Heart rate variability is associated with motor outcome 3-month after stroke

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Participation: All of the content. Substantial contributions: Provide support for designing, and implementation of the study, interpretation of the data and drafting of the manuscript.

Dr. Sethi, Dr. Callaway, Dr. Sejdic, Dr. Terhorst and Dr. Skidmore report no

disclosures.

Abstract

Objective: To determine whether heart rate variability (HRV) is associated with motor outcome 3 months after stroke.

Methods: Using a prospective longitudinal design, thirteen patients with acute stroke were recruited from an acute inpatient rehabilitation hospital. A Holter monitor was placed upon admission and Fugl Meyer Upper Extremity and Lower Extremity Subscales were used to assess the movement of the affected upper and lower extremity 3 months after admission. SDNN, which is a measure of the standard deviation of the R-R intervals was used to quantify HRV.

Results: A Spearman rank correlation revealed a strong positive and significant correlation between HRV upon admission and movement of the affected upper extremity (r =.70; p =.01) and affected lower extremity (r =.60; p =.03) at 3 months. For patients with severe initial motor impairments, HRV showed a strong positive association with the movement of the affected upper (r =.61; p =.04) and lower extremity (r =.70; p =.04) at 3 months than initial upper (r =.41; p =.14) and lower extremity (r =.26; p =.30) impairments.

Conclusion: HRV is strongly associated with motor outcome after stroke and provide a promising marker to explore the mechanisms associated with motor recovery after stroke.

Introduction

Among the 795,000 individuals who sustain a stroke annually in the United States, almost 85% exhibit motor impairments in one limb immediately after stroke.[1] These motor impairments are associated with a significant loss of long-term independence.[2, 3] For example: motor impairments in the affected upper extremity and lower extremity not only limit individuals from independently performing daily tasks such as dressing, or bathing but also restrict the ability to return to work or pre-stroke roles. This loss of independence is costly, with the cost of rehabilitation projected to be 1.29 billion dollars by 2050.[4] Thus, there is a major public health need to minimize long-term dependency after stroke, and reduce associated personal and societal costs. Accurate predictors of the future motor outcome will allow clinicians to establish realistic and attainable rehabilitation goals, provide targeted interventions to enhance long-term independence, reduce the length of inpatient stay, and the cost of stroke rehabilitation. Although initial motor impairment is the best predictor to date,[5, 6] it is still difficult to predict the long-term motor outcome in majority of individuals with severe motor impairments after stroke.[7] An exploration of the physiological mechanisms associated with the motor outcome may further elucidate our understanding of the prediction of long-term motor outcome after stroke.

Heart rate variability (HRV) or the temporal variations between consecutive heartbeats is one such physiological parameter, which may be associated with the future motor outcome after stroke. The cortical regions that control motor

function also modulate vagus nerve activity,[8] a cranial nerve that controls the autonomic functions of the heart. Vagal activity can be quantified using many analyses of HRV such as the standard deviation between the consecutive heartbeats (SDNN).[9] Fluctuations in HRV mediated by the vagal activity may be influenced by central or peripheral nervous system disorders.[10] Furthermore, HRV has been studied to investigate the physiological changes and prognostic factors associated with many pathological conditions including stroke.[10] When stroke damages the cortical pathways controlling the upper and lower extremities, concurrent reduction in vagal activity control reduces HRV.[11] Thus, HRV is a plausible proxy marker for the integrity of cortical pathways related to the motor impairments of the affected upper and lower extremities and stroke survivors with high HRV generally require less assistance to complete daily tasks.[12] However, the degree to which HRV is related to the future motor outcome remains unclear. We aimed to determine whether HRV upon admission to acute inpatient rehabilitation was associated with motor outcome three months after stroke. We hypothesized that individuals with higher HRV at acute inpatient rehabilitation admission would exhibit greater movement in the affected upper and lower extremities after 3 months. In addition, we also explored whether HRV at acute inpatient rehabilitation admission is associated with movement in the affected upper and lower extremities after 3 months in individuals with severe initial motor impairments.

