Intensive Social Interaction for Treatment of Post-Stroke Depression in Subacute Aphasia: The CONNECT Trial

Study Protocol

Benjamin Stahl, PhD[1, 2, 3 *]; Saskia Millrose, MSc[4, 5 *]; Petra Denzler, MSc[5]; Guglielmo Lucchese, MD, PhD[2]; Frank Jacobi, PhD[6]; Agnes Flöel, MD[2, 7]

[1] Faculty of Science, Medical School Berlin, Germany

[2] Department of Neurology, University Medicine Greifswald, Germany

[3] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

[4] Department of Psychology, Freie Universität Berlin, Germany

[5] Median-Klinik Berlin-Kladow, Germany

[6] Psychologische Hochschule Berlin, Germany

[7] German Centre for Neurodegenerative Diseases, Rostock and Greifswald, Germany

* Authors contributed equally.

Correspondence:

Prof. Dr. Benjamin Stahl
Medical School Berlin
Naturwissenschaftliche Fakultät
Rüdesheimer Straße 50
14197 Berlin, Germany
E-mail: *benjamin.stahl@medicalschool-berlin.de*

Clinical Trial Registration:

www.clinicaltrials.gov; identifier: NCT04318951.

Last Update:

March 2019

Methods

Study design and setting

Following the CONSORT guidelines, we here present a parallel-group, blinded-assessment, quasi-randomised controlled phase-IIB trial[a] in an outpatient rehabilitation centre in Berlin, Germany, between 2020 and 2022 (study acronym: CONNECT). This trial was approved by the ethics review board at University Medicine Greifswald, Germany (file number: BB 033/17). A team of neuropsychologists will obtain written informed consent from all participants, with ample time for questions and reflection to account for aphasia-immanent comprehension problems.

Study sample and power analysis

After routine referral to the study team, we will invite potential participants to a screening session to check their eligibility. Inclusion criteria will be: left-hemispheric cortical or subcortical ischemic or haemorrhagic event; subacute phase (0.5–6 months after the cerebrovascular lesion); German as first native language; right-handedness according to the Edinburgh Handedness Inventory;[29] diagnosis of PSD, as defined by international classification code F06.32;[5] diagnosis of aphasia, as confirmed by the Bielefeld Aphasia Screening, with no more than two standard deviations below the average score on the subscale "Auditory Comprehension" to ensure understanding of basic instructions.[30] Exclusion criteria will be: other psychopathological or neurological conditions; premorbid history of recurrent depressive disorder; severe uncorrected vision or hearing that may prevent intensive social interaction during therapy or testing; serious non-verbal cognitive deficits, as revealed by the Corsi Block-Tapping Task.[31]

A target sample of 60 individuals will participate in the present phase-IIB trial. This sample size was calculated in an *a-priori* power analysis ($\alpha = 0.05$; $1–\beta = 0.80$; Cohen's $f = 0.390$; numerator degrees of freedom: 1; number of groups: 2; number of covariates: 2; resulting $n = 54$; expected dropout rate = 10%; final $n = 60$).[32] Our effect size estimate derives from published phase-IIA RCT data on Beck's Depression Inventory (BDI), as specified below (converted from $\eta^2 = 0.132$).[20] Notably, an extended goal of the current phase-IIB trial will be to deliver a more precise effect size estimate for a subsequent phase-III RCT. We assumed a more conservative dropout rate for ILAT than seen in previous work.[19, 23]

[a] Study on aspects of feasibility and potential efficacy as an intermediate step to a phase-III RCT.

Quasi-randomisation and blinding

Eligible candidates will be assigned to one of two treatment arms (each $n = 30$). Our ILAT protocol requires three individuals with aphasia to be present simultaneously in a rehabilitation centre for daily sessions over a 1-month treatment period. During the recruitment phase, occasionally fewer than three eligible candidates per treatment period will stay at the rehabilitation centre. To meet this logistical challenge in our phase-IIB trial—with a focus on treatment feasibility in PSD—candidates will receive ILAT only if enough fellow players are available to form groups of three individuals. Otherwise, candidates will receive the control intervention. The quasi-randomisation procedure will be administered by a person who does not participate in any stage of therapy or testing. A neuropsychologist with expertise in aphasia will perform all diagnostic sessions. This person will be blinded to group assignment and will not have patient contact aside from the testing. Data will be unmasked for final evaluation purposes by the study team who will not attend any of the therapy or testing sessions.

