 2007). The interpretation of emotion through body movements has not yet been explored in MND,

however, a related study reported that individuals with MND performed significantly poorer on a test requiring the interpretation of facial expressions compared to control groups (Oh et al, 2016), with an effect size of .80. It is anticipated that a sample of 15 people with MND could be recruited to the present study, though a larger sample will be recruited if possible. With power at .80 with an alpha of .05, this would enable an effect size of .93 to be detected. Although this is a larger effect size than that found by Oh et al. (2016) the test used in this research should in theory be capable of detecting more subtle deficits. Rather than interpreting emotions portrayed by stereotyped and commonly known facial expressions (Oh et al, 2016), participants in the current study will be required to deduce emotions conveyed through more subtle body movements. The current study is, therefore, likely to be more sensitive to detecting impairments in social cognition.

Participants

Sample Size

We aim to recruit 20 participants per group if possible. This is to account for high drop out rates in this area of research, due to significant physical deterioration associated with the disease. We aim to recruit spouses of MND patients for the corntol group. For many of the control participants, carer burden may be high and as such we anticipate that drop out rates from the control group may also be high. We therefore, aim to recruit 20 people for the control group additionally.

Inclusion and Exclusion Criteria

Participants diagnosed with other psychiatric or neurological disorders including Frontal Temporal Dementia or who have a history of substance misuse will be excluded from taking part as control participants or as particpants in the MND group. In order to meet the inclusion

criteria, participants in the MND group will be fluent in English, over the age of 18 and have a diagnosis of MND. Neurotypical controls, fluent in English, over the age of 18 with no history of substance misuse, neurological or psychological disorder will be eligible to take part in the control group.

Recruitment of The MND Group

Participants with MND will be invited to take part through specialist MND Nurses at the Queen Elizabeth University Hospital (QEUH) Institute of Neurological Sciences. The specialist MND nurses will provide an initial study information sheet and contact details for the lead researchers. Should patients be interested to take part, they will contact the lead researcher directly to arrange a time to meet. There will be at least two days between the date the MND nurse provides the information sheet and the date of the first meeting to allow participants to consider whether they wish to take part. At the first meeting the lead researcher will discuss the study information sheet again and answer any questions. At this first meeting informed consent will be taken for those who wish to take part. Should participants wish to start testing that day, the assessment will be initiated.

Participants with MND will also be recruited via The Scottish MND Register, affiliated with the charity MND Scotland. The Scottish MND Register was set up to enable MND patients resident in Scotland to influence care services provided by Scottish health boards and local authorities. MND patients who have opted into the Scottish MND register can influence services through involvement in audit and research projects. Individuals who have opted to sign up to the Scottish MND register, provide consent for NHS researcher to invite them to take part in MND research studies. Participants on the MND register with addresses in the Scottish Highlands, Western Isles, Lanarkshire and Greater Glasgow and Clyde Health Board areas will

not be invited to take part via the MND register, as these areas are covered by the QEUH and these patients will already have been invited by their MND nurses to take part. Participants on the MND register with addresses in Ayrshire, Forth Valley, Fife, Lothian and Lanarkshire will be invited to take part via an invitation letter and study information sheet. Prospective participants with MND will, therefore, only be invited to take part in the study once. Patients on the MND register with addresses in the Scottish Borders, the Isle of Arran, Dumfries and Galloway, Grampian and Tayside will not be invited to take part as the distance of travel for the main researcher to the visit the patients in their homes would be unfeasible given the time period of the study. It is also deemed too demanding for patients from these areas to travel to Glasgow for testing at the QEUH or Gartnavel Hospital due to the distance involved and the physically disabling nature of MND.

Participants on the MND register who have addresses in Ayrshire, Forth Valley, Fife, Lothian and Lanarkshire will be invited to take part via a study information sheet and invite letter posted to them. This will be arranged through Shuna Coville, Director of the MND register who has agreed that the current study would be eligible following ethical approval. MND participants recruited via the register will contact the researcher via the details on their letter, should they wish to take part and a face to face meeting will be organized. There will be at least two days between the MND patients contacting the researcher and the date of the first meeting to allow the participants to consider whether they wish to take part. At the first meeting the lead researcher will discuss the study information sheet again and answer any further questions. At this first meeting informed consent will be taken for those who wish to take part. Should participants wish to start testing that day, the assessment will be initiated.

Recruitment of Control Participants

In order to match the MND group to the control group as closely as possible in terms of age and education, the researchers will aim to recruit spouses of MND patients who are participating in the research.

Specialist MND nurses at the QEUH have contact with spouses who care for their relatives with MND. The MND nurses will invite spouses of MND patients to take part in the study as control participants and will provide study information sheets with the contact details of the researcher. Control participant's who wish to take part will contact the researcher and arrange a face to face meeting. There will be at least two days between the prospective participant contacting the researcher and the date of the first meeting to allow the participants to consider whether they wish to take part. At the first meeting the lead researcher will discuss the study information sheet again and answer any further questions. At this first meeting informed consent will be taken for those who wish to take part. Should participants wish to start testing that day, the assessment will be initiated.

Letters sent to those on the MND Register with addresses in Ayrshire, Forth Valley, Fife, Lothian and Lanarkshire, will also state that MND patients spouses may contact us to take part as control participants should they wish to be involved. Control participants recruited via the MND register will contact the researcher via the details on the letter. Should they wish to take part a face to face meeting will be organized. There will be at least two days between the participant contacting the researcher and the date of the first meeting to allow the participants to consider whether they wish to take part. At the first meeting the lead researcher will discuss the study information sheet again and answer any further questions. At this first meeting

informed consent will be taken for those who wish to take part. Should participants wish to start testing that day, the assessment will be initiated.