Methods

A convenience sample of thirteen patients with acute stroke with a mean age of 61 years (SD =12) was recruited from an acute inpatient rehabilitation hospital. Participants were included if they: (1) were between ages of 18 -90 years of age; (2) had experienced a single episode of stroke, which was confirmed with MRI scans; (3) had unilateral UE weakness characterized by ≤ 3 on Medical Research Council Score of major muscle groups of UE to include patients with lesions to corticospinal pathways; (4) were able to follow two-step commands. We included patients taking anti-hypertensives (β blockers etc.) because these drugs only have modest effects upon HRV.[13, 14] We excluded patients who had a history of atrial fibrillation or other non-sinus arrhythmias, and used pacemakers because it is difficult to accurately measure and interpret HRV in these patients.[9] We also excluded patients with cerebellar lesions who typically do not exhibit unilateral UE weakness. Table 1 shows the demographic and clinical characteristics of the participants.

Procedures:

Eligible participants provided written informed consent approved by the University of Pittsburgh Institutional Review Board. After careful skin preparation, an H12+ Mortara Holter monitor (Mortara Instrument, Milwaukee, WI) was placed for 24 hours on eligible participants to measure HRV within three days of acute inpatient rehabilitation admission. All lead placements were checked routinely

through coordinated efforts with nursing and rehabilitation staff to avoid poor or missing data. A trained and experienced evaluator unaware of the HRV results of the patients used Fugl Meyer Upper Extremity Subscale (FMUE)[15] and Fugl Meyer Lower Extremity Subscale (FMLE)[15] to assess the movement of the affected UE and LE respectively three months after admission to the acute inpatient rehabilitation hospital. FMUE and FMLE are reliable and valid ordinal scales widely used to asses the movement of the affected upper and lower extremities after stroke.[16, 17] The total FMUE score ranges from 0-66, and the FMLE score ranges from 0-34, with higher scores indicating better movement of the affected upper and lower extremities.[15] Based upon the admission criteria of acute inpatient rehabilitation admission, all participants were medically able to participate in rehabilitation for at least three hours per day.

Data Analysis:

Data pre-processing: All electrocardiogram (ECG) streams were sampled at 1000 Hz. An expert technician manually annotated all the ECG streams to clean artifacts using H -Scribe 5.11 (Mortara Instrument). The raw continuous ECG streams were then preprocessed using Super ECG (Mortara Instrument) to eliminate (without interpolation) premature, missing or ectopic beats resulting in a data file with a columnar matrix of R-R intervals over 24 hours. We eliminated the R-R intervals that fall outside 5% and 95% of the distribution using a customized MatLab code (Natick, MA) to remove additional artifacts.

HRV analysis: SDNN was calculated as a measure of HRV using a customized MatLab code. SDNN is the standard deviation of the R-R intervals over 24 hours in milliseconds.[9]

Statistical Analysis: To address the primary aim, we performed two Spearman correlations between SDNN and 3-month FMUE scores; and SDNN and 3-month FMLE scores to determine the direction and magnitude of the association. To address the secondary aim, we used the cut-off scores[18] to divide the sample into individuals with severe (<21 FMUE and <15 FMLE scores) and mild-to-moderate (>21 FMUE and >15 FMLE scores) initial motor impairments. We conducted two Spearman correlations between SDNN and 3-month FMUE scores and; SDNN and 3-month FMLE scores of severe participants. The data were analyzed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) with statistical significance set at p <.05.

Results

Table 1 shows the clinical characteristics, SDNN, FMUE and FMLE scores of all the participants. Both HRV at admission (SDNN) (r =.70, p =.01) and initial upper extremity impairments (FMUE baseline) (r =.84, p =.005) showed a strong positive association with affected upper extremity at 3 months (FMUE at 3 months) (Figures 1a and 1b). HRV at admission (SDNN) showed a strong positive association (r =.60, p =.03) than initial lower extremity impairments

(FMLE baseline) (r =.48, p =.09) with the movement of the affected LE at 3 months (FMLE at 3 months) (Figures 2a and 2b). For patients with severe initial motor impairments, HRV at admission (SDNN) showed a strong positive association with the movement of the affected upper (r=.61; p=.04) and lower extremity (r=.70; p=.04) at 3 months than initial upper (FMUE baseline) (r=.41; p=.14) and lower extremity (FMLE) (r=.26; p=.30) impairments (Figures 3a, 3b, 4a and 4b).

Insert Table 1 here

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Discussion

Our findings suggest that HRV is positively associated with motor outcome 3 months after stroke. Previous studies suggest that individuals with lower HRV require greater assistance in daily tasks 60 days after stroke.[12] It is likely that patients with lower HRV do not gain adequate movement in the affected upper and lower extremities to perform daily tasks 3 months after stroke and therefore require greater assistance.