Treatment and procedures

ILAT requires individuals with aphasia to engage in everyday request and planning communication.[18] Groups of three individuals and a therapist are seated around a table and provided with picture cards showing different objects (e.g., bottle) or action scenes (e.g., drinking). Barriers on the table prevent players from seeing each other's cards. Each card has a duplicate that belonged to one of the other players. The goal is to obtain this duplicate from a fellow player by requesting the depicted object (e.g., "Give me the […]") or by proposing an action based on the visualised scene (e.g., "Let's […] together"). The rich turn-taking structure of ILAT serves as a vehicle for intensive use of formulaic expressions: (i) If the duplicate is available, the players compare the depicted objects or scenes; in the case of a match, the addressee hands over the corresponding card to the person who initiated the request or action-planning sequence (e.g., "Here you are"—"Thank you"—"You're welcome"). (ii) If the duplicate is not available, the addressee rejects the request or proposed action (e.g., "I'm sorry"—"No problem"—"Too bad"). (iii) In the event of misunderstandings, the players ask clarifying questions (e.g., "Pardon me?").

We will recreate training materials and procedures described previously.[23] The therapist will continuously apply positive reinforcement via encouraging feedback to diminish the likelihood of cognitive-affective distress caused by lack of social stimulation, in line with a common model of depression aetiology.[1] Practical experience with ILAT demonstrates that players often imitate the therapists' behaviour by starting to support one another verbally, thus

multiplying the amount of positive reinforcement exchanged during treatment (e.g., "Well done!"). Self-cueing strategies will be allowed, along with gestures to accompany—but not replace—spoken language. ILAT involves five weekly sessions, each with a duration of one hour, over a total treatment period of one calendar month. We do not set a minimum amount of treatment in our protocol to compensate for missed sessions, since dropout rates for ILAT have been extremely low in prior work.[19, 23] The treatment will be delivered by a team of speech-language therapists and neuropsychologists who will receive training and continuous supervision before and during the trial.

Standard care will conform to state-of-the-art procedures of rehabilitation centres certified in Germany. Depending on the participants' diagnoses and needs, standard care will include: antidepressant medication (drug and dosage defined individually by a physician blinded to group randomisation and study purpose; substance classes: selective serotonin reuptake inhibitors, tri- and tetracyclics), occupational therapy (2–3 hours weekly), physiotherapy (2–3 hours weekly), and non-intensive speech-language therapy (2–3 hours weekly with emphasis on phonology, lexicon and syntax, as detailed in a large-scale RCT protocol[33]).

Outcomes and testing

Feasibility, our *primary* outcome, will considered to be met if at least two-thirds of participants in Group I complete all ILAT sessions offered during the 1-month treatment period.

As a *co-primary* outcome of potential efficacy, we will administer a 20-item version of the BDI.[34] This self-report measure is known for its excellent psychometric properties, including construct validity and test-retest reliability, in individuals *without* aphasia. The BDI has been successfully piloted in individuals *with* aphasia, as indicated by phase-IIA RCT data.[20] To complement the BDI, we will use a clinician-rated measure with good psychometric properties as an additional *co-primary* outcome, a 7-item version of the Hamilton Rating Scale for Depression.[35]

Reflecting the potential influence of treatment-induced or spontaneous progress in verbal expression on change in depression severity, we will employ the combined Aachen Aphasia Test (AAT) subscales "Repetition" and "Naming" as a *secondary* outcome and covariate in our analyses.[36] These two AAT subscales proved to be most sensitive to ILAT-mediated gains in chronic aphasia, as shown by RCT data.[19, 23] Moreover, participants will complete the Self-Efficacy Questionnaire, a self-report measure conceived to quantify personal confidence in overcoming obstacles when accomplishing difficult tasks.[37] Low scores on this *secondary*

outcome constitute a risk factor for cognitive-affective distress, suggesting a significant negative relationship between results on the Self-Efficacy Questionnaire and BDI.[38] The Self-Efficacy Questionnaire will provide an external criterion to determine the psychometric adequacy of our self-report co-primary outcome, the BDI, in individuals with aphasia, given the possibility of serious deficits in understanding spoken instructions not ruled out during eligibility screening, as specified above.

A neuropsychologist blinded to group allocation will conduct all diagnostic sessions. The neuropsychologist will have substantial experience in communication with individuals suffering from aphasia-immanent comprehension problems. Testing will take place immediately before (baseline: T_1; BDI, HAM-D, and AAT) and within 24 hours after the 1-month treatment period (endpoint: T_2; BDI, HAM-D, AAT, and Self-Efficacy Questionnaire).

References

1 Lewinsohn PM. A behavioral approach to depression. Friedman RJ, Katz MM, editors. In: *Psychology of Depression: Contemporary Theory and Research*. Wiley; 1974. p. 157–178.

