# Hitting the right nerve: effects of transcutaneous vagus nerve stimulation on symptoms of anxiety

Burger, A.M.

# Curriculum Vitae

Andreas Burger was born in Reutlingen, Germany on the 23rd of December 1989. His family moved to Hoofddorp, The Netherlands, in 1990. Andreas finished high school at the Katholieke Scholengemeenschap Hoofddorp in 2008, and started his Bachelor's degree in Psychology at Leiden University later that year. In the third year of his Bachelor, he moved to Scotland, to spend one semester studying Psychology and Philosophy at the University of Glasgow. Afterwards, he finished his Bachelor's in Leiden and started a Research Master Clinical, Health and Neuropsychology at Leiden University.

During his Master's, Andreas completed a research internship at the Chronobiology department of PsyQ in The Hague, under the supervision of Dr. Judith Haffmans and Tess Naus, studying the clinical applicability of bright light therapy for patients suffering from Bipolar Disorder. Afterwards, he completed a clinical internship at the Anxiety and Chronobiology departments of PsyQ The Hague, under the supervision of Margreet Blaauw and Dr. Judith Haffmans. After graduation in 2014, Andreas continued working as a junior researcher at the Chronobiology department of PsyQ The Hague for half a year, before starting his PhD project.

In November 2014, Andreas started his PhD project at the department of Clinical Psychology at Leiden University, under the supervision of Prof. Dr. Willem van der Does, Prof. Dr. Jos Brosschot, and Dr. Bart Verkuil. During his PhD, Andreas spent three months at the KU Leuven, to further strengthen the collaboration with Prof. Dr. Ilse Van Diest and her lab. He finished his PhD project in November 2018 and started a postdoctoral position at the KU Leuven in Belgium, under the supervision of Prof. Dr. Ilse Van Diest.

# Publications

**Burger, A.M.**, Van der Does, W., Thayer, J.F., Brosschot, J.F., Verkuil, B., 2019. Transcutaneous vagus nerve stimulation reduces spontaneous but not induced negative thought intrusions in high worriers. Biol. Psychol. 142, 80–89. https://doi.org/10.1016/j.biopsycho.2019.01.014

Verkuil, B., **Burger, A.M.**, 2019. Transcutaneous vagus nerve stimulation does not affect attention to fearful faces in high worriers. Behav. Res. Ther. 113, 25–31. https://doi.org/10.1016/j.brat.2018.12.009

**Burger, A.M.**, Van Diest, I., van der Does, W., Hysaj, M., Thayer, J.F., Brosschot, J.F., Verkuil, B., 2018. Transcutaneous vagus nerve stimulation and extinction of prepared fear: A conceptual non-replication. Sci. Rep. 8, 11471. https://doi.org/10.1038/s41598-018-29561-w

**Burger, A.M.**, Verkuil, B., 2018. Transcutaneous nerve stimulation via the tragus: are we really stimulating the vagus nerve? Brain Stimul. 11, 945–946. https://doi.org/10.1016/j.brs.2018.03.018

**Burger, A.M.**, Verkuil, B., Fenlon, H., Thijs, L., Cools, L., Miller, H.C., Vervliet, B., Van Diest, I., 2017. Mixed evidence for the potential of non-invasive transcutaneous vagal nerve stimulation to improve the extinction and retention of fear. Behav. Res. Ther. 97, 64–74. https://doi.org/10.1016/j.brat.2017.07.005

**Burger, A.M.**, Verkuil, B., Van Diest, I., Van der Does, W., Thayer, J.F., Brosschot, J.F., 2016. The effects of transcutaneous vagus nerve stimulation on conditioned fear extinction in humans. Neurobiol. Learn. Mem. 132, 49–56. https://doi.org/10.1016/j.nlm.2016.05.007

Roopram, S.M., **Burger, A.M.**, van Dijk, D.A., Enterman, J., Haffmans, J., 2016. A pilot study of bright light therapy in schizophrenia. Psychiatry Res. 245, 317–320. https://doi.org/10.1016/j.psychres.2016.07.034

Mossink, J.C.L., Verkuil, B., **Burger, A.M.**, Tollenaar, M.S., Brosschot, J.F., 2015. Ambulatory assessed implicit affect is associated with salivary cortisol. Front. Psychol. 6, 1–10. https://doi.org/10.3389/fpsyg.2015.00111

Naus, T., **Burger, A.M.**, Malkoc, A., Molendijk, M., Haffmans, J., 2013. Is there a difference in clinical efficacy of bright light therapy for different types of depression? A pilot study. J. Affect. Disord. 151, 1135–7. https://doi.org/10.1016/j.jad.2013.07.017

# References


[1] Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychol Med 2013:897–910. doi:10.1017/S003329171200147X.

[2] Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2009;62:593–602. doi:10.1001/archpsyc.62.6.593.

[3] Whiteford H a., Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. Lancet 2013;382:1575–86. doi:10.1016/S0140-6736(13)61611-6.

[4] Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jönsson B. The economic cost of brain disorders in Europe. Eur J Neurol 2012;19:155–62. doi:10.1111/j.1468-1331.2011.03590.x.

[5] Schottenbauer MA, Glass CR, Arnkoff DB, Tendick V, Gray SH. Nonresponse and Dropout Rates in Outcome Studies on PTSD: Review and Methodological Considerations. Psychiatry Interpers Biol Process 2008;71:134–68. doi:10.1521/psyc.2008.71.2.134.

[6] Bados A, Balaguer G, Saldaña C. The efficacy of cognitive–behavioral therapy and the problem of drop-out. J Clin Psychol 2007;63:585–92. doi:10.1002/jclp.20368.

[7] Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds CF. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: A meta-analysis. World Psychiatry 2014;13:56–67. doi:10.1002/wps.20089.

[8] Bandelow B, Reitt M, Röver C, Michaelis S, Görlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. Int Clin Psychopharmacol 2015;30:183–92. doi:10.1097/YIC.0000000000000078.