Traditionally, little attempt has been paid to the autonomic system (controlling the fluctuations in HRV) when considering the impairments of the somatomotor system (controlling the voluntary movements of the upper and lower extremities) after stroke. However, recent evidence suggests that a common neural circuit comprising of dual function neurons simultaneously regulate the somatomotor and autonomic nervous systems.[19] These dual function neurons, which are located rostrally in the periaqueductal gray matter, hypothalamus, and areas of the sensorimotor cortex and caudally in the ventromedial medulla simultaneously, send polysynaptic projections to the somatomotor and autonomic targets.[19] The stroke location in our sample was either due to a hemorrhage in these areas or due to an infarct in an artery, which supplies these regions of the brain. Hence, it is possible that HRV could potentially capture the activity of the dual function neurons regulating the somatomotor and autonomic nervous systems, which may have been damaged due to the stroke. In addition, the overlap between the corticospinal pathways that primarily control the movement of the upper extremity and the vagus nerve, which provides parasympathetic

control of the heart, can explain the association between HRV and the movement of the upper extremity 3 months after stroke. The sensorimotor cortex and the corticospinal pathways that initiate and control the movement of the upper and lower extremities directly and indirectly modulate the vagus nerve.[8, 20] The corticobulbar and the corticospinal pathways directly project from the sensorimotor cortex to the vagus nerve nuclei including dorsal motor nucleus of the vagus nerve, the nucleus tractus solitarius and the nucleus ambiguous.[8, 20] When stroke damages the sensorimotor cortex and the corticospinal pathways it likely impairs vagal activity and reduces HRV.

Our preliminary findings suggest that HRV (SDNN) and initial upper extremity impairments (FMUE baseline) are equally robust to predict a large effect (>.50) in the movement of the affected upper extremity after 3 months. In contrast, HRV (SDNN) showed stronger association with the movement of the affected lower extremity after 3 months than initial lower extremity impairments (FMLE baseline). Although the exact mechanisms through which the autonomic nervous system mediates the lower extremity movement is unclear, a relationship can be supported by previous studies.[19, 21] Apart from the corticospinal pathways lower extremity movement is also controlled by several non-specific spinal interneurons common to the autonomic nervous system and lower extremity movement.[19] Although the extent to which the initial lower extremity impairments influence the spinal control of walking in unclear, it is possible that the damage to the dual function neurons due to stroke may also affect lower extremity movements and

potentially explain the association between HRV and the lower extremity movement after 3 months.

In our sample eight participants had severe upper extremity impairments and seven had severe lower extremity impairments upon admission to the acute inpatient hospital. Interestingly, HRV was more strongly associated with 3 month motor outcomes than initial upper and lower extremity impairments in patients with severe initial motor impairments. The anatomical and physiological linkages between the somatomotor and autonomic nervous systems can explain these novel findings.[8, 19, 20] Currently, it is difficult to predict the long-term motor outcome of patients with severe initial motor impairments. It is possible that HRV could potentially predict motor outcome and help clinicians to efficiently plan treatment to enhance long-term independence in patients with severe initial impairments after acute stroke. Although, our findings are based on a small sample of severe patients, further investigation with a large sample seems warranted. Nonetheless these findings are exciting because they provide an opportunity to explore novel biological markers to understand the physiological mechanism associated with long-term motor outcome after stroke. Furthermore, it is possible that exploring the linkages between the somatomotor and autonomic nervous systems could potentially also predict the responsiveness of patients to various rehabilitation interventions and help clinicians to efficiently provide targeted treatment to enhance long-term independence after acute stroke.

In conclusion, HRV is strongly associated with the motor outcome 3 months after stroke. Based upon our findings, HRV is a plausible biomarker to predict the motor outcome after stroke. HRV is novel, inexpensive, and easy to administer. Future studies will be required to explore the role of stroke location and volume, medications, underlying heart disease, time since stroke and other co-morbidities affect the ability of HRV to predict motor outcome after stroke.

