Neuronavigated Repetitive Transcranial Magnetic Stimulation as Novel Mapping Technique Provides Insights Into Language Function in Primary Progressive Aphasia

Felix Mueller-Sarnowski

Technical University Munich: Technische Universität München

Nico Sollmann

Technical University of Munich: Technische Universität München

Axel Schröder

Technical University Munich: Technische Universität München

Leen Hourii

Technical University of Munich: Technische Universität München

Sebastian Ille

Technical University of Munich: Technische Universität München

Timo Grimmer

Technical University of Munich: Technische Universität München

Sandro M. Krieg

Technical University of Munich: Technische Universität München

Janine Diehl-Schmid (✉ janine.diehl-schmid@tum.de)

Technical University of Munich: Technische Universität München <https://orcid.org/0000-0002-7745-1382>

Research Article

Keywords: navigated repetitive transcranial magnetic stimulation, primary progressive aphasia, language mapping, cortical plasticity

Posted Date: June 7th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-467598/v1>

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Version of Record: A version of this preprint was published at Brain Imaging and Behavior on December 28th, 2021. See the published version at <https://doi.org/10.1007/s11682-021-00605-6>.

Abstract

Neuronavigated repetitive transcranial magnetic stimulation (nrTMS) is an innovative technique that provides insight into language function with high accuracy in time and space. So far, nrTMS has mainly been applied in presurgical language mapping of patients with cranial neoplasms. For the present study nrTMS was used for language mapping in primary progressive aphasia

Seven patients (median age: 70 years, 4 males) with the non-fluent variant of primary progressive aphasia were included in this pilot study. Inhibitory nrTMS trains (5 Hz, 40 % resting motor threshold) caused virtual lesions at 46 standardized cortical stimulation targets per hemisphere. Patients' errors in a naming task during stimulation were counted.

The majority of errors induced occurred during frontal lobe stimulation (34.3 %). Timing errors and non-responses were most frequent. More errors were induced in the right hemisphere (58%) than in the left hemisphere (42%). Mapping was tolerated by all patients, however, discomfort or pain was reported for stimulation of frontal areas.

The elevated right-hemispheric error rate in our study supports the hypothesis of a partial shift of language function to the right hemisphere in neurodegenerative aphasia during the course of disease and therefore points to the existence of significant neuronal plasticity in primary progressive aphasia. While this is an interesting finding for neurodegenerative disorders per se, its promotion might also harbor future therapeutic targets.

Introduction

Primary progressive aphasia (PPAs) are gradually progressive, neurodegenerative disorders predominantly affecting speech and language. The non-fluent variant of PPA (nfvPPA) is characterized by a predominant posterior fronto-insular atrophy of the language-dominant hemisphere. Patients present with a non-fluent, effortful, halting speech that is dominated by obvious word-finding difficulties and agrammatism. Language production is simplified, phonematic paraphasias are frequent. Patients often present with apraxia of speech while dysarthria occurs less frequently (Gorno-Tempini et al., 2011).

Therapeutic options are scarce and consist mainly of speech therapeutic approaches. A few studies have made first, not very successful attempts to improve language function using repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) (Norise & Hamilton, 2016), (Cotelli et al., 2020), (Cotelli et al., 2012). However, targeted regions and stimulation parameters vary widely in these attempts, including anodal tDCS targeting of the left inferior frontal gyrus, high frequency rTMS of the whole left hemisphere, high-frequency rTMS of the left prefrontal cortex, or anodal (facilitative) stimulation of the left posterior peri-Sylvian region etc. This variability is the consequence of the sparse rationale for such interventions.

Knowledge about language function and compensatory mechanisms in the individual patient is a prerequisite for a more personalized and thus more efficient neurostimulation in nfvPPA. Positron emission tomography (PET) and functional magnetic resonance imaging (MRI) during a language task could generate such information, but only with limited resolution in time. Neuronavigated rTMS (nrTMS) has been shown to be a reliable technique in order to perform pre-surgical language mapping in patients with cranial neoplasms. Therefore, the primary aim of our pilot study was to investigate, which brain regions are involved in tasks of language and speech in patients with nfvPPA using nrTMS. Secondly, we wanted to investigate, how patients with nfvPPA tolerate nrTMS.