A poster will also be placed in waiting areas in Neurology and Neuropsychology Clinics, recruiting control participants without any neurological difficulties.

Informed consent

Explaining the study, answering any questions and signing the consent form is estimated to take approximately 10 minutes.

Background Measures

In order to obtain an estimated premorbid IQ the Test of Premorbid Functioning (TOPF) which takes approximately five to ten minutes, will be administered to all participants (Wechsler, 2011).

Cognitive Screening

Social intelligence may be affected by cognitive deficits. As such, the sample will also complete the Edinburgh Cognitive and Behavioural ALS Screen which takes approximately 30 minutes (ECAS) (Niven et al, 2015), to provide a measure of cognitive difficulties and executive dysfunction.

Psychological Assessment

Affective disturbance may also influence participants' performance on tests of emotional and cognitive abilities. Subsequently control subjects will complete the Hospital Anxiety and Depression Scale and the patient group will be provided with a version of adapted for use with

MND patients (HADS-M) both of which take approximately five minutes to administer (Gibbons et al, 2011).

Baseline Motor Skills

Both groups will also be asked to replicate a range of transitive and intransitive pantomime actions, which will take approximately 10 minutes, as a measure of the ability to interpret basic movements in the absence of emotional cues.

Test of Social Awareness

Subjects will be asked to complete subtests of The Awareness of Social Inference Test (TASIT, McDonald et al, 2003). This test requires participants to identify happiness, sadness, anger, anxiety and neutral emotion from videotaped social scenes and will take approximately 10 minutes to administer.

Test of the Perception of Emotional Body Gestures

Both groups will also complete the E-Motion test, a new thirty-five minute assessment tool created for the study, which involves identifying five key emotions portrayed through body movements. E-Motion video recordings show an individual portraying happiness, sadness, anger, anxiety and neutral emotion, through body movements without additional verbal cues or facial expressions.

Data Management & Analysis

Data will be stored in a secure password protected spreadsheet, in line with data protection regulations. Participants will be registered on a list with their names and ID numbers. Participant names will not be recorded on paper records, their ID numbers will be noted on paper records.

Names and signatures of participants will be on consent forms. Paper records containing participant numbers, demographic information and each participant's responses on the tests will be kept in a locked cupboard at the QEUH MND Research room. The consent forms with patient names will be kept in a separate locked cupboard in the QEUH MND research room. The Anonymised data set will be input into a excel spreadsheet on an NHS computer in the QEUH research room. This will then be uploaded to a secure password protected encrypted memory stick. Analysis of the anonymised data will be done on a University computer (with access to SPSS). In order to protect the identity of patients with MND, age rather than date of birth will be used in the anonymised data set. At end of project Jon Evans will be the custodian of the data. He will keep the psuedonomysed data in a locked cabinet in his office at the Gartnavel Administration Building for 10 years, following which it will be destroyed.

Assuming parametric assumptions are met, the data will be analysed using an independent T-test on SPSS to ascertain whether there is a statistically significant difference between the control and MND group's means on the E-Motion test. If the data does not meet parametric assumptions, then a Mann Whitney U test will be used. The relationship between social cognition tests and factors will be explored using Pearson's or Spearman's correlation depending on the normality of the data.

Settings and Equipment

MND patients often receive home visits from MND nurses and occasionally attend hospital for clinically necessary procedures. Due to the physical debilitation associated with MND, patients are often unable to travel, as such home visits will be offered to participants with MND who are unable to attend the QEUH or Gartnavel Hospital.

Control participants will have the option of being seen at the Mental Health and Wellbeing Centre at Gartnavel Hospital or at a research room at the QEUH. Additionally in cases where the control participant is the partner of a MND patient taking part in the study and the researcher is visiting their relative with MND at home to undertake the testing, the control participant (carer for the MND patient) will also be offered to be seen in their home, and to be tested in succession, following their partner. The rationale for this is to minimise travel costs which NESS will be refunding and disruption to families taking part in the study.

Ethical and Health and Safety Issues

For participants with MND being seen at the QEUH MND service, we may request to share information between our research team and their clinical care team regarding results of some of the tests. This is because some of the questionnaires and cognitive tests used in this study (HADS-M & ECAS) are routinely delivered at the QEUH MND service and as such by communicating with the QEUH team, we would prevent the participants from repeating any tests they have already undertaken.

Domiciliary visits are necessary to recruit participants with MND who may be housebound due to progressive physical disabilities. Precautions will be taken to mitigate risks and the University of Glasgow (2018) and NHS Greater Glasgow and Clyde (2012) Lone worker policies will be followed (see appendix G). The researcher will apprise themselves of the risk assessment by the clinical team at the QEUH. For participants being visited in their homes, recruited from the MND register, the invite letter will explain that in order to take part in the study participants must consent to the main researcher contacting the MND nurse involved in their care. This will enable the main researcher to contact the patients MND nurse to apprise themselves of the risk assessment and ensure the patient is suitable to be visited in their home. Should the main

researcher have any concerns regarding the safety of the MND patient or regarding their home environment these concerns will be passed on to the MND nurse in their care.