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Figure 1a: Title: Association between heart rate variability (SDNN) and movement of the upper extremity (FMUE) at 3 months

Abbreviations: SDNN =Standard deviation of R-R intervals; FMUE = Fugl Meyer Upper Extremity Subscale; correlation coefficient *r* =.70, *p*=.01)

Figure 1b: Title: Association between initial upper extremity impairment (FMUE baseline) and movement of the upper extremity (FMUE) at 3 months

Abbreviations: FMUE = Fugl Meyer Upper Extremity Subscale; correlation coefficient *r* =.84, *p*=.005)

Figure 2a: Title: Association between heart rate variability (SDNN) and movement of the lower extremity (FMLE) at 3 months

Abbreviations: SDNN =Standard deviation of R-R intervals; FMLE = Fugl Meyer Lower Extremity Subscale; correlation coefficient *r* =.60, *p*=.03)

Figure 2b: Title: Association between initial lower extremity impairment (FMLE baseline) and movement of the lower extremity (FMLE) at 3 months

Abbreviations: FMLE = Fugl Meyer Lower Extremity Subscale; correlation coefficient *r* =.48, *p*=.09)

Figure 3a: Title: Association between heart rate variability (SDNN) and movement of the upper extremity (FMUE) at 3 months in patients with severe initial upper extremity impairments

Abbreviations: SDNN =Standard deviation of R-R intervals; FMUE = Fugl Meyer Upper Extremity Subscale; correlation coefficient *r* =.61, *p*=.05)

Figure 3b: Title: Association between initial upper extremity impairment (FMUE baseline) and movement of the upper extremity (FMUE) at 3 months in patients with severe initial upper extremity impairments

Abbreviations: FMUE = Fugl Meyer Upper Extremity Subscale; correlation coefficient *r* =.41, *p*=.14)

Figure 4a: Title: Association between heart rate variability (SDNN) and movement of the lower extremity (FMLE) at 3 months in patients with severe initial upper extremity impairments

Abbreviations: SDNN =Standard deviation of R-R intervals; FMLE = Fugl Meyer Lower Extremity Subscale; correlation coefficient *r* =.70, *p*=.04)

Figure 4b: Title: Association between initial lower extremity impairment (FMLE baseline) and movement of the lower extremity (FMLE) at 3 months in patients with severe initial upper extremity impairments

Abbreviations: FMLE = Fugl Meyer Lower Extremity Subscale; correlation coefficient *r* =.26, *p*=.30)

Table 1: Title:

Participant characteristics

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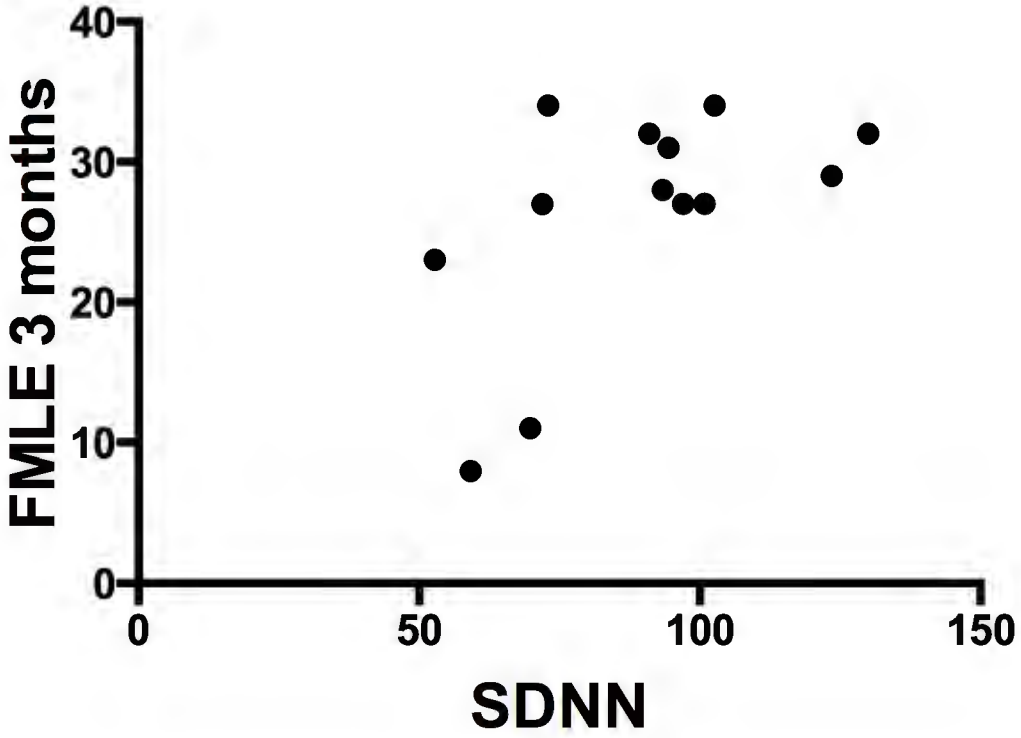
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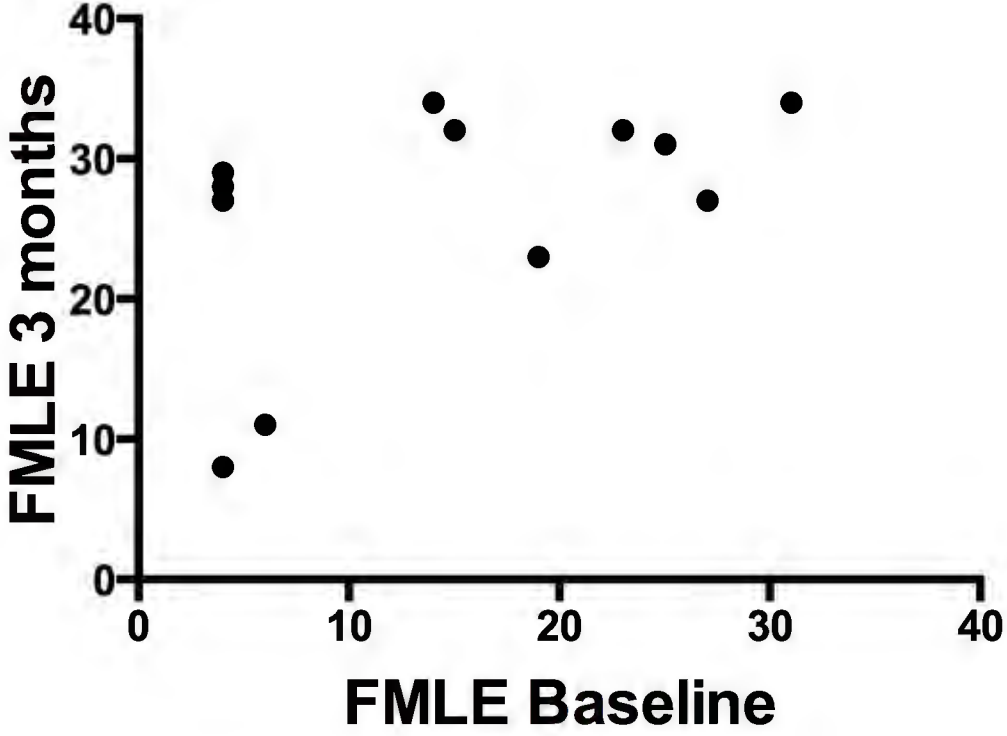