Methods

Patients

Patients with nfvPPA according to the Gorno-Tempini criteria (Gorno-Tempini et al., 2011) were enrolled from our outpatient clinic for cognitive disorders. Patient characterization comprised neurologic and psychiatric examination, extensive neuropsychological testing (see Table 1), structural MRI, and ^{18}F -fluoro-desoxy-glucose PET (^{18}F -FDG-PET).

Table 1
Patient characteristics

Patient		#1	#2	#3	#4	#5	#6	#7
sex		male	female	male	male	female	male	female
age		73	70	56	68	75	55	74
age at onset		70	66	54	67	72	52	71
education (years)		15	12	15	20	18	19	12
Handedness*		right	left mixed (forced right)	left (forced right)	right	right, mixed	right	right
FTLD-CDR	sum of boxes	3	1	0.5	3.5	2	5	5.5
	language	0.5	0.5	0.5	0.5	0.5	2	2
Semantic fluency (animals)		7 (-2.8 z)	9 (- 2.4 z)	16 (-1.6 z)	18 (-1.2 z)	15 (-2.2 z)	2 (-4.5 z)	6 (-2.9 z)
Phonematic fluency (S-words)		4 (-2.2 z)	7 (-1. z)	10 (-1.0 z)	5 (-2.6 z)	7 (-1.9 z)	3 (-3.3 z)	1 (-3.3 z)
15 item BNT (/15)		14 (-0.4 z)	15 (1.3 z)	15 (0.5 z)	15 (0.5 z)	15 (1.0 z)	4 (-5.9 z)	5 (-4.4 z)
MMSE (/30)		24 (-3.1 z)	29 (-0.2 z)	29 (-0.8 z)	29 (-0.7 z)	29 (- 0.6 z)	20 (-5.7 z)	17 (-6.0 z)
CERAD word list learning (/30)		12 (-2.3 z)	21 (-0.3 z)	24 (0.6 z)	24 (0.9 z)	19 (-1.2 z)	15 (-2.2 z)	16 (-1.8 z)
CERAD word list delayed recall (/10)		4 (-1.2 z)	8 (0.1 z)	8 (0 z)	7 (-0.4 z)	7 (-0.8 z)	2 (-3.0 z)	5 (-1.3 z)

CERAD = Consortium to Establish a Registry in Alzheimer's Disease - neuropsychological battery, BNT = Boston Naming Test, FTLD-CDR = FTLD specific clinical dementia rating; MMSE = Mini-Mental-State Exam, WMS = Wechsler Memory Scale, AAT Aachen Aphasia Test; * handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971)

Patient	#1	#2	#3	#4	#5	#6	#7
CERAD figure copy (/11)	7 (-2.9 z)	9 (-1.3 z)	11 (0.5 z)	10 (-1.4 z)	11 (0.6 z)	11 (0.3 z)	10 (0.5 z)
CERAD figure recall (/11)	4 (-2.5 z)	7 (-0.9 z)	11 (0.8 z)	9 (-1.0 z)	11 (1.0 z)	11 (0.7 z)	5 (-1.5 z)
trail making A (seconds)	> 180	82 (-1.8 z)	46 (-0.9 z)	70 (-1.8 z)	65 (-1.2 z)	45 (-0.7 z)	43 (0.3 z)
trail making B (seconds)	> 300 (-2.5 z)	> 300 (- 2.5 z)	138 (-1.7 z)	283 (-3.3 z)	194 (-2.2 z)	180 (-2.6 z)	121 (-0.2 z)
AAT token test	5	12	12	1	3	42	5
AAT token test age adjusted	0	6	9	0	0	38	3
AAT loud reading	29	26	26	30	28	27	29
AAT composing words	28	28	29	30	30	29	24
AAT writing to dictation	28	29	24	30	30	27	8
CERAD = Consortium to Establish a Registry in Alzheimer's Disease - neuropsychological battery, BNT = Boston Naming Test, FTLCD-CDR = FTLCD specific clinical dementia rating; MMSE = Mini-Mental-State Exam, WMS = Wechsler Memory Scale, AAT Aachen Aphasia Test; * handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971)							

Patients were examined with the German Version of the Consortium to Establish a Registry in Alzheimer's Disease (CERAD) neuropsychological battery (Morris et al., 1993), which includes the Mini-Mental-State Examination (Folstein, Folstein, & McHugh, 1975) and parts of the Aachener Aphasia test (Huber, Poeck, Weninger, & Willmes, 1983) (Table 1). Dementia severity was rated using the frontotemporal lobar degeneration-specific clinical dementia rating (FTLCD-CDR) (Knopman et al., 2008). Neuropsychological assessment was performed within a maximum of eight weeks (median 13 days) before or after the nTMS.