It is important to consider that participants with MND may be suffering from pain and fatigue. Including information giving, consent taking, the testing session and debriefing, the study will take approximately one hour forty five minutes. Breaks will be offered and participants will also be given the option to complete the testing over two sessions. With regards to travel expenses, as discussed it is likely that the majority of participants will be seen in their homes, particularly for MND participants who live further away. Some patients living within Greater Glasgow and Clyde or the Edinburgh region may wish to be seen at the QEUH or Gartnavel Hospital. For those who drive the cost of petrol is estimated to be around 16 pounds for a return trip and to be 13 pounds on public transport. Expenses will be offered for those who opt to travel to the QEUH or Gartnavel.

The study is funded by NHS Education for Scotland. The results will be disseminated via the University of Glasgow Special Collections Thesis Website and may be presented in a Poster presentation at conferences. We also intend to publish the study in a relevant journal. All information published will be anonymous. Should they opt into this, all participants will be sent a letter following the study to notify them of the results.

Practical Applications

This research has the potential to improve our understanding of social difficulties associated with MND and how to support patients with this. Furthermore, this study may also provide evidence regarding whether the putative MNS is compromised in MND.

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Appendix F MRP Ethical Approval

Health Research Authority

East Midlands - Nottingham 2 Research Ethics Committee

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

22 August 2018

Professor Evans & Iona Walker
University of Glasgow
Institute of Health & Wellbeing
Gartnavel Royal Hospital
Glasgow
G12 0XH

Dear Professor Evans

Study title:	**Investigating the Perception of Emotion Portrayed Through Body Movement in Motor Neuron Disease; An E-MOTION Pilot Study**
REC reference:	**18/EM/0234**
Protocol number:	**NA**
IRAS project ID:	**237392**

Thank you for your letter, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the

above study. The revised documentation has been reviewed and

approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Under very limited circumstances (e.g. for student research which has received an unfavorable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favorable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favorable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publicly accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required

timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favorable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favorable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Poster]	v2	26 May 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [TWIMC]	v1	26 May 2018
IRAS Application Form [IRAS_Form_11072018]		11 July 2018
Letters of invitation to participant [ApptoMNDreg]	v2	26 May 2018
Non-validated questionnaire [E-MOTION]	v2	26 May 2018
Other [TASIT Evaluation Test]		
Other [ECAS]		
Other [HADS]		
Other [Response Letter]		28 July 2018
Other [Hospital Anxiety and Depression Scale Adapted for Individuals with Motor Neuron Disease HADS-M]	1	29 July 2018
Participant consent form [Debrief form]	v2	26 May 2018
Participant consent form	3	29 July 2018
Participant information sheet (PIS)	3	29 July 2018
Research protocol or project proposal [MRP]	v2	26 May 2018
Summary CV for Chief Investigator (CI) [CICV]	v1	26 May 2018
Summary CV for student	v1	26 May 1918
Summary CV for supervisor (student research)		26 May 2018
Validated questionnaire [TOPF]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favorable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our RES Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

18/EM/0234	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of

this project. Yours sincerely

pp. V. Sutton

Dr Ian Ross Chair

Email: NRESCommittee.EastMidlands-Nottingham2@nhs.net Enclosures: *"After ethical review – guidance for researchers"*

Copy to: Ms Emma-Jane Gault & Ms Elaine O'Neill, NHS GGC

Appendix G MRP Health & Safety Form

UNIVERSITY OF GLASGOW
DOCTORATE IN CLINICAL PSYCHOLOGY
HEALTH AND SAFETY FOR RESEARCHERS

1. Title of Project	Investigating the Perception of Emotion Through Body Gestures in Motor Neuron Disease
2. Trainee	Iona Walker
3. University Supervisor	Professor Jon Evans
4. Other Supervisor(s)	Dr Steven Meldrum
5. Local Lead Clinician	Dr George Gorrie
6. Participants: (age, group or sub-group, pre- or post-treatment, etc)	Age 18 or over patients with Motor Neuron Disease & neurotypical controls.
7. Procedures to be applied (eg, questionnaire, interview, etc)	Questionnaires Cognitive Testing
8. Setting (where will procedures be carried out?) i) Details of all settings	Patients homes
ii) Are home visits involved	YES

9. Potential Risk Factors Considered (for researcher and participant safety): i) Participants ii) Procedures iii) Settings	This particular client group (Motor Neuron Disease patients) are not normally associated with dangerous or aggressive behaviour. This is due to physical disability caused with the condition. Participants with Motor Neuron Disease may be emotionally labile. Procedures (questionnaires and cognitive testing) are non-invasive, but may be cognitively demanding. In terms of the setting, due to their debilitating condition, patients with MND will be tested in their individuals homes so as to avoid the added distress of travel and mobility difficulties. As such, possible health and safety issues for participants and researchers may arise. Control participants who do not have any physical problems will be tested at the Queen Elizabeth University Hospital, where the environment is designed to be safe for clinical use.
10. Actions to minimise risk (refer to 9) i) Participants ii) Procedures iii) Settings	i) Participants Participants with MND will be in their own homes, so any risks identified in this setting will be raised with supervisors and the patient's clinical nurse specialist who would take any required actions. ii) Procedures Procedures are non-invasive and cognitive screening and psychological questionnaires administered would be administered during the course of patients' assessment at the QEUH MND service as standard. The only additional test employed is the new perception of emotion DVD made by our researchers and subtests of the TASIT. These tests are not designed to be and do not tend to be distressing, but should participants become distressed, testing will be stopped. Details of what the study entails will be provided before testing and it will be made clear that participants can opt out at any time. Details for psychological support organisations will be provided at the end of each session. To minimise the risk of people becoming fatigued, individuals will be offered breaks.

