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Title

Contingent negative variation: a biomarker of abnormal attention in Functional Movement Disorders

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Background

Contingent negative variation (CNV) is a negative cortical wave that precedes a pre-cued imperative stimulus requiring a quick motor response. It has been related with motor preparation and anticipatory attention.

We aimed to ascertain whether clinical improvement of functional movement disorders after physiotherapy would be associated with faster reaction times and modulation of CNV.

Methods

We analysed motor performance and CNV during a pre-cued choice reaction time task with varying cue validity. We compared 21 patients with functional movement disorders and 13 healthy controls at baseline. Patients then underwent physiotherapy. At follow-up after physiotherapy, patients were categorized as clinically improved (responders) or not improved (non-responders) and re-tested.

Results

At baseline, patients did not generate CNV, contrary to controls [mean amplitude (μV) at the end of preparation to move: patients [-0.47 (95%CI= -1.94, 1.00)] versus controls [-2.59 (95%CI= -4.46, -0.72)].

Responders performed faster after physiotherapy [mean natural logarithm (ln) (RT) (ms): follow-up 6.112 (95%CI= 5.923, 6.301) versus baseline 6.206 (95%CI= 6.019, 6.394), p 0.010], contrary to non-responders.

Simultaneously, responders showed a recovery of CNV after physiotherapy [follow-up -1.95 (95%CI= -3.49, -0.41) versus baseline -0.19 (95%CI= -1.73, 1.35), $p < 0.001$], contrary to non-responders [follow-up -0.32 (95%CI= -1.79, 1.14) versus baseline -0.72 (95%CI= -2.19, 0.75), p 0.381].

Conclusions

Clinical improvement of functional movement disorders after physiotherapy was associated with faster reaction times and normalisation of CNV, which was absent at baseline. These findings suggest that CNV may constitute a useful neurophysiological biomarker related with abnormal attention in functional movement disorders.

Introduction

One of the most characteristic clinical features of functional movement disorders (FMD) is their alteration with attention: when attention is focussed onto movement, movement is impaired; but with distraction, movement typically normalises.(1) This phenomenon of abnormal explicit control of movement and normal implicit control underlies commonly used clinical and electrophysiological diagnostic tests of FMD such as Hoover's sign and entrainment and distractibility tests in functional tremor.(2) Attentional focus towards the mechanics of moving (i.e. monitoring the current state of the limb to be moved) forms a central feature of neurobiological models of FMD, while "re-training" attentional focus is a key part of specific physiotherapy-based treatment programs.(1,3–5)

There is some evidence of a pathophysiological role for explicitly directed attention in FMD.(1,6) Therefore, experimental techniques that directly probe explicitly directed attention could help identifying potential biomarkers for FMD (6). A useful biomarker would be abnormal in people with FMD when they were symptomatic and would normalise if improvement of symptoms occurred.

We have previously explored the usefulness of a simple pre-cued reaction time (RT) task, based on the classic Posner paradigm, as a diagnostic biomarker for FMD.(1,6) In this paradigm a pre-cue predicts with varying probability which movement will be required (a button press with the right or left hand) following an up-coming "go" cue. In an initial behavioural study we showed that people with FMD, in contrast to healthy controls, did not improve their reaction time in response to a pre-cue that reliably predicted the type of movement they were required to make.(1) In a subsequent study we replicated this behavioural

effect and showed that the normal desynchronisation of beta power that can be detected in the EEG prior to cued movement was not present in people with FMD performing this task.(6) We found a non-significant trend for recovery of this beta desynchronization in people with FMD who had improved clinically following specific physiotherapy treatment.(6) This suggested that excessive synchronisation of brain activity on the beta band could constitute a biomarker for abnormal movement preparation in FMD.(6)

In this study we explore the utility of a different potential biomarker: the contingent negative variation. Contingent negative variation (CNV) is a slow negative cortical wave that develops following a pre-cue which signals that, within a few seconds, an imperative stimulus will arrive, requiring a quick motor response.(7,8) CNV is regarded as an "expectancy wave", reflecting anticipatory attention and motor preparation to react to the forthcoming cue.(8,9).