[9] Tolin DF. Can Cognitive Behavioral Therapy for Anxiety and Depression Be Improved with Pharmacotherapy? A Meta-analysis. Psychiatr Clin North Am 2017;40:715–38. doi:10.1016/j.psc.2017.08.007.

[10] Marin MF, Camprodon JA, Dougherty DD, Milad MR. Device-based brain stimulation to augment fear extinction: Implications for ptsd treatment and beyond. Depress Anxiety 2014;31:269–78. doi:10.1002/da.22252.

[11] Yuan H, Silberstein SD. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part I. Headache 2016;56:71–8. doi:10.1111/head.12647.

[12] Ruffoli R, Giorgi FS, Pizzanelli C, Murri L, Paparelli A, Fornai F. The chemical neuroanatomy of vagus nerve stimulation. J Chem Neuroanat 2011;42:288–96. doi:10.1016/j.jchemneu.2010.12.002.

[13] Waldman S. Chapter 11 - The Vagus Nerve—Cranial Nerve X. Pain Rev., 2009, p. 29–34. doi:10.1016/B978-1-4160-5893-9.00011-3.

[14] Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. Auton Neurosci 2000;85:1–17. doi:10.1016/S1566-0702(00)00215-0.

[15] Ardell JL, Randall WC. Selective vagal innervation of sinoatrial and atrioventricular nodes in canine heart. Am J Physiol 1986;251:H764-73.

[16] Pelleg A, Hurt CM, Soler-Baillo JM, Polansky M. Electrophysiological-anatomic correlates of ATP-triggered vagal reflex in dogs. AmJPhysiol 1993;265:H681–90. doi:10.1152/ajpheart.1994.267.3.H1093.

[17] Yuan H, Silberstein SD. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part II. Headache 2016;56:259–66. doi:10.1111/head.12650.

[18] Agostoni E, Chinnock JE, Daly MDB, Murray JG. Functional and histological studies of the vagus nerve and its branches to the heart, lungs and abdominal viscera in the cat. J Physiol 1957;135:182–205. doi:10.1113/jphysiol.1957.sp005703.

[19] Foley J, Dubois FS. Quantitative Studies of the Vagus Nerve in the Cat. J Comp Neurol 1936;67:49–67. doi:10.1002/cne.900670104.

[20] Longhurst JC, Fu L-W. Cardiac and Other Visceral Afferents. Prim Auton Nerv Syst 2012:171–6. doi:10.1016/B978-0-12-386525-0.00035-4.

[21] Engel D. The Gastroauricular Phenomenon and Related Vagus Reflexes. Arch Für Psychiatr Und Nervenkrankheiten 1979;277:271–7.

[22] Gupta D, Verma S, Vishwakarma SK. Anatomic basis of Arnold's ear-cough reflex. Surg Radiol Anat 1986;8:217–20. doi:10.1007/BF02425070.

[23] Sherrington CS. Experiments in examination of the peripheral distribution of the fibres of the posterior roots of some spinal nerves. - Part II. Philos Trans R Soc London Ser B, Contain Pap a Biol Character 1897.