In all patients cranial MRI was performed at 3 Tesla (Ingenia Elition X, Philips Healthcare, Best, The Netherlands). The protocol included a three-dimensional (3D) T1-weighted gradient echo sequence (repetition time/echo time: 9/4 ms, 1 mm³ isovoxel covering the whole head, no application of an intravenous contrast agent) for neuronavigation, subsequently referred to as 3D MRI. Furthermore, ¹⁸F-FDG-PET was performed in all patients.

Navigated rTMS

Examination of object naming performance

Naming task parameters were adapted to each individual participant's performance prior to the nrTMS. During two baseline sessions the patients had to name schematic black and white drawings of 80 common objects (one or two syllables), based on the Snodgrass and Vanderwart images (Snodgrass & Vanderwart, 1980). The objects were presented on a screen one after another. After each of two naming sessions the object was sorted out when the patient was not able to name the object promptly and correctly.

Two patients (#6 and #7) were not able to correctly name the majority of objects (errors in 84.4% and 59.7%, respectively). Consequently, the nrTMS examination based on object naming seemed not feasible. However, both patients showed less difficulties in a number naming task (patient #6: 24% errors; patient #7: 36.1% errors). Therefore, the object naming task was replaced by a number (Figs. 0–9) naming task in these two cases.

Language mapping

Language mapping by nrTMS was performed with the Nexstim eXimia 5.1 NBS system (Nexstim Plc., Helsinki, Finland) using a figure-of-8 coil. The technical procedure and the protocol for language mapping has been described in detail previously (Ille et al., 2016), (Sollmann et al., 2017), (Krieg et al., 2013). In brief, cortical tissue was temporarily inhibited by a train of five repetitive nrTMS pulses at standardized stimulation targets in each hemisphere during a naming task. For neuronavigation a co-registration of each patient's head and the according 3D MRI data was performed. Stimulation intensity was calibrated by the resting motor threshold (rMT) of hand muscles. The rMT is defined as lowest TMS intensity provoking a 50 μ V peak-to-peak amplitude in the relaxed first dorsal interosseus muscle in five out of ten stimulations (Rossini et al., 2015).

Forty-six standardized stimulation targets per hemisphere, distributed over 21 gyral segments, were set up on each patient's reconstructed head model within the nrTMS software according to a template based on a parcellation scheme described by Corina and colleagues (Corina et al., 2005). The pre-selected objects (and numbers) were presented time-locked to inhibitory nrTMS trains (5 Hz, 40% rMT). Keeping the coil perpendicular to the gyrus three nrTMS trains of five stimuli were applied at each target simultaneously with the picture presented on screen. The patients had to name the objects as quickly as possible. Then the stimulator was randomly moved to the next target during the inter-picture interval of 2.5 seconds. Picture-to-trigger-interval was 0 milliseconds, display time of each picture was 700 ms.

Classification of naming errors

In accordance with prior nTMS studies (Corina et al., 2010), (Krieg et al., 2017) errors were classified into „non-response“ (no, strongly distorted or incomplete utterance), „semantic error“ (incorrect choice of word), „performance error“ (correct choice of word, but utterance or assembly incorrect) and “timing error”

(delay, hesitation) resembling prior studies (Picht et al., 2013), (Sollmann et al., 2017), (Sollmann et al., 2014). The error classes “neologism” and “circumlocution” originally described as error classes by Corina and colleagues, were summarized as semantic errors. Phonological errors were subsumed among performance errors.