In people with FMD, we predicted that the excessive attention on to the current state of the limb to be moved and away from movement's goal, would be associated with an insufficient deployment of anticipatory attention and abnormal motor preparation. This would translate into slower reaction times to the imperative cues (thus replicating the findings of previous research)(1)and a reduction on CNV amplitudes. In line with our expectations, a previous study in 6 patients with functional weakness found a reduction in CNV amplitude, which was not evident in controls feigning weakness(10), and a pre-movement potential before self-paced voluntary movement has been reported to be absent in people with functional jerks.(11)

Therefore, in this study, we hypothesised that: 1. CNV amplitude would be reduced at baseline in comparison with healthy controls, 2. Clinical improvement after physiotherapy would be associated with faster RT and recovery of CNV.

Methods

Participants, experimental task and EEG recording

We performed a case-control study comparing patients with FMD and healthy volunteers. Patients with FMD were recruited from a pool of patients being enrolled in a randomized feasibility study comparing specialised with standard physiotherapy for FMD.(5) Please find a detailed description of the specialised physiotherapy program in the supplementary materials. These subjects were ≥18 years-old and had a clinically established diagnosis of FMD according to the Fahn-Williams criteria.(12) All patients attended a

consultation with the study neurologist (MJE). Additional inclusion criteria were a symptom duration of at least 6 months, functional motor symptoms causing significant disability, having completed the diagnostic investigation and acceptance of the diagnosis of FMD. Relevant exclusion criteria were the presence of pain or fatigue as the primary cause of disability, prominent dissociative seizures, clinically significant depression or anxiety and high level of disability preventing participation in an outpatient environment.(5)FMD participants were tested before starting physiotherapy (baseline) and at least 2 weeks after completing treatment (follow-up) (Table I). Matched HC were assessed only once.(6) Phenomenology at baseline was characterised based on video-rating by three neurologists, as described elsewhere (Table I).(13)

Assessment of clinical improvement after physiotherapy was based on Clinical Global Impression (CGI), Physical Function domain of Short Form (36) Health Survey (SF-36) (Version 1) and The Simplified Functional Movement Disorders Rating Scale (S-FMDRS).(14,13,5) We dichotomised patients with FMD as "responders" or "non-responders" to physiotherapy, based on their self-rated Clinical Global Impression (CGI).(5) "Responders" self-rated themselves as "improved" or "much improved" after physiotherapy. "Non-responders" self-rated as "unchanged", "worse" or "much worse". Our study was nested within a randomised feasibility trial that used the same criteria for collapsing the CGI.(5) The Physical Functional domain of SF-36 questionnaire focuses on motor function, inquiring about limitations on ten mobility activities.(14) Finally, the S – FMDRS is a simplified version of the Functional Movement Disorders Rating Scale and has shown good inter-rater reliability and sensitivity to change.(13) The raters of S – FMDRS were blinded for time-point of assessment (before vs after treatment), as reported elsewhere. (13)

Our behavioural experiment consisted of a Posner-type pre-cued choice RT task with varying cue validity (1,6,15), including: 1. A highly predictable condition, where preparation cues accurately predicted go cues in 95% of the trials (95% congruence); 2. An unpredictable condition, where preparation cues accurately predicted go cues in only 50% of the trials (50% congruence). Participants were instructed to press the key corresponding to the go cue as quickly as possible (either the left Ctrl key with left index finger or right Ctrl key with right index finger). We included a flowchart with the trial structure in a previous publication.(6)

Response time in milliseconds (ms) was calculated for each trial. Trials where the preparation cue accurately predicted the go cue (congruent) were separated from those where the prediction was incorrect (incongruent). Response times were separately averaged across trials for "congruent" and "incongruent" trials in each of the two conditions.

Continuous EEG was recorded using a 32-channel ANT-EEG® system conforming to the five percent

electrode system. Our reference was an average of all electrodes. We excluded trials with prominent artefacts and trials where participants pressed the wrong key or did not press any key.

A more detailed description of the participants, experimental task and EEG recording can be found elsewhere.(6)

Pre-processing

We used Statistical Parametric Mapping (12b) and MATLAB® for data processing. Data was downsampled from 2048 to 250 Hz and epoched to frames from -1 to +4 seconds relative to the onset of the preparation cue. We selected the interval preceding the preparation cue as baseline and baseline-corrected the epoched frames. Finally, we averaged data over trials for each participant and extracted data from Cz electrode (amplitude; μV) , which is considered to record CNV with greatest amplitude.(16) The midline location of Cz also facilitated combining data from right and left key presses. This maximised the statistical power to compare subgroups of patients with FMD who improved and did not improve after physiotherapy (see below).