[24] Fay T. Observations and results from intracranial section of the glossopharyngeus and vagus nerves in man. J Neurol Neurosurg Psychiatry 1927;S1-8:110–23. doi:10.1136/jnnp.s1-8.30.110.
[25] Peuker ET, Filler TJ. The nerve supply of the human auricle. Clin Anat 2002;15:35–7. doi:10.1002/ca.1089.
[26] Burger AM, Verkuil B. Transcutaneous nerve stimulation via the tragus: are we really stimulating the vagus nerve? Brain Stimul 2018;11:945–6. doi:10.1016/j.brs.2018.03.018.
[27] He W, Jing X-H, Zhu B, Zhu X-L, Li L, Bai W-Z, et al. The auriculo-vagal afferent pathway and its role in seizure suppression in rats. BMC Neurosci 2013;14:1. doi:10.1186/1471-2202-14-85.
[28] Nomura S, Mizuno N. Central distribution of primary afferent fibers in the Arnold's nerve (the auricular branch of the vagus nerve): A transganglionic HRP study in the cat. Brain Res 1984;292:199–205. doi:10.1016/0006-8993(84)90756-X.
[29] Safi S, Ellrich J, Neuhuber W. Myelinated Axons in the Auricular Branch of the Human Vagus Nerve. Anat Rec 2016;299:1184–91. doi:10.1002/ar.23391.
[30] Blackshaw LA, Grundy D. Effects of cholecystokinin (CCK-8) on two classes of gastroduodenal vagal afferent fibre. J Auton Nerv Syst 1990;31:191–201. doi:10.1016/0165-1838(90)90185-L.
[31] Page AJ, Martin CM, Blackshaw LA. Vagal Mechanoreceptors and Chemoreceptors in Mouse Stomach and Esophagus. J Neurophysiol 2002;87:2095–103. doi:10.1152/jn.00785.2001.
[32] Ben-Menachem E. Vagus Nerve Stimulation, Side Effects, and Long-Term Safety. J Clin Neurophysiol 2001;18:415–8. doi:10.1097/00004691-200109000-00005.
[33] Corning JL. Electrization of the Sympathetic and pneumogastric nerves, with simultaneous bilateral compression of the carotids. New York Med J 1884;39:212–5.
[34] Lanska DJ. J.L. Corning and vagal nerve stimulation for seizures in the 1880s. Neurology 2002;58:452–9. doi:10.1212/WNL.58.3.452.
[35] Penry JK, Dean JC. Prevention of Intractable Partial Seizures by Intermittent Vagal Stimulation in Humans: Preliminary Results. Epilepsia 1990;31:S40–3. doi:10.1111/j.1528-1157.1990.tb05848.x.
[36] Ventureyra ECG. Transcutaneous vagus nerve stimulation for partial onset seizure therapy. A new concept. Child's Nerv Syst 2000;16:101–2. doi:10.1007/s003810050021.
[37] Helmers SL, Begnaud J, Cowley A, Corwin HM, Edwards JC, Holder DL, et al. Application of a computational model of vagus nerve stimulation. Acta Neurol Scand 2012;126:336–43. doi:10.1111/j.1600-0404.2012.01656.x.
[38] Degiorgio CM, Thompson J, Lewis P, Arrambide S, Naritoku D, Handforth A, et al. Vagus nerve stimulation: Analysis of device parameters in 154 patients during the long-term XE5 study. Epilepsia 2001;42:1017–20. doi:10.1046/j.1528-1157.2001.0420081017.x.
[39] Mollet L, Grimonprez A, Raedt R, Delbeke J, El Tahry R, De Herdt V, et al. Intensity-dependent modulatory effects of vagus nerve stimulation on cortical excitability. Acta Neurol Scand 2013;128:391–6. doi:10.1111/ane.12135.
[40] Larsen LE, Wadman WJ, Marinazzo D, van Mierlo P, Delbeke J, Daelemans S, et al. Vagus Nerve Stimulation Applied with a Rapid Cycle Has More Profound Influence on Hippocampal Electrophysiology Than a Standard Cycle. Neurotherapeutics 2016:1–11. doi:10.1007/s13311-016-0432-8.
[41] Evans MS, Verma-Ahuja S, Naritoku DK, Espinosa JA. Intraoperative human vagus nerve compound action potentials. Acta Neurol Scand 2004;110:232–8. doi:10.1111/j.1600-0404.2004.00309.x.
[42] Binks AP, Paydarfar D, Schachter SC, Guz A, Banzett RB. High strength stimulation of the vagus nerve in awake humans: A lack of cardiorespiratory effects. Respir Physiol 2001;127:125–33. doi:10.1016/S0034-5687(01)00252-3.
[43] Heck C, Helmers SL, DeGiorgio CM. Vagus nerve stimulation therapy, epilepsy and device parameters. Neurology 2002;59:S31–7. doi:10.1212/WNL.59.6.
[44] Tehovnik E. Electrical stimulation of neural tissue to evoke behavioral responses. TL - 65. J Neurosci Methods 1996;65 VN-r:1–17. doi:10.1016/0165-0270(95)00131-X.
[45] Chen CC, Williams CL. Interactions between epinephrine, ascending vagal fibers, and central noradrenergic systems in modulating memory for emotionally arousing events. Front Behav Neurosci 2012;6:35. doi:10.3389/fnbeh.2012.00035.
[46] King SO, Williams CL. Novelty-induced arousal enhances memory for cued classical fear conditioning: interactions between peripheral adrenergic and brainstem glutamatergic systems. Learn Mem 2009;16:625–34. doi:10.1101/lm.1513109.
[47] Miyashita T, Williams CL. Epinephrine administration increases neural impulses propagated along the vagus nerve : Role of peripheral -adrenergic receptors. Neurobiol Learn Mem 2006;85:116–24. doi:10.1016/j.nlm.2005.08.013.