Analysis

For the detailed and standardized assessment – blinded to the sites of cortical stimulation – the baseline examination of the naming performance and the nrTMS examination with patients’ answers were video-recorded (Sollmann et al., 2014), (Picht et al., 2013). The videos recorded during nrTMS language mapping were analyzed, and any naming impairment was compared with the corresponding baseline response. Videos were rated in ELAN, an annotation tool for multi-media resources developed by the Max Planck Institute for Psycholinguistics (Wittenburg, Brugman, Russel, Klassmann, & Sloetjes, 2006), that integrates tightly with Praat (Boersma & vanheugen), a software for phonetic analysis from the University of Amsterdam. The spatial distribution of the naming errors that resulted from the virtual lesions revealed a map of cortical language areas. Additionally, the calculation of error rates was performed for each subject and each hemisphere by dividing the number of errors by the number of stimulations (per stimulated spot).

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request. The data are not publicly available due to ethical and legal restrictions. Due to German data protection rules transfer of data that is considered to be personal by local laws (for example video and sound recordings) is forbidden. For the same legal reasons transmission of data might be possible within the European Union only.

Results

Seven patients with nvPPA participated in the study. Patient characteristics and neuropsychological test results are displayed in Table 1. Clinical Gorno-Tempini criteria for nvPPA were fulfilled in all patients. All participants showed a frontal and temporal atrophy in cranial MRI and a left frontal hypometabolism in ¹⁸F-FDG-PET.

Error counts

As displayed in Table 2a total of 353 naming errors during 1932 stimulations was observed in nvPPA patients, which amounts to an error rate of 18.2%. The majority of errors occurred during stimulation of the frontal lobes (34.3%), followed by the temporal lobes (24.6%) and the central lobes (22.1%).

Table 2
Errors per lobe and hemisphere during object naming (patient 1–5) and number naming (patient 6, 7)

patient	hemisphere	frontal	central	temporal	parietal	Sum hemisphere	Sum brain
1	left	31	12	14	17	74	144
	right	20	15	18	17	70	
2	left	3	1	0	0	4	11
	right	3	3	0	1	7	
3	left	7	8	2	3	20	55
	right	12	6	13	4	35	
4	left	4	0	1	0	5	11
	right	4	1	1	0	6	
5	left	7	1	5	1	14	37
	right	6	2	12	3	23	
6	left	4	6	4	5	19	64
	right	7	17	9	12	45	
7	left	4	2	3	4	13	31
	right	9	4	5	0	18	
Sum left		121	78	87	67	149 (42%)	
Sum right		(34.3 %)	(22.1 %)	(24.6 %)	(19.0 %)	204 (58%)	
Sum total						353 (100%)	
Error counts per hemisphere and lobe summed up to the overall error count in the last column.							
Of note: Patient #2 an #3 are forced right handed;							

Error classes and distribution of errors in both hemispheres are shown in Table 3. Overall, more errors were induced in the right hemisphere (204/353 errors, 58%) than in the left hemisphere (149/353 errors, 42%). Timing errors and non-responses were most frequent (39% and 35% of all errors).

Table 3
Error classes per hemisphere

error class	errors left hemisphere	errors right hemisphere	total errors
non-response	49 (32.9 %)	76 (37.2 %)	125 (35.4 %)
semantic	21 (14.1 %)	24 (11.8 %)	45 (12.8 %)
performance	18 (12.1 %)	28 (13.7 %)	46 (13.0 %)
timing	61 (40.9 %)	76 (37.3 %)	137 (38.8 %)
total	149 (100 %)	204 (100 %)	353 (100 %)

Tolerability

Overall, the nrTMS examination was tolerated well by six out of seven patients. All of the patients stated after the examination that they would be willing to undergo further nrTMS sessions. However, the majority of patients disclosed considerable discomfort and pain (Table 4). As observed in the video recordings and confirmed by the participants, pain and discomfort were limited to stimulation of frontal regions.

Table 4
Discomfort and pain – patient estimation on a 10 level Likert scale (0 = no discomfort/ pain)

patient	#1	#2	#3	#4	#5	#6	#7
pain left hemisphere	5	7	2	0	5	1	0
pain right hemisphere	6	5	3	0	5	1	8
discomfort left hemisphere	6	4	2	0	5	0	0
discomfort right hemisphere	7	3	3	0	5	0	0

Discussion

To our knowledge the present study is the first that performed language mapping in neurodegenerative aphasia using nrTMS. Specifically, nrTMS induced an overall error rate of 18% in nvfPPA patients. Previous studies using nrTMS in healthy individuals have described similar error rates (Sollmann et al., 2017); (Sollmann et al., 2014). Timing errors and non-responses were most frequent in nvfPPA patients (39% and 35% of all errors), in line with the fact that halting speech is one of the two core features of nvfPPA (Gorno-Tempini et al., 2011).