Pre-processing resulted in 4 datasets of Cz amplitude as a function of time: a) 95% trial, right key press (right index finger); b) 95% trial, left press (left index finger); c) 50% trial, right press; d) 50% trial, left press.

Statistical analysis

Statistical analysis was performed using Stata® (version 13.1). Continuous variables were expressed as means [standard deviation (SD)] if normally distributed or medians [interquartile range (IQR)] if not normally distributed. Categorical variables were expressed as frequencies and proportions. The normality assumption was assessed by visually inspecting the distribution of the continuous variable and confirmed by Kolmogorov–Smirnov testing.

Reaction times (RT) were non-normally distributed and were therefore transformed into their natural logarithms (Ln), in order to fulfil the normality assumption and thus be able to fit a multilevel mixed effect liner model.

Participants could pre-plan the forthcoming key-press in the interval between appearance of preparation and go cues (interval duration: 1950 ms). We analysed CNV amplitude (μV) at moment of maximum

preparation by restricting our analysis to the last 12 ms preceding the go cue (averaging data from 3 data-points).

Our outcome measures were RT (ms) and CNV amplitude (μV) at the end of preparation to move. Mixed effects multilevel linear modelling allowed us to take into account the dependency in data caused by repeated measurements within-subjects. We fitted the following models:

1) Baseline comparison of patients with FMD and healthy controls:

1.1) Behavioural results (reaction times) for baseline comparison were presented in our previous paper focusing on beta oscillations (see summary below).(6)

1.2) For CNV amplitude we included the effects of "group", "predictability" and "hand", their interactions and an individual level random effects factor.

2) Comparison of FMD “responders” and “non-responders” to physiotherapy, before and after this intervention:

2.1) For RT, we restricted our analysis to trials with congruent preparation and go cues, as those were the ones thought to reflect motor preparation. We fitted a model including the effects of “timepoint” (baseline vs follow-up), “response” (responder vs non-responder) and “predictability” (95% vs 50%), their respective interactions and an individual level random effects factor.

2.2) For CNV amplitude we included the effects of "group", "predictability" and "hand", their interactions and an individual level random effects factor.

Finally, we investigated the relationship between changes in CNV and changes in RT at follow-up. We calculated the grand average of end-of-preparation CNV (μV) and RT (ms) at baseline and at follow-up, for each participant. We then subtracted the baseline averages from the follow-up averages for both parameters. We planned to regress the average change of RT against the average change of end-of-preparation CNV.

Statistical significance was predefined as p-value (p) < 0.05.

Ethics

This study was approved by the local ethics committee. Participants gave their informed written consent to take part in the studies.

Results

Clinical and Demographic Characteristics

We recruited and performed a baseline assessment of 21 patients with FMD and 13 HC. Nine patients with FMD were randomized to undergo specialized physiotherapy and another 12 to receive standard physiotherapy. Groups at baseline were well matched for age, sex and proportion of left-handed participants (reported elsewhere(6)].

Patients with FMD were evaluated after a mean period of 4.7 weeks (SD 1.7) after treatment. Ten patients with FMD were classified as "responders" and 11 as "non-responders", in accordance with their self-rated CGI. FMD responders, contrary to non-responders, showed an increase in SF-36 and a decrease in S-FMDRS at follow-up (Table I). The age and sex proportions were similar in both groups. Eight out of 10 "responders" and 1 out of 11 "non-responders" had been randomized to receive specialized physiotherapy, while the others underwent standard physiotherapy.(5)

FMD patients at baseline vs Healthy Controls

Behavioural results

For RT, we have previously reported elsewhere(6) that healthy controls performed faster in trials with predictive pre-cues as compared with trials with non-predictive pre-cues [mean Ln(RT) predictive pre-cues 6.104 (95%CI= 5.947, 6.261) versus non-predictive pre-cues 6.162 (95%CI= 6.006, 6.319), p 0.032] (Figure 1). In contrast, in patients with FMD, response times were similar in predictive and non-predictive pre-cues [mean Ln(RT) predictive pre-cues 6.287 (95%CI= 6.166, 6.408) versus non-predictive pre-cues 6.314 (95%CI= 6.194, 6.435), p 0.206].