[48] Klarer M, Arnold M, Günther L, Winter C, Langhans W, Meyer U. Gut vagal afferents differentially modulate innate anxiety and learned fear. J Neurosci 2014;34:7067–76. doi:10.1523/JNEUROSCI.0252-14.2014.
[49] McIntyre CK. Is there a role for vagus nerve stimulation in the treatment of posttraumatic stress disorder? Bioelectron Med 2018;1:95–9. doi:10.2217/bem-2018-0002.
[50] Peña DF, Childs JE, Willett S, Vital A, McIntyre CK, Kroener S. Vagus nerve stimulation enhances extinction of conditioned fear and modulates plasticity in the pathway from the ventromedial prefrontal cortex to the amygdala. Front Behav Neurosci 2014;8:327. doi:10.3389/fnbeh.2014.00327.
[51] Peña DF, Engineer ND, McIntyre CK. Rapid remission of conditioned fear expression with extinction training paired with vagus nerve stimulation. Biol Psychiatry 2013;73:1071–7. doi:10.1016/j.biopsych.2012.10.021.
[52] Noble LJ, Gonzalez IJ, Meruva VB, Callahan KA, Belfort BD, Ramanathan KR, et al. Effects of vagus nerve stimulation on extinction of conditioned fear and post-traumatic stress disorder symptoms in rats. Transl Psychiatry 2017;7:e1217. doi:10.1038/tp.2017.191.
[53] Alvarez-Dieppa AAC, Griffin K, Cavalier S, Mcintyre CK. Vagus nerve stimulation enhances extinction of conditioned fear in rats and modulates Arc protein, CaMKII, and GluN2B-containing NMDA receptors in the basolateral amygdala. Neural Plast 2016:1–19.
[54] De Houwer J, Thomas S, Baeyens F. Associative learning of likes and dislikes: a review of 25 years of research on human evaluative conditioning. Psychol Bull 2001;127:853–69.
[55] Mitchell CJ, De Houwer J, Lovibond PF. The propositional nature of human associative learning. Behav Brain Sci 2009;32:183-198+238-246. doi:10.1017/S0140525X09000855.
[56] Lovibond PF, Shanks DR. The role of awareness in Pavlovian conditioning: Empirical evidence and theoretical implications. J Exp Psychol Anim Behav Process 2002;28:3–26. doi:10.1037//0097-7403.28.1.3.
[57] Mineka S, Zinbarg R. A contemporary learning theory perspective on the etiology of anxiety disorders: It's not what you thought it was. Am Psychol 2006;61:10–26. doi:10.1037/0003-066X.61.1.10.
[58] Rescorla RA, Wagner AR. A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. Class Cond II Curr Res Theory 1972;21:64–99. doi:10.1101/gr.110528.110.
[59] Askew C, Field AP. The vicarious learning pathway to fear 40 years on. Clin Psychol Rev 2008;28:1249–65. doi:10.1016/j.cpr.2008.05.003.
[60] Rachman S. The conditioning theory of fear acquisition: A critical examination. Behav Res Ther 1977;15:375–87. doi:10.1016/0005-7967(77)90041-9.
[61] Craske MG, Treanor M, Conway C, Zbozinek T, Vervliet B. Maximizing Exposure Therapy : An Inhibitory Learning Approach. Behav Res Ther 2014;58:10–23. doi:10.1016/j.brat.2014.04.006.Maximizing.
[62] Grillon C. Models and mechanisms of anxiety: Evidence from startle studies. Psychopharmacology (Berl) 2008;199:421–37. doi:10.1007/s00213-007-1019-1.
[63] Bouton M, Mineka S, Barlow D. A contemporary learning theory perspective on the etiology of panic disorder. Psychol Rev 2001;108:4–32. doi:10.1037//0033-295X.108.1.4.
[64] Thayer J, Lane R. Claude Bernard and the heart-brain connection: Further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev 2009;33:81–8. doi:10.1016/j.neubiorev.2008.08.004.
[65] Thayer J, Friedman B, Borkovec T, Johnsen B, Molina S. Phasic heart period reactions to cued threat and nonthreat stimuli in generalized anxiety disorder. Psychophysiology 2000;37:361–8. doi:10.1111/1469-8986.3730361.
[66] Thayer J, Brosschot J. Psychosomatics and psychopathology: looking up and down from the brain. Psychoneuroendocrinology 2005;30:1050–8. doi:10.1016/j.psyneuen.2005.04.014.
[67] Verkuil B, Brosschot J, Gebhardt W, Thayer J. When Worries Make You Sick: A Review of Perseverative Cognition, the Default Stress Response and Somatic Health. J Exp Psychopathol 2010;1:87–118. doi:10.5127/jep.009110.
[68] Thayer J, Lane R. Perseverative Thinking and Health: Neurovisceral Concomitants. Psychol Health 2002;17:685–95. doi:10.1080/08870440290025867.
[69] Gillie BL, Thayer JF. Individual differences in resting heart rate variability and cognitive control in posttraumatic stress disorder. Front Psychol 2014;5:758. doi:10.3389/fpsyg.2014.00758.
[70] Chalmers J, Quintana D, Abbott M, Kemp A. Anxiety Disorders are Associated with Reduced Heart Rate Variability: A Meta-Analysis. Front Psychiatry 2014;5:1–11. doi:10.3389/fpsyt.2014.00080.
[71] Chalmers J, Heathers J, Abbott M, Kemp A, Quintana D. Worry is associated with robust reductions in heart rate variability: a transdiagnostic study of anxiety psychopathology. BMC Psychol 2016;4:32.

doi:10.1186/s40359-016-0138-z.
[72] Brosschot JF, Van Dijk E, Thayer JF. Daily worry is related to low heart rate variability during waking and the subsequent nocturnal sleep period. Int J Psychophysiol 2007;63:39–47. doi:10.1016/j.ijpsycho.2006.07.016.
[73] Ottaviani C, Watson D, Meeten F, Makovac E, Garfinkel S, Critchley H. Neurobiological substrates of cognitive rigidity and autonomic inflexibility in generalized anxiety disorder. Biol Psychol 2016;119:31–41. doi:10.1016/j.biopsycho.2016.06.009.
[74] Ottaviani C, Shapiro D, Couyoumdjian A. Flexibility as the key for somatic health: From mind wandering to perseverative cognition. Biol Psychol 2013;94:38–43. doi:10.1016/j.biopsycho.2013.05.003.
[75] Levine JC, Fleming R, Piedmont JI, Cain SM, Chen WJ. Heart rate variability and generalized anxiety disorder during laboratory-induced worry and aversive imagery. J Affect Disord 2016;205:207–15. doi:10.1016/j.jad.2016.07.019.
[76] Llera SJ, Newman MG. Effects of worry on physiological and subjective reactivity to emotional stimuli in generalized anxiety disorder and nonanxious control participants. Emotion 2010;10:640–50. doi:10.1037/a0019351.
[77] Verkuil B, Brosschot J, Borkovec T, Thayer J. Acute autonomic effects of experimental worry and cognitive problem solving: Why worry about worry? Int J Clin Heal Psychol 2009;9:439–53.
[78] Pieper S, Brosschot JF, van der Leeden R, Thayer JF. Prolonged cardiac effects of momentary assessed stressful events and worry episodes. Psychosom Med 2010;72:570–7. doi:10.1097/PSY.0b013e3181dbc0e9.
[79] Yakunina N, Kim SS, Nam E-C. Optimization of Transcutaneous Vagus Nerve Stimulation Using Functional MRI. Neuromodulation Technol Neural Interface 2017;20:290–300. doi:10.1111/ner.12541.
[80] Liu J, Fang J, Wang Z, Rong P, Hong Y, Fan Y, et al. Transcutaneous vagus nerve stimulation modulates amygdala functional connectivity in patients with depression. J Affect Disord 2016;205:319–26. doi:10.1016/j.jad.2016.08.003.
[81] Kim MJ, Loucks RA, Palmer AL, Brown AC, Solomon KM, Marchante AN, et al. The structural and functional connectivity of the amygdala: From normal emotion to pathological anxiety. Behav Brain Res 2011;223:403–10. doi:10.1016/j.bbr.2011.04.025.
[82] Liu W, Yin D, Cheng W, Fang M, You M, Men W, et al. Abnormal Functional Connectivity of the Amygdala-Based Network in Resting-State fMRI in Adolescents with Generalized Anxiety Disorder. Med Sci Monit 2015;21:459–67. doi:10.12659/MSM.893373.
[83] Makovac E, Meeten F, Watson D, Herman A, Garfinkel S, Critchley H, et al. Alterations in Amygdala-Prefrontal Functional Connectivity Account for Excessive Worry and Autonomic Dysregulation in Generalized Anxiety Disorder. Biol Psychiatry 2016;80:786–95. doi:10.1016/j.biopsych.2015.10.013.
[84] Makovac E, Watson DR, Meeten F, Garfinkel SN, Cercignani M, Critchley HD, et al. Amygdala functional connectivity as a longitudinal biomarker of symptom changes in generalized anxiety. Soc Cogn Affect Neurosci 2016;11:1719–28. doi:10.1093/scan/nsw091.
[85] Vonck K, Raedt R, Naulaerts J, De Vogelaere F, Thiery E, Van Roost D, et al. Vagus nerve stimulation…25 years later! What do we know about the effects on cognition? Neurosci Biobehav Rev 2014;45C:63–71. doi:10.1016/j.neubiorev.2014.05.005.
[86] Jacobs HIL, Riphagen JM, Razat CM, Wiese S, Sack AT. Transcutaneous vagus nerve stimulation boosts associative memory in older individuals. Neurobiol Aging 2015;36:1860–7. doi:10.1016/j.neurobiolaging.2015.02.023.
[87] Steenbergen L, Sellaro R, Stock A, Verkuil B, Beste C, Colzato L. Transcutaneous vagus nerve stimulation (tVNS) enhances response selection during action cascading processes. Eur Neuropsychopharmacol 2015;25:773–8. doi:10.1016/j.euroneuro.2015.03.015.
[88] Sellaro R, Leusden J Van, Tona K, Verkuil B, Nieuwenhuis S, Colzato L. Transcutaneous Vagus Nerve Stimulation Enhances Post-error Slowing 2015:2126–32. doi:10.1162/jocn.
[89] Beste C, Steenbergen L, Sellaro R, Grigoriadou S, Zhang R, Chmielewski W, et al. Effects of Concomitant Stimulation of the GABAergic and Norepinephrine System on Inhibitory Control – A Study Using Transcutaneous Vagus Nerve Stimulation. Brain Stimul 2016. doi:10.1016/j.brs.2016.07.004.
[90] Price RB, Mohlman J. Inhibitory control and symptom severity in late life generalized anxiety disorder. Behav Res Ther 2007;45:2628–39. doi:10.1016/j.brat.2007.06.007.
[91] Rong P, Liu J, Wang L, Liu R, Fang J, Zhao J, et al. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: A nonrandomized controlled pilot study. J Affect Disord 2016;195:172–9. doi:10.1016/j.jad.2016.02.031.
[92] Fang J, Rong P, Hong Y, Fan Y, Liu J, Wang H, et al. Transcutaneous Vagus Nerve Stimulation Modulates