2 Carson AJ, MacHale S, Allen K, Lawrie SM, Dennis M, House A, Sharpe M. Depression after stroke and lesion location: A systematic review. *Lancet.* 2000; 356:122–126. doi: 10.1016/s0140-6736(00)02448-x

3 Bhogal SK, Teasell R, Foley N, Speechley M. Lesion location and poststroke depression: Systematic review of the methodological limitations in the literature. *Stroke.* 2004; 35:794–802. doi: 10.1161/01.str.0000117237.98749.26

4 Robinson RG, Jorge RE. Post-stroke depression: A review. *Am J Psychiatry.* 2016; 173:221–231. doi: 10.1176/appi.ajp.2015.15030363

5 World Health Organization. *International Classification of Diseases for Mortality and Morbidity Statistics: 11th Revision*. World Health Organization; 2019.

6 Hackett ML, Pickles K. Frequency of depression after stroke: An updated systematic review and meta-analysis of observational studies. *Int J Stroke.* 2014; 9:1017–1025. doi: 10.1111/ijs.12357

7 Chun HYY, Ford A, Almeida OP, Mead GE. Depression, anxiety, and suicide after stroke: A narrative review of the best available evidence. *Stroke.* 2022; 53:1402–1410. doi: 10.1161/strokeaha.121.035499

8 Zanella C, Laures-Gore J, Dotson VM, Belagaje SR. Incidence of post-stroke depression symptoms and potential risk factors in adults with aphasia in a comprehensive stroke center. *Top Stroke Rehabil.* 2022. doi: 10.1080/10749357.2022.2070363

9 Wang S, Wang CX, Zhang N, Xiang YT, Yang Y, Shi YZ, Deng YM, Zhu MF, Liu F, Yu P, et al. The association between post-stroke depression, aphasia, and physical independence in stroke patients at 3-month follow-up. *Front Psychiatry.* 2018; 10:3389. doi: 10.3389/fpsyt.2018.00374

10 Allida S, Cox KL, Hsieh CF, Lang H, House A, Hackett ML. Pharmacological, psychological and non-invasive brain stimulation interventions for preventing depression after stroke. *Cochrane Database Syst Rev.* 2020; 5:CD003689. doi: 10.1002/14651858.cd003437.pub4

11 Thomas SA, Walker MF, Macniven JA, Haworth H, Lincoln NB. Communication and low mood (CALM): A randomized controlled trial of behavioural therapy for stroke patients with aphasia. *Clin Rehabil.* 2013; 27:398–408. doi: 10.1177/0269215512462227

12 Thomas SA, Drummond AER, Lincoln NB, Palmer RL, das Nair R, Latimer NR, Hackney GL, Mandefield L, Walters SJ, Hatton RD, et al. Behavioural activation therapy for post-stroke depression: The BEADS feasibility RCT. *Health Technol Assess.* 2019; 23:1–176. doi: 10.3310/hta23470

13 Hilari K, Behn N, James K, Northcott S, Marshall J, Thomas S, Simpson A, Moss B, Flood C, McVicker S, et al. Supporting wellbeing through peer-befriending (SUPERB) for people with aphasia: A feasibility randomised controlled trial. *Clin Rehabil.* 2021; 35:1151–1163. doi: 10.1177/0269215521995671

14 Stahl B. *Music and Social Interaction in the Treatment of Post-Stroke Aphasia*. Technische Universität Dresden; 2021. doi: 10.25368/2021.69

15 Särkämö T, Tervaniemi M, Laitinen S, Forsblom A, Soinila S, Mikkonen M, Autti T, Silvennoinen HM, Erkkilä J, Laine M, et al. Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. *Brain.* 2008; 131:866–876. doi: 10.1093/brain/awn013

16 Baylan S, Haig C, MacDonald M, Stiles C, Easto J, Thomson M, Cullen B, Quinn TJ, Stott D, Mercer SW, et al. Measuring the effects of listening for leisure on outcome after stroke (MELLO): A pilot randomized controlled trial of mindful music listening. *Int J Stroke.* 2020; 15:149–158. doi: 10.1177/1747493019841250

17 Sihvonen AJ, Leo V, Ripollés P, Lehtovaara T, Ylönen A, Rajanaro P, Laitinen S, Forsblom A, Saunavaara J, Autti T, et al. Vocal music enhances memory and language

recovery after stroke: Pooled results from two RCTs. *Ann Clin Transl Neurol.* 2020; 7:2272–2287. doi: 10.1002/acn3.51217

18 Difrancesco S, Pulvermüller F, Mohr B. Intensive Language-Action Therapy (ILAT): The methods. *Aphasiology.* 2012; 26:1317–1351. doi: 10.1080/02687038.2012.705815

19 Stahl B, Mohr B, Dreyer FR, Lucchese G, Pulvermüller F. Using language for social interaction: Communication mechanisms promote recovery from chronic non-fluent aphasia. *Cortex.* 2016; 85:90–99. doi: 10.1016/j.cortex.2016.09.021

20 Mohr B, Stahl B, Berthier ML, Pulvermüller F. Intensive communicative therapy reduces symptoms of depression in chronic non-fluent aphasia. *Neurorehabil Neural Repair.* 2017; 31:1053–1062. doi: 10.1177/1545968317744275