	Settings In terms of settings, being in patients' homes may present certain risks to the researcher. This potential risk will be mitigated by the researcher communicating the location and time of all home visits to supervisors and checking in at the end of each session. Additionally, the researcher will carry a personal alarm and a mobile phone at all times. It is not possible to see the participants in the staffed facility and there is a significant risk of sampling bias if participants requiring home visits were excluded from the study. Many patients with MND have significant disabilities which mean that they would be unable to attend the QEUH. All participants will have had contact with a member of the clinical team at the QEUH involved with the patient and a risk assessment carried out. Patients without risk assessments will not be eligible for home visits. As the trainee I will apprise myself of the risk assessment in all cases prior to the visit. As the trainee I will discuss potential for risk with a member of the clinical team who has had contact with the patient recently. As a result of 3 and 4 the risk to myself as the trainee is deemed to be low. I will discuss any doubts or concerns about any particular patients with the University supervisor and/or a senior member of the clinical team that have responsibility for management of the patient. The overall appraisal of risk for each patient will take into account what is known about the participant, a risk assessment of their living environment by the clinical team and consideration of the geographical siting of the visit. This will include assessment of any risk

	associated with travelling to and from the participant's home. Home visits will be conducted in normal work hours. The lone worker policy for the QEUH and GGC will be followed.

Trainee signature: Date: 15/01/2018

University supervisor signature: Date:28/01/2019

Appendix H MRP Participant Information Sheet

Participant Information Sheet Version 3 Date 29th July 2018 IRAS Project ID: **237392**

Study Title: Investigating the Perception of Emotion Portrayed Through Body Movement in Motor Neuron Disease

Dear Prospective Participant,

My name is Iona Walker, I am a Trainee Clinical Psychologist, studying at the University of Glasgow and working in the NHS. As part of my doctoral training to become a Clinical Psychologist I am conducting research to understand more about Motor Neuron Disease and the effects this condition has on emotion perception. This research is supervised by Professor Jon Evans at the University of Glasgow and Dr Steven Meldrum, Clinical Psychologist at the Queen Elizabeth University Hospital (QEUH). Before you decide whether you would like to take part, please take the time to read the information below about why the research is being conducted and what it would involve for you. Please don't hesitate to contact us if you have any questions or would like more information.

Why are we conducting the research?

Recent research suggests that MND may affect people's ability to perceive other people's emotions. To date research has not yet explored whether people with MND have difficulties interpreting emotions portrayed by body movements. The current study aims to investigate whether MND affects the ability to interpret emotional body language. This research has the potential to improve our understanding of social difficulties people with MND may face. The study will involve people with MND and people who do not have any neurological conditions.

Who is able to take part?

We are inviting participants who have a diagnosis of Motor Neuron Disease (MND) to take part. We are also inviting partners of people who have MND, who do not have any neurological conditions, to take part in the study as a comparison group, often known as the control group.

In order to take part, participants with MND will be fluent in English, over the age of 18 and have a diagnosis of MND. In order to take part, participants in the control group must be fluent in English, over the age of 18 with no history of substance misuse, neurological or psychiatric disorder.

Participants diagnosed with other psychiatric or neurological disorders or who have a history of substance misuse are not able to take part in the MND group or control group.

Do I have to take part?

No, it is up to you to decide. Even if you say yes now, but later change your mind, you can do so without giving a reason and without your medical care being affected now or in the future.

What would taking part involve?

Participants can be visited in their homes to complete the study, or alternatively should you wish to be seen in a clinical venue, you can be seen at the Queen Elizabeth University Hospital (QEUH) or Gartnavel Royal Hospital Administration Building.

At the first session, the researcher will explain what the study involves and give you an opportunity to read through the information sheet and ask any questions, before asking whether you wish to take part. If you wish to take part, you will be asked to sign a consent form. If you should wish to start testing at

this first session, we can do so. If you would rather arrange a separate time to complete the testing this is also an option for you. This initial step of gaining informed consent may take fifteen minutes.

The study involves completing a questionnaire about anxiety and low mood and cognitive tests which examine skills such as social perception and memory. Participants will also be asked to complete a test which involves interpreting the emotion portrayed through body movements. Including gaining consent, administering the tests and debriefing after the session, this will take approximately one hour 45 minutes. This can be completed with breaks in between or over two sessions, depending on individual preference.

Please note that for patients with MND, in order to take part in the study, you must consent to our research team having contact with your MND Nurse Specialist. The reason for this is to ensure we have the means to communicate with a professional involved in your care, should any concerns about your health or wellbeing arise.

You may leave the study without completing the questionnaires or tests without providing a reason at any time.

Will I receive Expenses?

There are no direct benefits to taking part in the study and participation is voluntary. Travel expenses to and from the QEUH or Gartnavel can be applied for, unless the participant is visited in the home.

Are there any risks associated with the study?

The study is non-invasive in nature and involves pen and paper based tests and watching videos. Responses will be recorded in writing by the Trainee Psychologist and the participant will not be required to write, although a signature on the consent form will be required. Please note that should information arise during the course of the study which should indicate that you are at risk in any way, the researcher will contact your MND nurse on your behalf to pass on any concerns. For control participants, who do not have an MND nurse, should you raise concerns that you require support, details will be provided of appropriate organisations to access support.