Default Mode Network in Major Depressive Disorder. Biol Psychiatry 2016;79:266–73. doi:10.1016/j.biopsych.2015.03.025.
[93] Ottaviani C, Shahabi L, Tarvainen M, Cook I, Abrams M, Shapiro D. Cognitive, behavioral, and autonomic correlates of mind wandering and perseverative cognition in major depression. Front Neurosci 2015;9:1–9. doi:10.3389/fnins.2014.00433.
[94] Grimonprez A, Raedt R, Baeken C, Boon P, Vonck K. The antidepressant mechanism of action of vagus nerve stimulation: Evidence from preclinical studies. Neurosci Biobehav Rev 2015;56:26–34. doi:10.1016/j.neubiorev.2015.06.019.
[95] Dorr AE, Debonnel G. Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. J Pharmacol Exp Ther 2006;318:890–8. doi:10.1124/jpet.106.104166.and.
[96] Groves DA, Bowman EM, Brown VJ. Recordings from the rat locus coeruleus during acute vagal nerve stimulation in the anaesthetised rat. Neurosci Lett 2005;379:174–9. doi:10.1016/j.neulet.2004.12.055.
[97] Manta S, El Mansari M, Debonnel G, Blier P. Electrophysiological and neurochemical effects of long-term vagus nerve stimulation on the rat monoaminergic systems. Int J Neuropsychopharmacol 2013;16:459–70. doi:10.1017/S1461145712000387.
[98] Hulsey DR, Riley JR, Loerwald KW, Rennaker RL, Kilgard MP, Hays SA. Parametric characterization of neural activity in the locus coeruleus in response to vagus nerve stimulation. Exp Neurol 2017;289:21–30. doi:10.1016/j.expneurol.2016.12.005.
[99] Manta S, Dong J, Debonnel G, Blier P. Enhancement of the function of rat serotonin and norepinephrine neurons by sustained vagus nerve stimulation. J Psychiatry Neurosci 2009;34:272–80.
[100] Grassi G, Esler M. How to assess sympathetic activity in humans. J Hypertens 1999;17:719–34. doi:10.1097/00004872-199917060-00001.
[101] Brázdil M, Chadim P, Daniel P, Kuba R, Rektor I, Novák Z, et al. Effect of vagal nerve stimulation on auditory and visual event-related potentials. Eur J Neurol 2001;8:457–61. doi:ene262 [pii].
[102] Desbeaumes Jodoin V, Lespérance P, Nguyen DK, Fournier-gosselin M, Richer F, Hospitalier C, et al. Effects of vagus nerve stimulation on pupillary function. Int J Psychophysiol 2015;98:455–9. doi:10.1016/j.ijpsycho.2015.10.001.
[103] Hammond EJ, Uthman BM, Reid SA, Wilder BJ. Electrophysiologic Studies of Cervical Vagus Nerve-Stimulation in Humans .2. Evoked-Potentials. Epilepsia 1992;33:1021–8. doi:10.1111/j.1528-1157.1992.tb01753.x.
[104] Schevernels H, van Bochove ME, De Taeye L, Bombeke K, Vonck K, Van Roost D, et al. The effect of vagus nerve stimulation on response inhibition. Epilepsy Behav 2016;64:171–9. doi:10.1016/j.yebeh.2016.09.014.
[105] Stewart RE, Chambless DL. Cognitive–behavioral therapy for adult anxiety disorders in clinical practice: A meta-analysis of effectiveness studies. J Consult Clin Psychol 2009;77:595–606. doi:10.1037/a0016032.
[106] Blechert J, Michael T, Vriends N, Margraf J, Wilhelm FH. Fear conditioning in posttraumatic stress disorder: Evidence for delayed extinction of autonomic, experiential, and behavioural responses. Behav Res Ther 2007;45:2019–33. doi:10.1016/j.brat.2007.02.012.
[107] Orr SP, Metzger LJ, Lasko NB, Macklin ML, Peri T, Pitman RK. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. J Abnorm Psychol 2000;109:290–8. doi:10.1037/0021-843X.109.2.290.
[108] Lissek S, Powers A, McClure E, Phelps E, Woldehawariat G, Grillon C, et al. Classical fear conditioning in the anxiety disorders: a meta-analysis. Behav Res Ther 2005;43:1391–424. doi:10.1016/j.brat.2004.10.007.
[109] Duits P, Cath DC, Lissek S, Hox JJ, Hamm AO, Engelhard IM, et al. Updated meta-analysis of classical fear conditioning in the anxiety disorders. Depress Anxiety 2015;32:239–53. doi:10.1002/da.22353.
[110] Singewald N, Schmuckermair C, Whittle N, Holmes A, Ressler KJ. Pharmacology & Therapeutics Pharmacology of cognitive enhancers for exposure-based therapy of fear , anxiety and trauma-related disorders. Pharmacol Ther 2015;149:150–90. doi:10.1016/j.pharmthera.2014.12.004.
[111] Hermans D, Craske MG, Mineka S, Lovibond PF. Extinction in human fear conditioning. Biol Psychiatry 2006;60:361–8. doi:10.1016/j.biopsych.2005.10.006.
[112] Berlau DJ, McGaugh JL. Enhancement of extinction memory consolidation: the role of the noradrenergic and GABAergic systems within the basolateral amygdala. Neurobiol Learn Mem 2006;86:123–32. doi:10.1016/j.nlm.2005.12.008.
[113] Mueller D, Cahill SP. Noradrenergic modulation of extinction learning and exposure therapy. Behav Brain Res 2010;208:1–11. doi:10.1016/j.bbr.2009.11.025.