End-of-preparation CNV

We found a significant effect for "group" (p = 0.050) but not for "predictability" (p 0.484), "hand" (p 0.496) or the interactions "group x predictability" (p 0.459), "group x hand" (p 0.245), "predictability x hand" (p 0.923) and "group x predictability x hand" (p 0.361) (Figure 2, Supplementary Table IV).

After eliminating all non-significant factors from our model, the p-value for the pairwise comparison between FMD and HC was 0.081 [means: FMD -0.47 (95%CI= -1.94, 1.00) versus HC -2.59 (95%CI= -4.46, -

0.72)]. Importantly, patients with FMD failed to generate the negative wave that defines CNV (p = 0.532 for rejecting the null hypothesis of CNV amplitude being zero), contrary to HC (p = 0.007).

FMD patients at follow-up vs baseline

Behavioural results

In our predefined model of normalised RT, the only significant effect was for the interaction "response" x "timepoint" (p 0.012). None of the other terms were significant, including "response" (p 0.184), "timepoint" (p 0.140), "predictability" (p 0.755), "response x predictability" (p 0.691), "timepoint x predictability" (p 0.466) and "response x timepoint x predictability" (p 0.498). Responders at follow-up were unable to take advantage of predictive conditions (95% congruence) to perform faster, as compared with non-predictive conditions (50% congruence) (p 0.643 for the corresponding pairwise comparison). This specific finding is similar to what we described elsewhere for patients with FMD at baseline.(6)

In order to dissect the significant interaction between "response" x "timepoint", we then performed a pairwise comparison analysis in a model only including response, timepoint and their interaction. In accordance with our predictions, responders performed faster at follow-up than at baseline [mean Ln(RT) follow-up 6.112 (95%CI= 5.923,6.301) versus baseline 6.206 (95%CI= 6.019, 6.394), p 0.010] while non-responders' performance was similar [mean Ln(RT) follow-up 6.444 (95%CI= 6.265, 6.623) versus baseline 6.401 (95%CI= 6.222, 6.579), p 0.185].

Please see Supplementary table I for non-normalised RT, Figure 1 and Supplementary Table II for the corresponding natural logarithms and Supplementary Table III for the accuracy results.

End-of-preparation CNV

In our predefined model, the effects of "response" (p 0.626) and "timepoint" (p 0.381) were non-significant but their interaction was significant (p 0.001) (Figure 3, Supplementary Table IV)

In order to clarify this interaction, we performed a pairwise comparison analysis. After physiotherapy, the power at the end of preparation to move became more negative in responders [means: "follow-up" -1.95 (95%CI= -3.49, -0.41) versus "baseline" -0.19 (95%CI= -1.73, 1.35), p < 0.001] but not in non-responders [means: follow-up -0.32 (95%CI= -1.79, 1.14) versus baseline -0.72 (95%CI= -2.19, 0.75), p 0.381]. Notably,

only responders at follow-up generated a negative wave at the end of preparation to move [mean -1.95 (95%CI= -3.49, -0.41), p 0.013].

Relationship between changes in RT and in CNV at follow-up

In responders, RT became -41 ms (SD 31) faster at follow-up, while the end-of-preparation CNV became -1.97 (SD 2.12) more negative at follow-up. In contrast, in non-responders, RT became 12 ms (SD 159) slower and the end-of-preparation CNV 0.40 (SD 4.56) more positive at follow-up.

In the linear regression of changes in RT against changes in end-of-preparation CNV, the RT became -19 ms faster for each -1 μV increase in CNV negativity (p 0.004) (Figure 4).

Discussion

Here we report that contingent negative variation is abnormal in people with FMD, and that clinical improvement that occurred following treatment is associated with its normalisation. In contrast, people with FMD who did not experience clinical improvement with treatment continued to demonstrate abnormal contingent negative variation at follow up assessment.

Suppression of CNV and abnormal motor preparation in FMD

We have previously observed that people with FMD are unable to take advantage of highly predictable conditions to prepare for the forthcoming movement and improve performance (i.e. generate faster reaction times).(1,6) This finding is in accordance with their difficulty in performing movements in an explicit context (e.g. to command during a physical examination), but retained ability for normal movement to occur when happening in an automatic or implicit manner. We have previously proposed that this reflects a misdirection of attention towards the "mechanics" of a movement and away from its goal, in line with neurobiological accounts of FMD.(1,17) We have recently demonstrated that this behavioural phenomenon is associated with persistent beta synchronization during motor preparation, which showed a non-significant trend towards recovery of normal beta suppression prior to movement, following clinical improvement after treatment.(6)