Although we observed an obvious inter-individual variability regarding error rates and language maps, stimulation of the temporal, central and parietal lobes induced fewer errors than stimulation of frontal areas. This goes along with the fact that nvfPPA is characterized by imaging abnormalities in the posterior fronto-insular region (Gorno-Tempini et al., 2011). However, nrTMS showed very well, that

language function in nvfPPA is by no means confined to these regions, but widespread. In five out of seven patients (all except patients #4 and #5) nTMS language maps point towards a particular role of the central gyri in nvfPPA language production. This is consistent with findings in stroke patients who showed involvement of the precentral gyrus in apraxia of speech (Itabashi et al., 2016).

Surprisingly, more errors were induced in the right hemisphere (58%) than in the left hemisphere (42%). A shift of language function towards the right hemisphere has already been demonstrated in stroke, epilepsy and cranial neoplasms (Anglade, Thiel, & Ansaldo, 2014), (Baciu & Perrone-Bertolotti, 2015) (Krieg et al., 2013). There is broad consensus that this phenomenon indicates cortical reorganization.

Despite some evidence from functional imaging for a language shift in nvfPPA patients (Vandenbulcke, Peeters, Hecke, & Vandenberghe, 2005), the general understanding so far is that patients with nvfPPA subtypes are not remapping language functions to contralateral networks. They appear to use pre-existing language areas, but with progressively declining efficiency (Norise & Hamilton, 2016). Notably, these assumptions are based on comparatively weak evidence (Wilson et al., 2010).

The present study has some obvious limitations. First, the sample size is small and the patient sample was not homogenous regarding handedness. Second, not all patients were able to perform an object naming task so that a number naming task was used in two patients. Third, a general obstacle of language mapping with nrTMS is, that stimulation targets at the edge of the frontal lobe are not included since stimulation at these targets causes intolerable discomfort in many patients. Consequently, the anterior parts of the superior and middle frontal gyrus as well as the orbital part of the inferior frontal gyrus are not covered.

However, the present study is the first to show that language mapping in neurodegenerative aphasia using nrTMS is feasible and offers unique insights into language function by combining good temporary with good spatial resolution. Evaluating the individual language function might be a prerequisite for any targeted, personalized stimulation therapy. The elevated right-hemispheric error rate in our study supports the hypothesis of a (partial) shift of language function to the right hemisphere in nvfPPA patients during the course of disease and therefore points to the existence of significant neuronal plasticity in neurodegenerative aphasia. The evidence of neuronal plasticity in nvfPPA fuels hope that nrTMS might become a treatment option: either by stimulation of compensatory right-hemispheric networks or by stimulation of pathologically weakened left-hemispheric networks in order to enhance language function.

Further, longitudinal studies are needed including larger patient samples and healthy controls to further investigate language function and brain plasticity in nvfPPA. In such larger cohort studies, our current data justifies investigating nTMS as a new neurophysiological biomarker especially for the early phase of PPA.

Conclusion

Our pilot study showed that nrTMS is a feasible tool for language mapping in nvPPA. Evaluating the individual language function might be a prerequisite for any targeted, personalized stimulation therapies. Study results suggests the existence of neuronal plasticity in neurodegenerative aphasia.

Declarations

Acknowledgements

We would like to thank all patients for their invaluable contribution to this project. Further, we would like to thank the bioinformatiX research group of the Munich Medical Society for supporting this trial by providing access to its technical infrastructure.

Ethical approval

The study was approved by the local ethics committee (#377/18 S) and conducted in line with the principles expressed in the Declaration of Helsinki.

Consent to participate

Each participant provided written informed consent prior to enrollment.

Consent to publish

Not applicable

Authors contributions

Conception and study design (JDS, FMS, SK, NS, SI), data collection and acquisition (FMS, AS, LH, JDS), analyses (FMS, LH, TG), interpretation of results (FMS, JDS, NS, SI, TG, SK), drafting the manuscript (FMS, JDS), revising the manuscript critically for important intellectual content (JDS, NS, SI, TG, SK), approval of final version (all authors).