[114] McIntyre CK, McGaugh JL, Williams CL. Interacting brain systems modulate memory consolidation. Neurosci Biobehav Rev 2012;36:1750–62. doi:10.1016/j.neubiorev.2011.11.001.
[115] Hassert DL, Miyashita T, Williams CL. The effects of peripheral vagal nerve stimulation at a memory-modulating intensity on norepinephrine output in the basolateral amygdala. Behav Neurosci 2004;118:79–88. doi:10.1037/0735-7044.118.1.79.
[116] Clark KB, Smith DC, Hassert DL, Browning RA. Posttraining Electrical Stimulation of Vagal Afferents with Concomitant Vagal Efferent Inactivation Enhances Memory Storage Processes in the Rat 1998;373:364–73.
[117] Groves D a, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Biobehav Rev 2005;29:493–500. doi:10.1016/j.neubiorev.2005.01.004.
[118] Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord 2000;61:201–16.
[119] Nemeroff CB, Mayberg HS, Krahl SE, McNamara J, Frazer A, Henry TR, et al. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. Neuropsychopharmacology 2006;31:1345–55. doi:10.1038/sj.npp.1301082.
[120] George MS, Ward HE, Ninan PT, Pollack M, Nahas Z, Anderson B, et al. A pilot study of vagus nerve stimulation (VNS) for treatment-resistant anxiety disorders. Brain Stimul 2008;1:112–21. doi:10.1016/j.brs.2008.02.001.
[121] Kreuzer PM, Landgrebe M, Husser O, Resch M, Schecklmann M, Geisreiter F, et al. Transcutaneous vagus nerve stimulation: retrospective assessment of cardiac safety in a pilot study. Front Psychiatry 2012;3:70. doi:10.3389/fpsyt.2012.00070.
[122] Frangos E, Ellrich J, Komisaruk BR. Non-invasive Access to the Vagus Nerve Central Projections via Electrical Stimulation of the External Ear: fMRI Evidence in Humans. Brain Stimul 2014;8:624–36. doi:10.1016/j.brs.2014.11.018.
[123] Kraus T, Hösl K, Kiess O, Schanze A, Kornhuber J, Forster C. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. J Neural Transm 2007;114:1485–93. doi:10.1007/s00702-007-0755-z.
[124] Hartley C a, Phelps E a. Changing fear: the neurocircuitry of emotion regulation. Neuropsychopharmacology 2010;35:136–46. doi:10.1038/npp.2009.121.
[125] Soeter M, Kindt M. Dissociating response systems: erasing fear from memory. Neurobiol Learn Mem 2010;94:30–41. doi:10.1016/j.nlm.2010.03.004.
[126] Squire L, Stark C, Clark R. The medial temporal lobe. Annu Rev Neurosci 2004;27:279–306. doi:10.1146/annurev.neuro.27.070203.144130.
[127] Marek R, Strobel C, Bredy TW, Sah P. The amygdala and medial prefrontal cortex: partners in the fear circuit. J Physiol 2013;591:2381–91. doi:10.1113/jphysiol.2012.248575.
[128] Vervliet B, Vansteenwegen D, Baeyens F, Hermans D, Eelen P. Return of fear in a human differential conditioning paradigm caused by a return to the original acquistion context. Behav Res Ther 2005;43:323–36. doi:10.1016/j.brat.2004.01.001.
[129] Bradley MM, Lang PJ. International affective digitized sounds (IADS): Stimuli, instruction manual and affective ratings (Tech. Rep. No. B-2). Gainesville, FL: 1999.
[130] Kindt M, Soeter M, Vervliet B. Beyond extinction: erasing human fear responses and preventing the return of fear. Nat Neurosci 2009;12:256–8. doi:10.1038/nn.2271.
[131] Blumenthal TD, Cuthbert BN, Filion DL, Hackley S, Lipp O V., Van Boxtel A. Committee report: Guidelines for human startle eyeblink electromyographic studies. Psychophysiology 2005;42:1–15. doi:10.1111/j.1469-8986.2005.00271.x.
[132] Hamm A, Vaitl D. Affective learning: Awareness and aversion. Psychophysiology 1996;33:698–710. doi:10.1111/j.1469-8986.1996.tb02366.x.
[133] Bradley MM, Codispoti M, Cuthbert BN, Lang PJ. Emotion and motivation I: Defensive and appetitive reactions in picture processing. Emotion 2001;1:276–98. doi:10.1037/1528-3542.1.3.276.
[134] Van Diest I, Bradley M, Guerra P, Van den Bergh O, Lang P. Fear-conditioned respiration and its association to cardiac reactivity. Biol … 2009;80:212–7. doi:10.1016/j.biopsycho.2008.09.006.Fear.
[135] Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State Worry Questionnaire. Behav Res Ther 1990;28:487–95. doi:10.1016/0005-7967(90)90135-6.
[136] Verkuil B, Brosschot J, Thayer J. Capturing worry in daily life: Are trait questionnaires sufficient? Behav Res Ther 2007;45:1835–44. doi:10.1016/j.brat.2007.02.004.
[137] van der Ploeg HM. De Zelf-Beoordelings Vragenlijst (STAI-DY). De ontwikkeling en validatie van een