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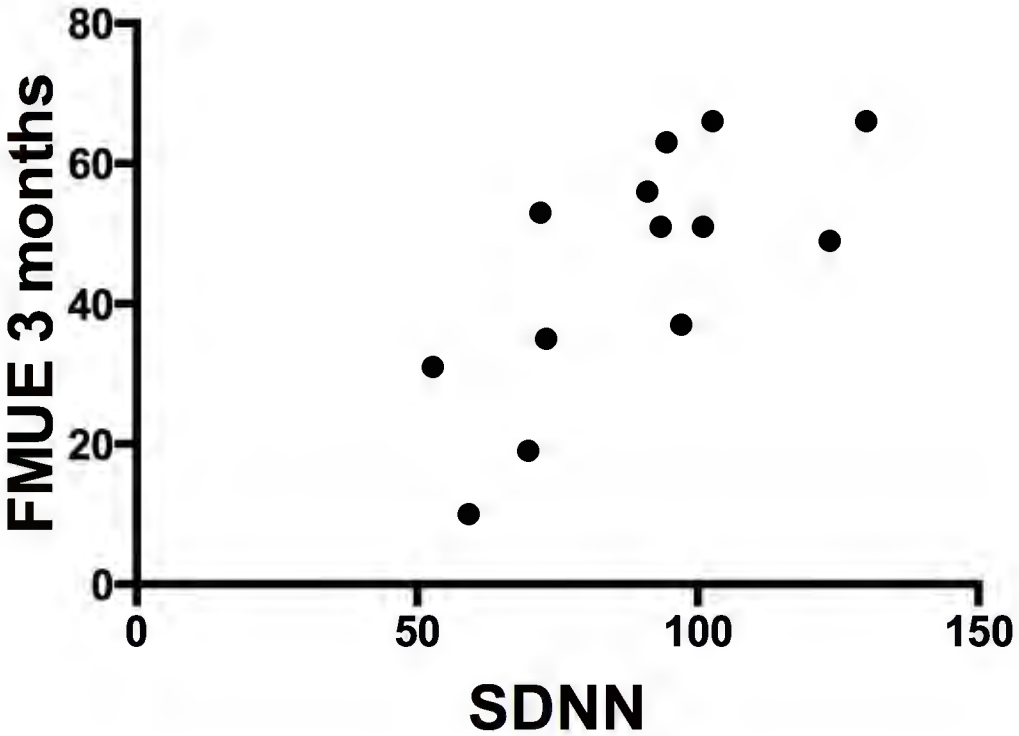
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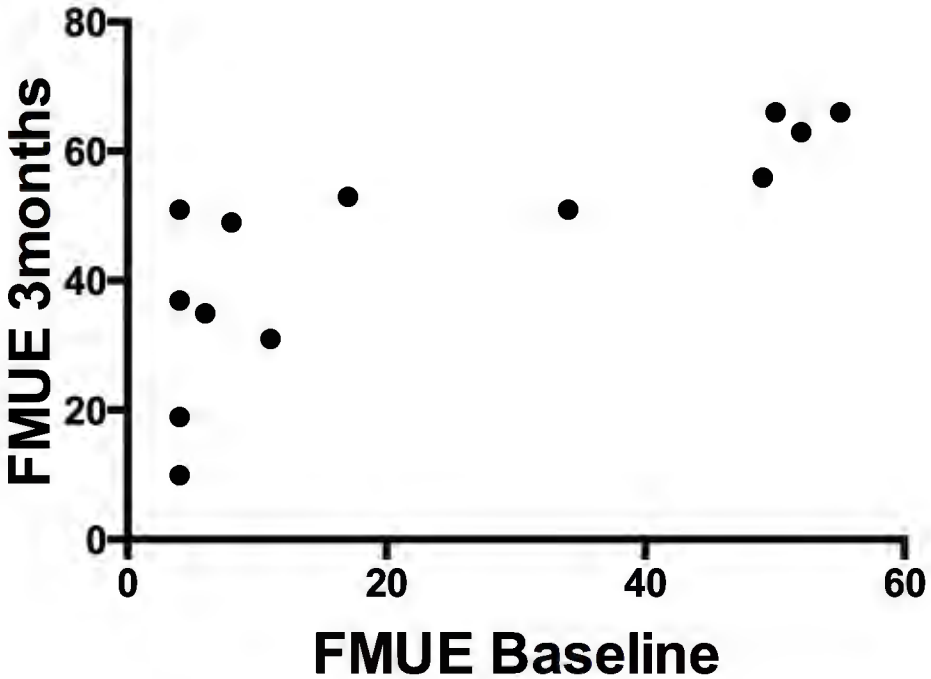