Funding

No funding.

Competing interests

Felix Müller-Sarnowski, Timo Grimmer and Janine Diehl-Schmid have no competing interests with regard to the submitted manuscript. Outside the submitted manuscript TG received consulting fees from Abbvie, Anavex, Biogen, Bracket, Eli Lilly, Functional Neuromodulation, Iqvia/Quintiles, Novartis, Novo Nordisk, NuiCare, Roche Pharma, Toyama, and Vivoryon; lecture fees from Actelion, B.Braun, Biogen, Eli Lilly, Life Molecular Imaging, Novartis, Parexel, and Roche Pharma; and grants to his institution from Actelion and Novartis. Sandro Krieg is consultant for Ulrich Medical (Ulm, Germany) and received honoraria from Nexstim Plc (Helsinki, Finland), Spineart Deutschland GmbH (Frankfurt, Germany), Medtronic (Meerbusch,

Germany) and Carl Zeiss Meditec (Oberkochen, Germany). Sandro Krieg and Sebastian Ille are consultants for Brainlab AG (Munich, Germany). Sebastian Ille and Nico Sollmann received honoraria from Nexstim Plc (Helsinki, Finland).

Availability of data and material

The data that support the findings of this study are available from the corresponding author, upon reasonable request. The data are not publicly available due to ethical and legal restrictions. Due to German data protection rules transfer of data that is considered to be personal by local laws (for example video and sound recordings) is forbidden. For the same legal reasons transmission of data might be possible within the European Union only.

References

1. Anglade, C., Thiel, A., & Ansaldo, A. I. (2014). The complementary role of the cerebral hemispheres in recovery from aphasia after stroke: a critical review of literature. *Brain Inj*, 28(2), 138-145. doi:10.3109/02699052.2013.859734
2. Baciú, M., & Perrone-Bertolotti, M. (2015). What do patients with epilepsy tell us about language dynamics? A review of fMRI studies. *Rev Neurosci*, 26(3), 323-341. doi:10.1515/revneuro-2014-0074
3. Boersma, P., & vanheugen, V. Doing Phonetics by Computer. <http://www.praat.org>. Accessed August 31, 2020.
4. Corina, D. P., Gibson, E. K., Martin, R., Poliakov, A., Brinkley, J., & Ojemann, G. A. (2005). Dissociation of action and object naming: evidence from cortical stimulation mapping. *Hum Brain Mapp*, 24(1), 1-10. doi:10.1002/hbm.20063
5. Corina, D. P., Loudermilk, B. C., Detwiler, L., Martin, R. F., Brinkley, J. F., & Ojemann, G. (2010). Analysis of naming errors during cortical stimulation mapping: implications for models of language representation. *Brain Lang*, 115(2), 101-112. doi:10.1016/j.bandl.2010.04.001
6. Cotelli, M., Manenti, R., Alberici, A., Brambilla, M., Cosseddu, M., Zanetti, O., . . . Borroni, B. (2012). Prefrontal cortex rTMS enhances action naming in progressive non-fluent aphasia. *Eur J Neurol*, 19(11), 1404-1412. doi:10.1111/j.1468-1331.2012.03699.x
7. Cotelli, M., Manenti, R., Ferrari, C., Gobbi, E., Macis, A., & Cappa, S. F. (2020). Effectiveness of language training and non-invasive brain stimulation on oral and written naming performance in Primary Progressive Aphasia: A meta-analysis and systematic review. *Neurosci Biobehav Rev*, 108, 498-525. doi:10.1016/j.neubiorev.2019.12.003
8. Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). 'Mini Mental State'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res*, 12, 189-198.
9. Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., . . . Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology*, 76(11), 1006-1014. doi:WNL.0b013e31821103e6 [pii] 10.1212/WNL.0b013e31821103e6