CNV is related to anticipatory attention and motor preparation.(8,9) Therefore, the suppression of CNV observed in our patients at baseline likely reflects abnormalities in motor preparation and attention, in keeping with the mechanism hypothesised in the introduction.(1,17)

Only one previous study reported suppression of CNV in FMD, in a group of 6 patients with functional weakness. Suppression of CNV was not observed in a group of 24 participants feigning paralysis, despite similar motor performances, or in a group of 12 healthy subjects.(10)

In addition, FMD patients were highly accurate in their performance (95.3% vs 98.8% in controls) which we believe is evidence against feigning as an explanation for their lack of CNV (Supplementary Table III).

Functional improvement and recovery of CNV

We found that clinical improvement in responders was associated not only with faster RT but also with a recovery of CNV after treatment. The same was not observed in non-responders, ruling out confounding by a simple re-testing effect. Physiotherapy for FMD is based on movement retraining with the aim of restoring normal movement by redirecting the focus of motor attention towards the movement goal and away from movement mechanics.(4,5) CNV recovery at follow-up could therefore plausibly reflect a successful retraining of movement, with a re-focusing of motor attention towards the movement goal. To our knowledge only one previous study has reported change in a neurobiological marker of nervous system dysfunction following successful treatment.(18) Vuilleumier observed decrease in thalamic and basal ganglia SPECT activation in response to contralateral limb vibration in 7 patients with unilateral functional motor symptoms, which normalised after symptom improvement at follow up.(18)

Cues to interpret previous findings on Bereitschaftspotentials

Our results may help explain rather unusual results from assessment of Bereitschaftspotentials (BP, pre-movement potentials recorded prior to self-paced movement) in people with functional myoclonus.(11) In these patients the functional jerks were associated with the expected presence of a BP, but intriguingly, voluntarily mimicked jerks were not associated with a BP. Taken together, these results point to a general problem in voluntary movement (self-paced or externally paced), which is reflected in abnormalities of cortical potentials associated with movement preparation.

Relevance of symptom distribution

A crucial facet of the data we present here is that we recorded CNV relating to movement preparation for right or left arm movement, but many of the patients did not have symptoms in their arms, or in some others, only one arm was affected. Despite this, we found no systematic difference in our findings between those with or without clinical involvement of the upper limbs. This fits with our clinical experience that it is very common for functional motor signs be triggered through the act of physical examination, even in patients who do not complain of specific symptoms in the limb being examined.

Indeed we commonly see this phenomenon in people with non-motor functional symptoms, for example chronic pain, functional sensory loss, chronic fatigue. In such patients, examination of power commonly reveals give-way patterns of weakness, a positive Hoover's sign, or flurries of jerks and tremors. This is in accordance with the common co-occurrence of functional symptoms in different domains (motor, exteroception, interoception) and with neurobiological accounts of functional neurological disorders which make no separation between the mechanism of functional symptoms that occur in different domains. This is important information for the potential use of CNV as a neurophysiological diagnostic biomarker, as it does not require people to have symptoms in the limbs being studied, and it also may be of use in those with non-motor functional symptoms. This requires further study, but could indicate a more general utility of CNV as a biomarker related with abnormal attention in functional neurological disorder.

Limitations

We acknowledge several limitations to our study. We decided to use data from lead Cz because this is previously reported to provide CNV with the largest amplitude. Our main interest here was studying FMD responders and non-responders, which restricted our sample size. Therefore, we decided to prioritize testing for differences on CNV amplitudes over investigating CNV lateralization, which is obviously not possible with Cz.

We dichotomised patients into "responders" and "non-responders" based on one self-rated outcome measure (CGI). However, changes in SF-36 (self-reported quality of life measure) and S-FMDRS (video rating blinded for timepoint(13)) after treatment also supported our criteria for collapsing groups over CGI (Supplementary Table). We acknowledge that abnormalities in CNV (using different paradigms from ours) have been reported in other disorders. For example, CNV attenuation has been described in Parkinson's disease(19), schizophrenia(20) and attention-deficit hyperactivity disorder(21), and an enhancement was observed in Gilles de la Tourette Syndrome.(22) It would be useful for future studies to include movement disorder disease control groups to understand the nature of overlap between CNV abnormalities in people with FMD and those with other disorders.