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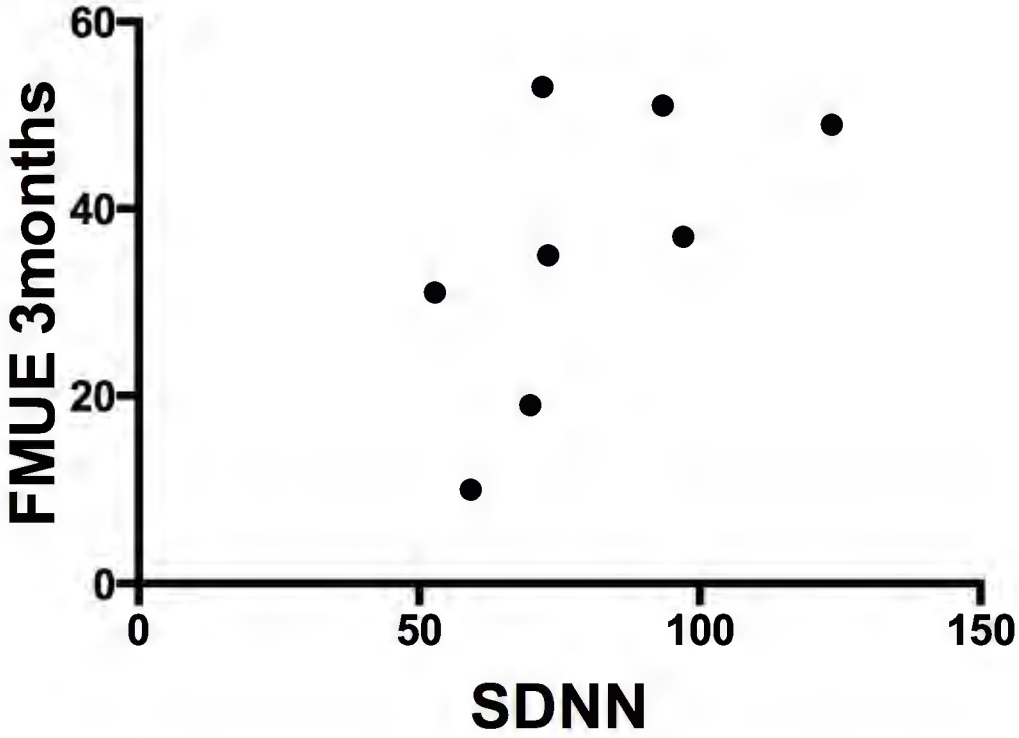
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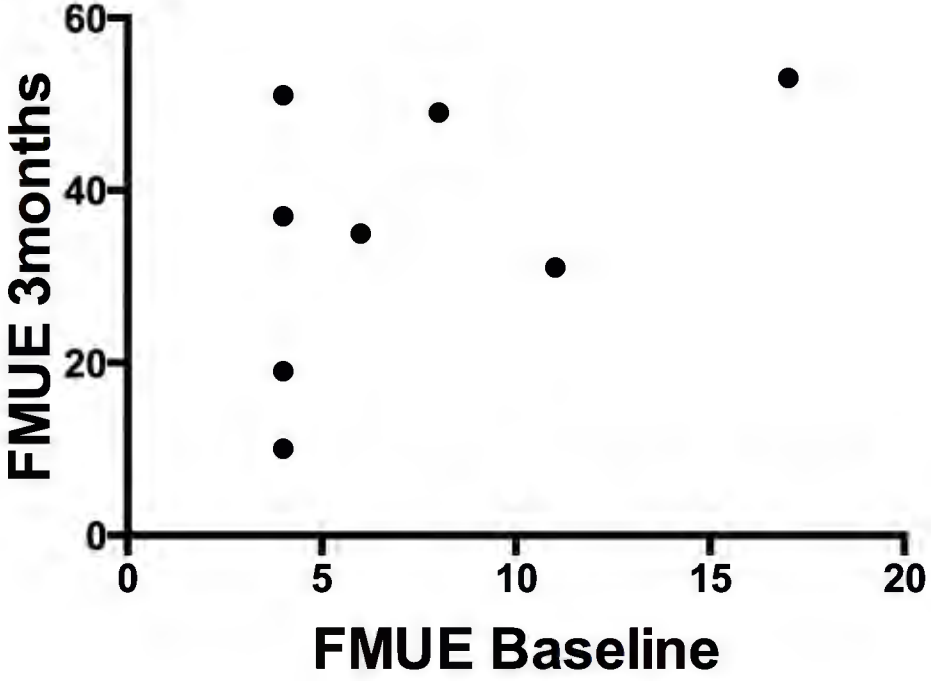
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