What will happen to the information I give?

Anonymised participant information will be stored in the MND QEUH service in a locked room, uploaded to a secure database on a secure NHS computer and all original copies destroyed 12 months after the study. Anonymised data in a password protected spreadsheet will be stored in a memory stick in a locked cabinet at Glasgow University and destroyed after 10 years.

This study will be written up as part of my University Thesis. It is hoped that this study will be published in a journal at the end of the study and presented at a conference in a poster presentation. All information used in the published literature would be completely anonymous. A summary of findings will also be sent to all participants who would like us to do so. Please note that identifiable data from the study may be accessed by representatives of the study Sponsor, NHS Greater Glasgow &Clyde, for audit purposes. The anonymised data may also be shared with other researchers for use in future approved research studies.

For participants with MND being seen at the QUEH MND service, we may request to share information between our research team and your clinical care team regarding results of some of the tests. This is because some of the questionnaires and cognitive tests used in this study are administered at the QEUH MND service as part of your routine care and as such by communicating with the QEUH team, we would prevent you from repeating any tests you have already undertaken.

NHS Greater Glasgow and Clyde is the sponsor for this study based in Scotland. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. NHS Greater Glasgow and Clyde will keep identifiable information about you until the study is completed. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information by contacting the researcher.

NHS Greater Glasgow and Clyde will keep your name and other identifiable information confidential and will not pass on this information. NHS Greater Glasgow and Clyde will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. In the event that the study is audited, NHS Greater Glasgow and Clyde and regulatory organisations may review identifiable information to check that the informed consent process was followed and to check the accuracy of the research study. With the exception of auditing, no identifiable information will be shared with anyone outwith the research team.

What if something goes wrong?

We do not anticipate any problems with this study, however, please don't hesitate to contact the researcher with any queries or concerns. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during your participation in the research study NHS GGC complaints procedure are available to you. As this study is sponsored by NHS GGC individuals participating as either control participants or as part of the Motor Neuron Disease group, may register concerns or complaints with NHS GGC.

To register a complaint through NHS Greater Glasgow and Clyde please contact 0141 201 4500. You can also call the NHS Patient Advice and Support Service PASS should you require further advice or support about how to register a concern or a complaint on 0800 917 2127. Lines are open Monday-Friday, 9am-5pm. You can find more information about PASS on the website at www.cas.org.uk/pass.

How do I ask for more information or opt into take part?

Participation in this study does not affect any aspect of routine clinical care. If you would like more information or to take part in this study please contact Iona Walker, the main researcher **by email: i.walker.1@research.gla.ac.uk or by Phone: 07971570999. Professor Jonathan Evans and Dr Steven Meldrum are supervising the project. (email:** Jonathan.Evans@glasgow.ac.uk; Steven.Meldrum@ggc.scot.nhs.uk). If you make contact with us, we will offer to arrange a time convenient to you to discuss the study further and obtain your consent to partake, by visiting you at home or by arranging an appointment at the Queen Elizabeth University Hospital or Gartnavel Hospital, depending on your individual preference.
Yours sincerely,

Iona Walker

Trainee Clinical Psychologist
NHS Greater Glasgow and Clyde

Thank you for reading this Information Sheet

Appendix I MRP Consent Form

Version 3 Date 29th July 2018 IRAS Project ID: **237392**

Participant Identification Number for this trial:

Study Title: The Perception of Emotion Portrayed Through Body Movements in Motor Neuron Disease

Name of Researcher: Iona Walker

	Please initial the boxes	
	Yes	Not Applicable
1. I confirm that I have read the information sheet dated 29th July (version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐	☐
3. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.	☐	☐
4. I agree to any necessary exchange of information about me between my MND Nurse and the research team.	☐	☐
5. I give permission for my data to be looked at by representatives of the study Sponsor, NHS GG&C, for audit purposes.	☐	☐
6. *This question pertains to participants with MND who are being seen at the Queen Elizabeth University Hospital.	☐	☐

I understand that relevant sections of my medical notes and data collected during the study, may be shared between the researchers of this study and the clinical staff at the MND Service at the Queen Elizabeth University Hospital.

7. I agree to take part in the above study.	☐	☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix J MRP Debrief Form

STUDY DEBRIEF FORM Version 2 Date 26th May 2018 IRAS Project ID: **237392**

Study Title: The Perception of Emotion Portrayed Through Body Movements in Motor Neuron Disease

Dear Sir/Madam,

We would like to sincerely thank you for taking the time to be a part of this research study to help us improve our understanding of Motor Neuron Disease (MND).

What was the purpose of the research study?

This study is part of my qualification in Clinical Psychology which I am undertaking at the University of Glasgow, in collaboration with NHS Greater Glasgow and Clyde. I am supervised by Professor Jonathan Evans at the University of Glasgow and Dr Steven Meldrum at the Queen Elizabeth University Hospital. Recent research suggests that MND may affect people's ability to perceive other people's emotions. To date research has not yet explored whether people with MND have difficulties interpreting emotions portrayed by body movements. The current study aims to investigate whether MND affects the ability to interpret emotional body language. This research has the potential to improve our understanding of social difficulties people with MND may face. The study will involve people with MND and people who do not have any neurological conditions.