21 Stokman-Meiland DCM, Groeneveld IF, Arwert HJ, van der Pas SL, Meesters JJL, Mishre RDR, Vliet Vlieland TPM, Goossens PH. The course of depressive symptoms in the first 12 months post-stroke and its association with unmet needs. *Disabil Rehabil.* 2022; 44:428–435. doi: 10.1080/09638288.2020.1769746

22 Franklin S, Harhen D, Hayes M, Demos Mc Manus S, Pollock A. Top 10 research priorities relating to aphasia following stroke. *Aphasiology.* 2018; 32:1388–1395. doi: 10.1080/02687038.2017.1417539

23 Stahl B, Mohr B, Büscher V, Dreyer FR, Lucchese G, Pulvermüller F. Efficacy of intensive aphasia therapy in patients with chronic stroke: A randomised controlled trial. *J Neurol Neurosurg Psychiatry.* 2018; 89:586–592. doi: 10.1136/jnnp-2017-315962

24 Pulvermüller F, Neininger B, Elbert T, Mohr B, Rockstroh B, Koebbel P, Taub E. Constraint-induced therapy of chronic aphasia after stroke. *Stroke.* 2001; 32:1621–1626. doi: 10.1161/01.str.32.7.1621

25 Meinzer M, Djundja D, Barthel G, Elbert T, Rockstroh B. Long-term stability of improved language functions in chronic aphasia after Constraint-Induced Aphasia Therapy. *Stroke.* 2005; 36:1462–1466. doi: 10.1161/01.str.0000169941.29831.2a

26 Meinzer M, Streiftau S, Rockstroh B. Intensive language training in the rehabilitation of chronic aphasia: Efficient training by laypersons. *J Int Neuropsychol Soc.* 2007; 13:846–853. doi: 10.1017/s1355617707071111

27 Berthier ML, Green C, Lara JP, Higueras C, Barbancho MA, Dávila G, Pulvermüller F. Memantine and Constraint-Induced Aphasia Therapy in chronic poststroke aphasia. *Ann Neurol.* 2009; 65:577–585. doi: 10.1002/ana.21597

28 Szaflarski JP, Ball AL, Vannest J, Dietz AR, Allendorfer JB, Martin AN, Hart K, Lindsell CJ. Constraint-Induced Aphasia Therapy for treatment of chronic post-stroke aphasia: A randomized, blinded, controlled pilot trial. *Med Sci Monit.* 2015; 21:2861–2869. doi: 10.12659/msm.894291

29 Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia.* 1971; 9:97–113. doi: 10.1016/0028-3932(71)90067-4

30 Richter K, Hielscher-Fastabend M. *Bielefelder Aphasie Screening Akut und Reha*. NAT-Verlag; 2018.

31 Kessels RP, van Zandvoort MJ, Postma A, de Haan EH. The Corsi Block-Tapping Task: Standardization and normative data. *Appl Neuropsychol.* 2000; 7:252–258. doi: 10.1207/s15324826an0704_8

32 Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods.* 2009; 41:1149–1160. doi: 10.3758/brm.41.4.1149

33 Breitenstein C, Grewe T, Flöel A, Ziegler W, Springer L, Martus P, Huber W, Willmes K, Ringelstein EB, Haeusler KG, et al. Intensive speech and language therapy in patients with chronic aphasia after stroke: A randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *Lancet.* 2017; 389:1528–1538. doi: 10.1016/s0140-6736(17)30067-3

34 Schmitt M, Beckmann M, Dusi D, Maes J, Schiller A, Schonauer K. Messgüte des vereinfachten Beck-Depressions-Inventars (BDI-V). *Diagnostica.* 2003; 49:147–156. doi: 10.1026//0012-1924.49.4.147

35 McIntyre RS, Konarski JZ, Mancini DA, Fulton KA, Parikh SV, Grigoriadis S, Grupp LA, Bakish D, Filteau MJ, Gorman C, et al. Measuring the severity of depression and remission in primary care: Validation of the HAMD-7 scale. *CMAJ.* 2005; 173:1327–1334. doi: 10.1503/cmaj.050786

36 Huber W, Poeck K, Willmes K. The Aachen Aphasia Test. *Adv Neurol.* 1984; 42:291–303.

37 Schwarzer R, Jerusalem M. *Skalen zur Erfassung von Lehrer- und Schülermerkmalen. Dokumentation der psychometrischen Verfahren im Rahmen der Wissenschaftlichen Begleitung des Modellversuchs Selbstwirksame Schulen*. Freie Universität Berlin; 1999.

38 Rimm H, Jerusalem M. Adaptation and validation of an Estonian version of the General Self-Efficacy Scale (ESES). *Anxiety Stress Coping.* 1999; 12:329–345. doi: 10.1080/10615809908250481