10. Huber, W., Poeck, K., Weninger, D., & Willmes, K. (1983). Aachener Aphasie Test. In. Göttingen: Hogrefe.
11. Ille, S., Kulchytska, N., Sollmann, N., Wittig, R., Beurskens, E., Butenschoen, V. M., . . . Krieg, S. M. (2016). Hemispheric language dominance measured by repetitive navigated transcranial magnetic stimulation and postoperative course of language function in brain tumor patients. *Neuropsychologia*, 91, 50-60. doi:10.1016/j.neuropsychologia.2016.07.025
12. Itabashi, R., Nishio, Y., Kataoka, Y., Yazawa, Y., Furui, E., Matsuda, M., & Mori, E. (2016). Damage to the Left Precentral Gyrus Is Associated With Apraxia of Speech in Acute Stroke. *Stroke*, 47(1), 31-36. doi:10.1161/strokeaha.115.010402
13. Knopman, D., Kramer, J., Boeve, B., Caselli, R., Graff-Radford, N., Mendez, M., . . . Mercaldo, N. (2008). Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain*, 131, 2957 - 2968.
14. Krieg, S. M., Lioumis, P., Mäkelä, J. P., Wilenius, J., Karhu, J., Hannula, H., . . . Picht, T. (2017). Protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report. *Acta Neurochir (Wien)*, 159(7), 1187-1195. doi:10.1007/s00701-017-3187-z
15. Krieg, S. M., Sollmann, N., Hauck, T., Ille, S., Foerschler, A., Meyer, B., & Ringel, F. (2013). Functional language shift to the right hemisphere in patients with language-eloquent brain tumors. *PLoS One*, 8(9), e75403. doi:10.1371/journal.pone.0075403
16. Morris, J., Edland, S., Clark, C., Galasko, D., Koss, E., Mohs, R., . . . Heyman, A. (1993). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer's disease. *Neurology*, 43, 2457 - 2465.
17. Norise, C., & Hamilton, R. H. (2016). Non-invasive Brain Stimulation in the Treatment of Post-stroke and Neurodegenerative Aphasia: Parallels, Differences, and Lessons Learned. *Front Hum Neurosci*, 10, 675. doi:10.3389/fnhum.2016.00675
18. Oldfield, R. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, 9, 97 - 113.
19. Picht, T., Krieg, S. M., Sollmann, N., Rösler, J., Niraula, B., Neuvonen, T., . . . Ringel, F. (2013). A comparison of language mapping by preoperative navigated transcranial magnetic stimulation and direct cortical stimulation during awake surgery. *Neurosurgery*, 72(5), 808-819. doi:10.1227/NEU.0b013e3182889e01
20. Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R., . . . Ziemann, U. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol*, 126(6), 1071-1107. doi:10.1016/j.clinph.2015.02.001
21. Snodgrass, J., & Vanderwart, M. (1980). A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *J Exp Psychol Hum Learn.*, 6(2), 174 - 215.

22. Sollmann, N., Ille, S., Negwer, C., Boeckh-Behrens, T., Ringel, F., Meyer, B., & Krieg, S. M. (2017). Cortical time course of object naming investigated by repetitive navigated transcranial magnetic stimulation. *Brain Imaging Behav*, 11(4), 1192-1206. doi:10.1007/s11682-016-9574-x
23. Sollmann, N., Tanigawa, N., Ringel, F., Zimmer, C., Meyer, B., & Krieg, S. M. (2014). Language and its right-hemispheric distribution in healthy brains: an investigation by repetitive transcranial magnetic stimulation. *Neuroimage*, 102 Pt 2, 776-788. doi:10.1016/j.neuroimage.2014.09.002
24. Vandenbulcke, M., Peeters, R., Hecke, P. V., & Vandenberghe, R. (2005). Anterior temporal laterality in primary progressive aphasia shifts to the right. *Ann Neurol*, 58, 362 - 370.
25. Wilson, S. M., Henry, M. L., Besbris, M., Ogar, J. M., Dronkers, N. F., Jarrold, W., . . . Gorno-Tempini, M. L. (2010). Connected speech production in three variants of primary progressive aphasia. *Brain*, 133(Pt 7), 2069-2088. doi:awq129 [pii] 10.1093/brain/awq129
26. Wittenburg, P., Brugman, H., Russel, A., Klassmann, A., & Sloetjes, H. (2006). ELAN: a professional framework for multimodality research. *Proceedings of the 5th International Conference on Language Resources and Evaluation (LREC 2006)*, 1556 - 1559.

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