Nederlandstalige vragenlijst voor het meten van angst. Tijdschr Psychiatr 1982;24:576–88.
[138] Spielberger CD, Gorsuch RL, Lushene RE. STAI Manual for the State-Trait Anxiety Inventory. Palo Alto: Consulting Psychologists Press; 1970.
[139] Barnes LLB, Harp D, Jung WS. Reliability Generalization of Scores on the Spielberger State-Trait Anxiety Inventory. Educ Psychol Meas 2002;62:603–18. doi:10.1177/0013164402062004005.
[140] Lissek S, Pine DS, Grillon C. The strong situation: a potential impediment to studying the psychobiology and pharmacology of anxiety disorders. Biol Psychol 2006;72:265–70. doi:10.1016/j.biopsycho.2005.11.004.
[141] Wendt J, Neubert J, Koenig J, Thayer J, Hamm A. Resting heart rate variability is associated with inhibition of conditioned fear. Psychophysiology 2015;52:1161–6. doi:10.1111/psyp.12456.
[142] Van Der Heiden C, Muris P, Bos AER, Van Der Molen H, Oostra M. Normative data for the Dutch version of the Penn State Worry Questionnaire. Neth J Psychol 2009;65:69–75. doi:10.1007/BF03080129.
[143] Crawford J, Cayley C, Lovibond PF, Wilson PH, Hartley C. Percentile Norms and Accompanying Interval Estimates from an Australian General Adult Population Sample for Self-Report Mood Scales (BAI, BDI, CRSD, CES-D, DASS, DASS-21, STAI-X, STAI-Y, SRDS, and SRAS). Aust Psychol 2011;46:3–14. doi:10.1111/j.1742-9544.2010.00003.x.
[144] Follesa P, Biggio F, Gorini G, Caria S, Talani G, Dazzi L, et al. Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. Brain Res 2007;1179:28–34. doi:10.1016/j.brainres.2007.08.045.
[145] Warren CM, Breuer AT, Kantner J, Fiset D, Blais C, Masson MEJ. Target-distractor interference in the attentional blink implicates the locus coeruleus-norepinephrine system. Psychon Bull Rev 2009;16:1106–11. doi:10.3758/PBR.16.6.1106.
[146] Boddez Y, Baeyens F, Luyten L, Vansteenwegen D, Hermans D, Beckers T. Rating data are underrated: Validity of US expectancy in human fear conditioning. J Behav Ther Exp Psychiatry 2013;44:201–6. doi:10.1016/j.jbtep.2012.08.003.
[147] Bouton ME. Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. Biol Psychiatry 2002;52:976–86. doi:10.1016/S0006-3223(02)01546-9.
[148] Vansteenwegen D, Iberico C, Vervliet B, Marescau V, Hermans D. Contextual fear induced by unpredictability in a human fear conditioning preparation is related to the chronic expectation of a threatening US. Biol Psychol 2008;77:39–46. doi:10.1016/j.biopsycho.2007.08.012.
[149] Glenn CR, Lieberman L, Hajcak G. Comparing electric shock and a fearful screaming face as unconditioned stimuli for fear learning. Int J Psychophysiol 2012;86:214–9. doi:10.1016/j.ijpsycho.2012.09.006.
[150] Guhn A, Dresler T, Andreatta M, Müller LD, Hahn T, Tupak S V, et al. Medial prefrontal cortex stimulation modulates the processing of conditioned fear. Front Behav Neurosci 2014;8:44. doi:10.3389/fnbeh.2014.00044.
[151] Taylor JM, Whalen PJ. Fearful, but not angry, expressions diffuse attention to peripheral targets in an attentional blink paradigm. Emotion 2014;14:462–8. doi:10.1037/a0036034.
[152] Fendt M, Fanselow MS. The neuroanatomical and neurochemical basis of conditioned fear. Neurosci Biobehav Rev 1999;23:743–60.
[153] Indovina I, Robbins TW, Nunez-Elizalde AO, Dunn BD, Bishop SJ. Fear-Conditioning Mechanisms Associated with Trait Vulnerability to Anxiety in Humans. Cell 2011:563–71. doi:10.1016/j.neuron.2010.12.034.
[154] Hofmann SG. Enhancing exposure-based therapy from a translational research perspective. Behav Res Ther 2007;45:1987–2001.
[155] Mcgaugh JL, Roozendaal B. Role of adrenal stress hormones in forming lasting memories in the brain James L McGaugh and Benno Roozendaal. Curr Opin Neurobiol 2002;12:205–10.
[156] McGaugh JL. Memory consolidation and the amygdala: A systems perspective. Trends Neurosci 2002;25:456–61. doi:10.1016/S0166-2236(02)02211-7.
[157] Cahill L, Mcgaugh JL. Mechanisms of emotional arousal and lasting declarative memory. Trends Neurosci 1998;2236:22983–6.
[158] Cain CK, Blouin AM, Barad M. Adrenergic Transmission Facilitates Extinction of Conditional Fear in Mice. Learn Mem 2004;11:179–87. doi:10.1101/lm.71504.
[159] Friedman BH. An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. Biol Psychol 2007;74:185–99. doi:10.1016/j.biopsycho.2005.08.009.
[160] Pappens M, Schroijen M, Sütterlin S, Smets E, Van Den Bergh O, Thayer JF, et al. Resting heart rate variability predicts safety learning and fear extinction in an interoceptive fear conditioning paradigm.