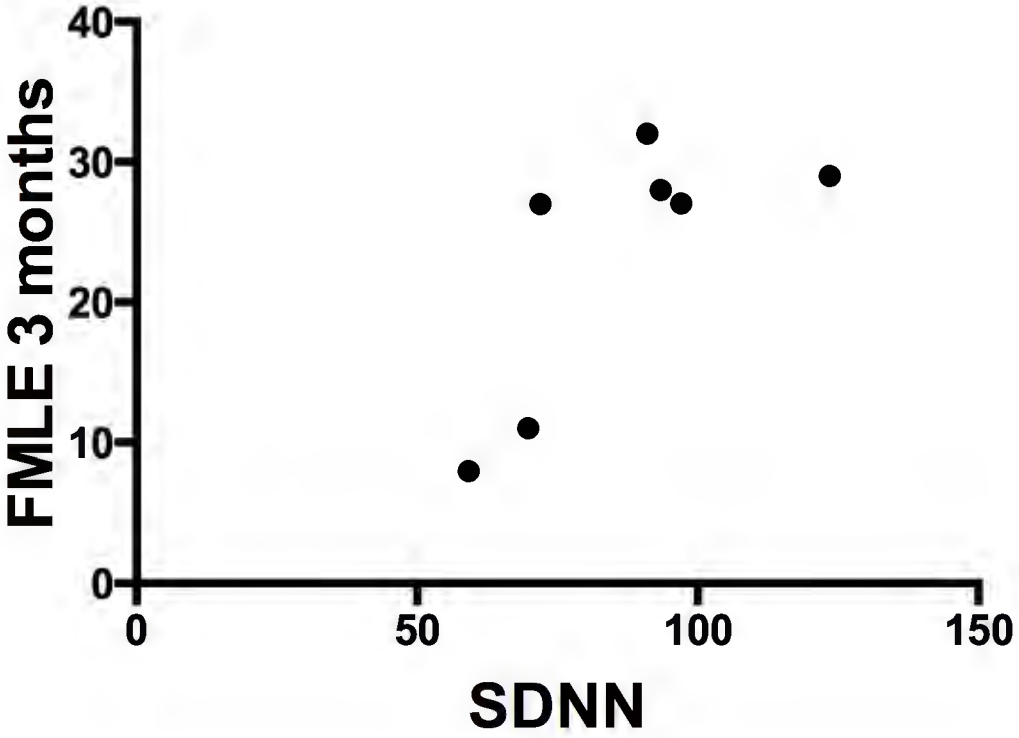
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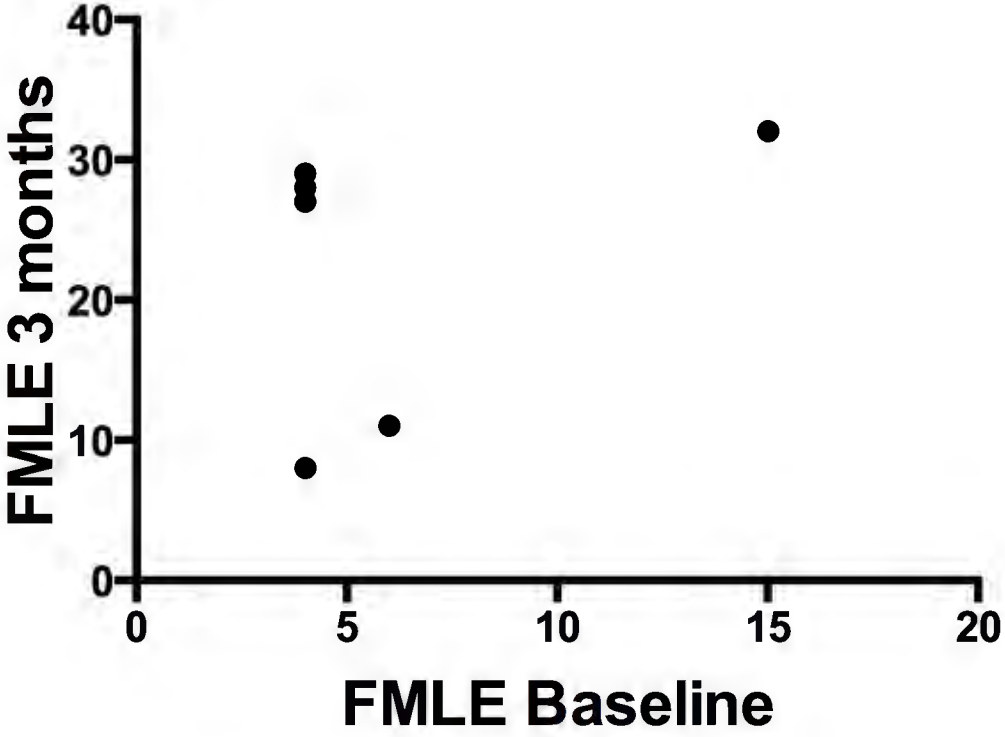
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