Experiments with long intervals between preparation and go cues have described an early and late component of CNV. Notwithstanding significant controversy, late CNV was proposed to be more closely related with the bereitschaftspotential. Although the rules for decomposing CNV in its early and late component are not "set in stone", foreperiods of at least 3 seconds duration are often used. Therefore, we consider that our interval was too short to allow a precise separation of these components.

Responders RT's in congruent trials overall became faster at follow-up, contrary to what was observed in non-responders. However, there was a persistence of some behavioural abnormalities, with patients with FMD remaining unable to take advantage from predictive pre-cues to perform even faster (contrary to HC, as reported elsewhere(6)).

CNV abnormalities were previously described in other movement disorders, including Parkinson's disease(19), writer's cramp(23), cervical dystonia(24) and Huntington disease(25). Therefore, abnormal CNV is not specific to patients FMD, which limits its utility for the differential diagnosis with other movement disorders.

In conclusion, we describe a recovery of CNV in the context of a clinical and behavioural improvement after physiotherapy. These findings suggest that CNV is a potential candidate biomarker for treatment response in FMD, and indeed may have utility outside the setting of those with functional movement disorders, and be useful in functional neurological disorder in general.

Authors' Roles

1) Research project:

A. Conception: MJE, AL, TT, IP, SL, AMM

B. Organization: AMM, IP, TT, GN, SL, MJE

C. Execution: AMM, IP, TT, GN, AM, IP

2) Statistical Analysis:

A. Design: TT, AK

B. Execution: TT, AK

C. Review and Critique: TT, AK, MJE, SL, IP, JJF

3) Manuscript:

A. Writing of the first draft: TT

B. Review and Critique: AK, AMM, SL, GN, AM, JJF, IP, AL, MJE

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Advisory Boards: BIAL, Sunovion Pharmaceuticals

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Legends:

Figure 1: Natural logarithms of reaction times per group, predictability, and cue congruence

"50%" - 50% congruence blocks (including congruent cues in 50% trials);

"95%" – 95% congruence blocks;

"C" – trials with congruent cues;

"I" – trials with incongruent cues;

Figure 2: End-of-preparation CNV - FMD patients at baseline vs HC

Figure 3: End-of-preparation CNV - FMD responders and non-responders at baseline vs follow-up

Figure 4: Relationship between changes in RT and in CNV at follow-up

Table I: FMD patients at baseline vs follow-up – demographics and response to treatment

Groups		FMD "Responders"	FMD "Non-responders"
N total		10	11
Sex (Males / Females)		2/8	2/9[#NS]
Age [years; median, (IQR)]		43 (30-45)	41 (36-53)[#NS]
Phenomenology[(*)]			
Gait impairment		7	7
Motor slowness		0	1
Incoordination		1	1
Upper limb tremor		2	4
Head tremor		0	2
Trunk tremor		1	1
Axial myoclonus		1	1
Functional dystonia		1	1
Upper limb involvement (any)		3	5
Bilateral involvement		6	7
Right-sided involvement		0	3
Left-sided involvement		3	1
Number of patients who received specialized physiotherapy		8/10	1/11[#S]
SF-36 [median, (IQR)]	Baseline	30 (20-50)	25 (10-30)
	Follow-up at 6 months	60 (35-80)**[S]	15 (5-40)**[NS]
S-FMDRS [median, (IQR)]	Baseline	15 (9-21)	14 (12-18)
	Follow-up at 6 months	5 (2-13)**[S]	24 (16-33)**[NS]

(*) – based on baseline video rating by three neurologists (13)

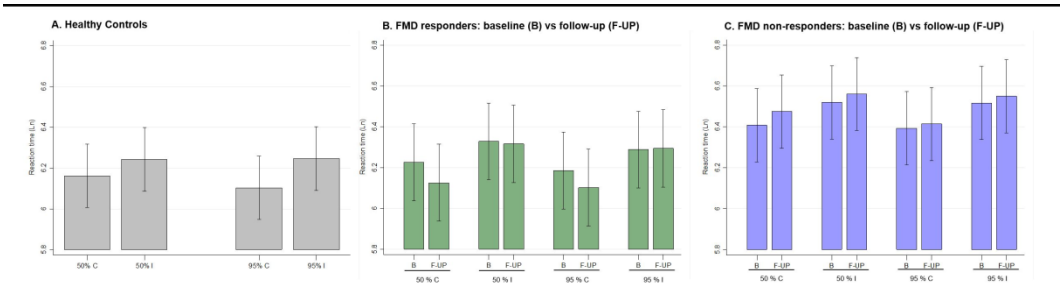
(**) – baseline vs follow-up

(#) – responders vs non-responders

(S) - $p < 0.05$; (NS) - $p \geq 0.05$

SF-36 baseline vs follow- up (Wilcoxon sign-rank test): For Responders: p 0.021; For Non-responders: p 0.433