What happens to the results and the data you have collected about me?

Information collected in this study is anonymised. Anonymised data from this study may be shared anonymously with other researchers for use in other approved studies. Identifiable data may be looked at by representatives of the study Sponsor, NHS GG&C, for audit purposes. For participants with MND being seen at the QUEH MND service only: as discussed, we may share information between our research team and your clinical care team regarding results of some of the tests. This is because some of the questionnaires and cognitive tests used in this study are routinely delivered at the QUEH MND service and as such by communicating with the QUEH team, we would prevent you from repeating any tests you have already undertaken.

Anonymised participant information will be stored in the MND QEUH service in a locked room, uploaded to a secure database on a secure NHS computer and all original copies destroyed 12 months after the study. Anonymised data in a password protected spreadsheet will be stored in a memory stick in a locked cabinet at Glasgow University and destroyed after 10 years.

At the end of the study the research team aims to publish the results in a journal and present a poster at a conference. The study will also be submitted as part of my thesis on the Doctorate of Clinical

Psychology Course and may be uploaded to the Thesis Collection on the University of Glasgow Library Website.

Who can I contact if I need to access support?

If you have been affected by any of the issues discussed in the course of this research study, or are requiring support for reasons unrelated to this study, you can contact the organisations below for advice and support. If you require immediate help or would like a referral to an NHS service please contact your GP or if relevant your MND nurse.

- For support related to living with MND, for people with MND and their carers: MND Connect Helpline: **0808 802 6262** or email: **mndconnect@mndassociation.org**
- For emotional support for mental health problems, SANEline is a national out-of-hours telephone: 0300 304 7000

Thank you again for your time. Should you have any further questions about the study you can contact me **by email: i.walker.1@research.gla.ac.uk**

I wish you all the very best for your future,

Yours sincerely,

Trainee Clinical Psychologist
NHS Greater Glasgow and Clyde

Thank you for reading this Debriefing Sheet

Appendix K MRP Research Cost & Equipment Form

RESEARCH EQUIPMENT, CONSUMABLES AND EXPENSES

Year of Course 2nd year **Intake Year 2016**

Item	Details and Amount Required	Cost or Specify if to Request to Borrow from Department
Stationary	26 envelopes A4 (1 per participant) 2x sheets of labels (To enable 1 per participants to aid filing)	0.94 0.03 Subtotal: 0.97
Postage	26 letters to post (1 per participant)	16.12
Photocopying and Laser Printing	260 pages of photocopying (10x per participant) 52 sheets of printing (2x per participant)	13.00 2.60 Subtotal: 15.60
Equipment and Software	NA	:NA
Measures	Already available	NA
Miscellaneous	Travel expenses for participants (this will be applied for on a case by case basis as participants will be offered to be seen in their homes, but have the option of asking to be seen in clinical space at the QEUH or Gartnavel Hospital) Travel expenses for the researcher will be refunded via the NHS GGC expenses website as part of the researcher's usual employment.	Based on a small percentage of our sample requesting to travel to a clinical setting. Travel expenses for 10 participants would cost an estimated: 160 pounds. (this estimate is based on car mileage cost).
Total		192.69

For any request over £200 please provide further justification for all items that contribute to a high total cost estimate. Please also provide justification if costing for an honorarium:

Trainee Signature: Date: 11th June 2018

Supervisor's Signature : Date: 11th June2018

Appendix L Development of E-Motion Task

Development Phase 1 Conception

- The idea for the E-Motion task emerged from discussions between Iona Walker, Trainee Clinical Psychologist, Professor Jon Evans and Dr Steven Meldrum relating to recent research findings that individuals with Motor Neuron Disease (MND) can develop difficulties with ToM in the course of the illness. The hypothesized relationship between mirror neurons and ToM was discussed and it was noted that it may be valuable to understand whether the ability to discern emotions from body movements (an ability associated with mirror neurons) may be impaired in the course of MND.
- The idea of developing a novel test aiming to measure people's ability to discern emotions from body movements to investigate this in the MND population in comparison to a control group was discussed.
- It was noted that it would be necessary to obscure facial expressions to ensure the test isolated the ability to understand emotion through body movements, rather than through other cues.
- It was suggested that the name of the proposed test be E-Motion.

Development Phase 2 Preliminary Stimuli Selection

- Ma, Paterson & Pollick (2006) had previously developed a body movement library to capture many different aspects of human movement, including emotion. The movements of 30 individuals (15 male, 15 female) were captured using body sensors whilst they walked, knocked, lifted and threw whilst wearing sensors and were asked to depict happiness, sadness, anger or fear through their movements.
- Details of this library are accessible here: Ma, Y., Paterson, & Pollick, F.E. (2006). A motion-capture library for the study of identity, gender, and emotion perception from biological motion. *Behavior Research Methods, Instruments, & Computers*, **38**, 134-141.
- Professor of Psychology, Frank Pollick and Mr Hyuga Tanimoto, Computer Programmer at the University of Glasgow were contacted regarding using data from the motion capture library (Ma, Paterson & Pollick, 2006). Stimuli showing people knocking, lifting, throwing and walking depicting happiness, sadness, fear and anger for use in a proposed new test of understanding emotions through body movements were requested.
- Hyuga Tanimoto, Computer Programmer, supervised by Professor Pollick, selected 40 stimuli from the motion capture library in "full figure" mode depicting happiness, sadness, anger and fear in a combination of knocking, throwing, lifting and walking actions. Stimuli were selected based on which videos they considered displayed the clearest movements as judged by Hyuga Tanimoto.
- Full figures were gender neutral.
- Character Studio (plug-ins for 3D Studio Max, AutoDesk Inc.) or Matlab (The Mathworks) or a combination of these two were used to convert the data into videos.
- The 40 files in "full figure" format were transferred onto a PowerPoint presentation to enable the stimuli to be presented on a Mac computer.
- It was decided that the format by which participants would provide responses to stimuli would be by selecting from one of four options presented in front of them - "happy, sad, afraid or angry."

- 10 people were recruited by Iona Walker via opportunity sampling. Five males and five females between the ages of 29-63 years (average age of 37.9 years) with no past or present neurological or mental health difficulties were shown the 40 full figure files using a power point presentation (see table L.1)
- Each were tested individually and the ten participants chose from four emotions (happy, sad, afraid or angry) on a card in front of them.

Development Phase 3 Item Selection

- In order to ensure that we only included stimuli that could be classified with a reasonable level of consistency, we excluded stimuli which were correctly classified by less than 30% of participants.
- Stimuli with 30% or higher pass rate were considered for inclusion in the final test and the best performing stimuli from each type of emotion and action subtype were selected. This ensured each movement and emotion pairing were equally represented in the final E-Motion test.
- Where more than one stimuli demonstrating the same action and emotion pairing scored the same in % accuracy, the lead researcher (Iona Walker) chose the video which had the most exaggerated movement and therefore which was deemed to be the more discernible of the options.
- Four of the highest rated "full figure" stimuli (in terms of % accuracy correct from the 10 control participants) were selected for each emotion (happiness, sadness, fear and anger) comprising of throwing, lifting, walking and knocking movements.
- This resulted in 16 "full figure" stimuli being selected for inclusion in the E-Motion test.
- In the sample of 10 people testing the stimuli the mean accuracy for the chosen set of 16 full figure stimuli was 66.90% (mean score 10.7).

Development Phase 4 Final E-Motion Test Development

- Hyuga Tanimoto developed the point light "dot" and "line" versions of the same 16 full figure files selected from development phase 3 and sent them to Iona Walker for inclusion in the final set of stimuli.
- The final test administered through a Power Point presentation featured 48 stimuli comprising of three phases of the same 16 stimuli: 1.full figure (n=16 stimuli); 2.point light line (n=16 stimuli); 3. Point light dot (n=16 stimuli) (See table L2 for order presented).
- At the top right hand side of each slide the action type was noted, for example "walking." The purpose of this design was to ensure the participants' attention was focused on determining the correct emotion, rather than the action type.
- Phase 1 only featured full figure stimuli. Within phase 1 the order of 16 stimuli was randomised to create the final test.
- Phase 2 only featured point light "line" figures. Within phase 2 the order of 16 stimuli was randomised to create the final test.
- Phase 3 only featured point light "dot" figures. Within phase 3 the order of 16 stimuli was randomised to create the final test.
- All participants viewed the same stimuli in the same order. This entailed watching phase 1 full figure stimuli (n=16) showing happiness, sadness, anger and fear demonstrated through throwing, lifting, walking and knocking movements.
  Then watching phase 2 point light display line stimuli (n=16) showing happiness, sadness, anger and fear demonstrated through four movements throwing, lifting,

walking and knocking. Finally all participants watched phase three point light display dot stimuli (n=16) showing happiness, sadness, anger and fear demonstrated through four movements throwing, lifting, walking and knocking.

- Participants provided the answer from four options from a card in front of them with the words printed happy, sad, angry, afraid.
- Participants could point to the option if they had speech difficulties (commonly experienced by individuals with MND). Participants could verbalise their response if they had motor difficulties affecting hand movements (commonly experienced by individuals with MND).
- **Time of Test**
  The test takes 35 minutes to administer including explanation prior to the beginning to the test and time to answer any questions. Each stimuli takes approximately 30 seconds at the end of which the participant has ten seconds to give their response.
- **Insight Rating**
  Participants were also asked to rate their confidence in each answer they provided from 0% indicating they were not certain at all to 100% indicating they were completely certain. Confidence ratings from 48 items were added and then the total was divided by 48 to provide an average confidence rating for the E-Motion test.
  The actual % accuracy was then estimated (% of items correct out of 48). The actual % accuracy was deducted from the confidence rating to produce an insight rating (either positive or negative value depending on if confidence was overestimated or underestimated for each participant. This was designed with the aim of providing an estimation of an individual's insight into their ability on E-Motion.
  For participants with speech difficulties (common in MND) a chart with 0-100% was displayed for them to choose the relevant percentage. For participants with motor difficulties affecting hand movements (common in MND) they were able to verbalise their answers.
- **Administration instructions**
  The examiner read the below script to the examinee verbatim:
  E-MOTION is a new test which aims to investigate how we understand emotions through body movements. Actors/actresses were asked to act out four motor actions whilst portraying a particular emotion. Actors were asked to throw, walk, lift or knock in an angry, sad, happy or afraid manner. The actors/actresses performed these movements with sensors on them. Then this data was transformed into a computer generated figure doing the actions. We have obscured the face of the computer generated figure. This is because the aim of this study is to understand how people perceive emotions through body movements rather than facial expressions. The bodies depicted are gender neutral. I will play you a series of videos which show computer generated figures portraying emotions through movements. There are three sets, the first a full body image, the second a "stick" figure and the third shows a figure represented by dots. I will ask you after each trial how confident you are from 0-100% that your response was correct. As this is a new task we aren't used to doing on a daily basis, it is normal to be uncertain or to find some of the videos difficult to decipher. You won't receive feedback as to whether you are choosing the correct response. Just give it your best guess and select the emotion you think the video is closest to from these four options. Please note, I can only play each video once and cannot repeat the video. Do you have any questions? If an individual has speech difficulties explain that they can also point to the preferred option. After every block provide verbal encouragement "your concentrating well" "your half way" "Keep going." Participants

are presented with the four options on a card: AFRAID; HAPPY; SAD; ANGRY. How confident are you that your response is accurate? 0-100%