S-FMDRS baseline vs follow- up (Wilcoxon sign-rank test): For Responders: 0.044; For Non-responders: 0.074



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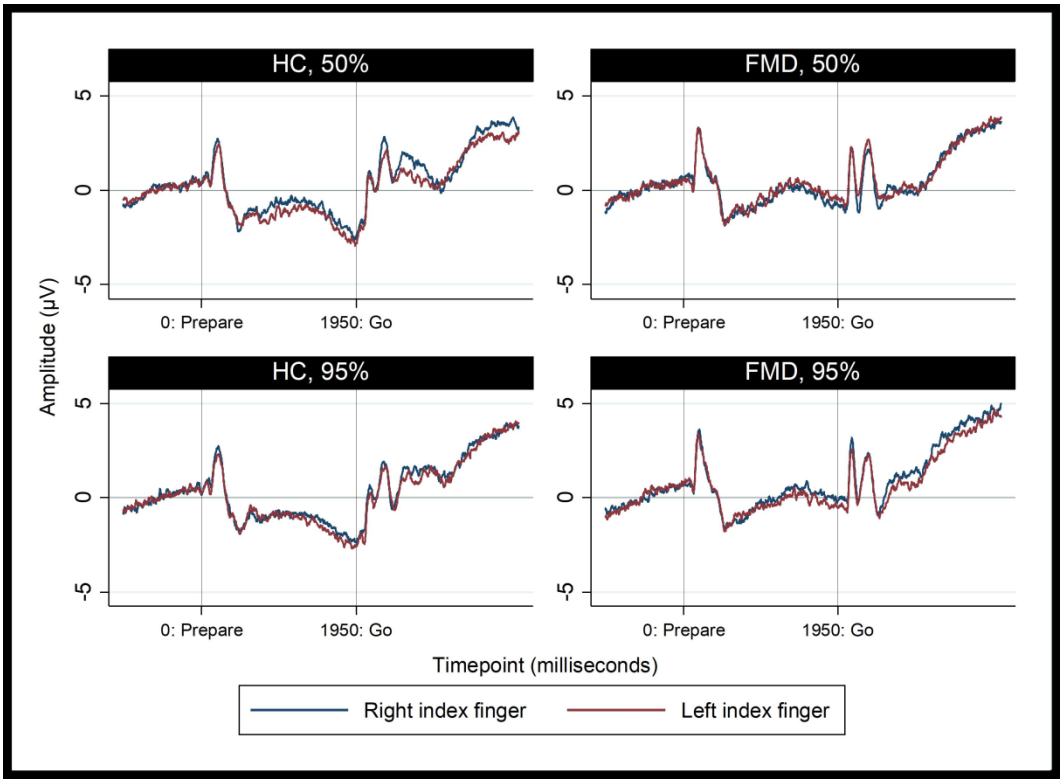