Phase 5 E-Motion Study administered with individuals with MND (n=15) and further separate 15 control participants (n=15 controls)

- In the main study the final E-Motion test comprising of 48 stimuli was administered to 15 controls (see table L3 below). The mean accuracy for the 15 control participants was 70.81% (mean score=11.33) at full figure stage, 65.00% for line phase (mean score=10.40) and 68.30% at dot stage (mean score=10.93). The total combined three phases of 16 trials each comprise the full E-Motion total score. The average E-Motion total score for the control group (n=15) was 68.06%. (mean score=32.67).
- In the main study individuals in the MND group (n=15) completed the full E-Motion test (Table L4). The mean accuracy for the 15 participants who had MND was 60.81% at full figure phase (mean=28.53), 56.25% for the line phase of the test (mean score=9.00) and 61.25% at dot phase (mean=9.80). The scores from three phases are combined to produce the E-Motion total score. The MND group E-Motion total score was an average of 59.44% (average score=28.53).

Table L1. Test Control Participants (n=10) % Accuracy on 40 Stimuli

Stimuli Number/ (NS=not selected)	Stimuli name	% Accuracy
16	Jua_knock_Afraid_1	70
2	Jan_lift_afriad_2	30
10	Jan_throw_afraid_1	60
14	Jan_walk_afraid_2	70
NS	Jua_knock_afraid_2	60
NS	Lin_lift_afraid_1	30
NS	Lin_walk_afraid_1	60
NS	Mac_knock_afraid_1	40
NS	Pet_knock_afraid_1	60
NS	Jua_knock_afraid_1	50
15	Jan_knock_Angry_1	90
11	Boo_lift_angry_1	30
7	Ali_throw_angry_2	100
8	Chr_walk_angry_2	80
NS	Amc_knock_angry_1	90
NS	Bar_throw_angry_2	100
NS	Boo_throw_angry_2	90
NS	Chr_lift_angry_1	20
NS	Chr_throw_angry_1	90
NS	Chr_walk_angry_1	70
5	Kat_Lift_happy_1	60
12	Dav_knock_happy_1	70
6	Ste_throw_happy_2	40
1	Ale_walk_happy_1	100

NS	Ale_lift_happy_2	50
NS	Ali_throw_happy_2	20
NS	Boo_knock_happy_1	60
NS	Boo_lift_happy_2	30
NS	Dav_knock_happy_2	70
NS	Emm_walk_happy_2	90
13	Alx_knock_sad_1	40
4	Alx_lift_sad_2	40
9	Jua_throw_sad_2	90
3	Jan_walk_sad_2	100
NS	Ale_knock_sad_2	40
NS	Ali_knock_sad_2	40
NS	Ali_lift_sad_1	30
NS	Ali_throw_sad_1	70
NS	Alx_walk_sad_2	80
NS	Jua_throw _sad_2	90

*The stimuli name is comprised of the start of actors identifier, action type, emotion type and take number.

TABLE L2. Final E-Motion Test of Full Figure, Line and Dot stimuli in Order Presented to Control and MND Participants in Main Study

FIGURE
1. Happy walk
2. Afraid lift
3. Sad walk
4. Sad lift
5. Happy lift
6. Happy throw
7. Angry throw
8. Angry walk
9. Sad throw
10. Afraid throw
11. Angry lift
12. Happy knock
13. Sad knock
14. Afraid walk
15. Angry knock
16. Afraid knock
LINE
17. Afraid walk
18. Happy throw
19. Sad walk
20. Angry lift
21. Happy knock
22. Sad knock
23. Angry walk

24. Angry throw
25. Afraid throw
26. Angry knock
27. Happy lift
28. Sad lift
29. Happy walk
30. Afraid knock
31. Afraid lift
32. Sad throw
DOT POINT LIGHT
33. Happy walk
34. Sad lift
35. Happy lift
36. Angry lift
37. Happy throw
38. Angry walk
39. Sad throw
40. Angry knock
41. Sad walk
42. Afraid throw
43. Afraid lift
44. Afraid knock
45. Angry throw
46. Afraid walk
47. Happy knock
48. Sad knock

Table L3. Control Participants in Main Study (n=15) Performance on E-Motion

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Emototal	15	11	25	36	32.67	2.968
emofig	15	4	9	13	11.33	1.543
emoline	15	6	7	13	10.40	1.404
emodots	15	5	8	13	10.93	1.534

Table L4. MND Participants in the Main Study (n=15) Performance on E-Motion

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Emototal	15	11	23	34	28.53	3.044
emofig	15	5	7	12	9.73	1.387
emoline	15	5	6	11	9.00	1.512
emodots	15	6	7	13	9.80	1.781