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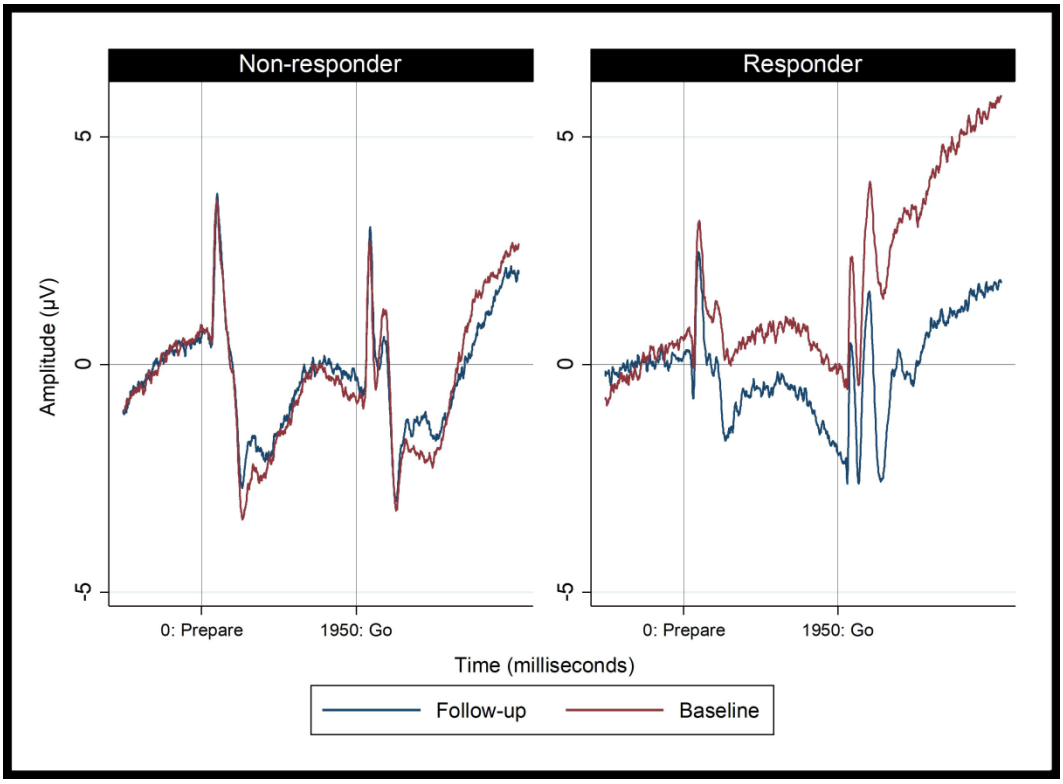

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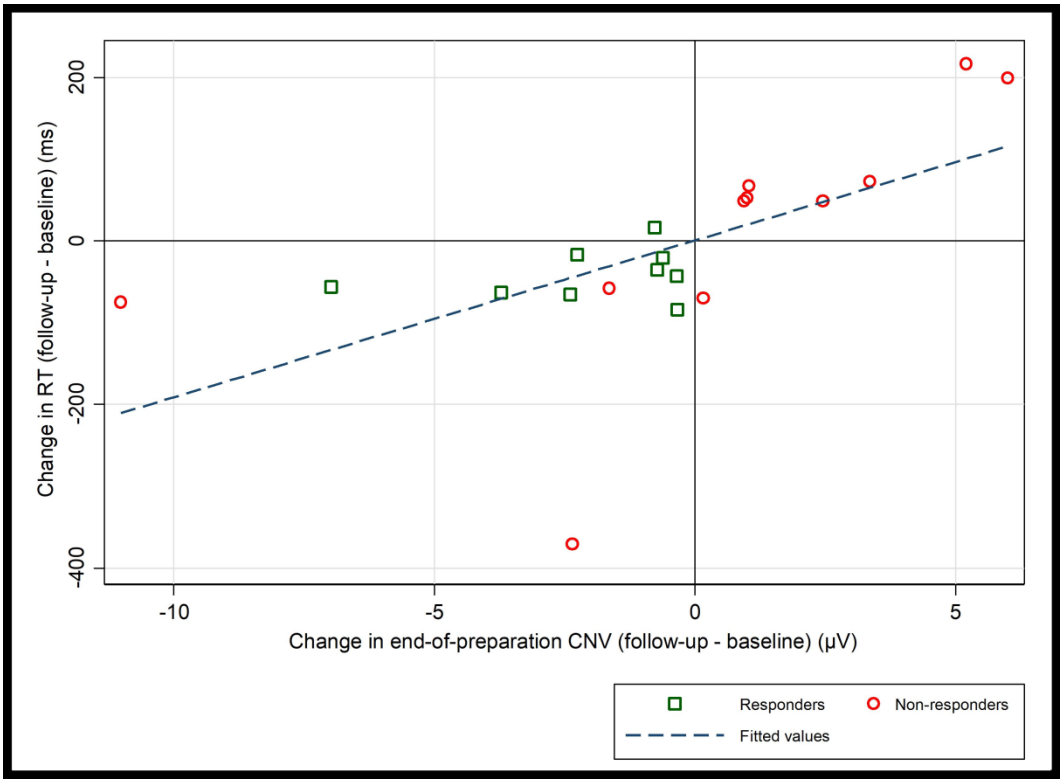

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