PLoS One 2014;9:e105054. doi:10.1371/journal.pone.0105054.
[161] Fang J, Rong P, Hong Y, Fan Y, Liu J, Wang H, et al. Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder. Biol Psychiatry 2015;79:1–8. doi:10.1016/j.biopsych.2015.03.025.
[162] Fanselow MS. Fear and anxiety take a double hit from vagal nerve stimulation. Biol Psychiatry 2013;73:1043–4. doi:10.1016/j.biopsych.2013.03.025.
[163] Ben-Menachem E, Revesz D, Simon BJ, Silberstein S. Surgically implanted and non-invasive vagus nerve stimulation: A review of efficacy, safety and tolerability. Eur J Neurol 2015;22:1260–8. doi:10.1111/ene.12629.
[164] Sellaro R, Leusden J Van, Colzato L. Transcutaneous vagus nerve stimulation ( tVNS ) enhances post-error slowing. J Cogn Neurosci 2015;27:2126–32.
[165] Burger AM, Verkuil B, Van Diest I, Van der Does W, Thayer JF, Brosschot JF. The effects of transcutaneous vagus nerve stimulation on conditioned fear extinction in humans. Neurobiol Learn Mem 2016;132:49–56. doi:10.1016/j.nlm.2016.05.007.
[166] Clark K, Smith D, Hassert D, Browning R, Naritoku D, Jensen R. Posttraining electrical stimulation of vagal afferents with concomitant vagal efferent inactivation enhances memory storage processes in the rat. Neurobiol Learn Mem 1998;70:364–73. doi:10.1006/nlme.1998.3863.
[167] Clark KB, Naritoku DK, Smith DC, Browning R a, Jensen R a. Enhanced recognition memory following vagus nerve stimulation in human subjects. Nat Neurosci 1999;2:94–8. doi:10.1038/4600.
[168] Scerbo AS, Freedman LW, Raine A, Dawson ME, Venables PH. A major effect of recording site on measurement of electrodermal activity. Psychophysiology 1992;29:241–6. doi:10.1111/j.1469-8986.1992.tb01693.x.
[169] Dawson ME, Schell AM, Filion DL, Berntson GG. The Electrodermal System. In: Cacioppo JT, Tassinary LG, Berntson G, editors. Handb. Psychophysiol., Cambridge: Cambridge University Press; 2007, p. 157–81. doi:10.1017/CBO9780511546396.007.
[170] Crombez G, Vlaeyen J. De Pain Catastrophizing Scale (PCS). Ongepubliceerde geautoriseerde Nederlandstallige bewerking. 1996.
[171] Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychol Assess 1995;7:524–32. doi:10.1037/1040-3590.7.4.524.
[172] Taylor S, Zvolensky MJ, Cox BJ, Deacon B, Heimberg RG, Ledley DR, et al. Robust Dimensions of Anxiety Sensitivity: Development and Initial Validation of the Anxiety Sensitivity Index-3. Psychol Assess 2007;19:176–88. doi:10.1037/1040-3590.19.2.176.
[173] DW M, AJ R. Development of the Fear of Pain Questionnaire—III. J Behav Med 1998;21:389–410.
[174] Engelen U, De Peuter S, Victoir A, Van Diest I, Van den Bergh O. Verdere valideren van de Positive and Negative Affect Schedule (PANAS) en vergelijking van twee Nederlandstalige versies. Gedrag En Gezondh 2006:89–102.
[175] Watson D, Clark L, Tellegen A. Development and Validation of Brief Measures of Positive and Negative Affect: The PANAS Scales. J Pers Soc Psychol 1988;54:1063–70. doi:G022-35l4/88/$00.75.
[176] Gueorguieva R, Krystal JH. Move over ANOVA. Arch Gen Psychiatry 2011;61:310–7. doi:10.1001/archpsyc.61.3.310.
[177] Burnham KP, Anderson RP. Multimodel Inference: Understanding AIC and BIC in Model Selection. Sociol Methods Res 2004;33:261–304. doi:10.1177/0049124104268644.
[178] Wijk AJ Van, Hoogstraten J. Dutch translation of the Fear of Pain Questionnaire : Factor structure , reliability and validity 2006;10:479–86. doi:10.1016/j.ejpain.2005.06.008.
[179] Osman A, Gutierrez PM, Smith K, Fang Q, Lozano G, Devine A, et al. The Anxiety Sensitivity Index – 3 : Analyses of Dimensions , Reliability Estimates , and Correlates in Nonclinical Samples The Anxiety Sensitivity Index – 3 : Analyses of Dimensions , Reliability Estimates , and Correlates in Nonclinical Samples 2010;3891. doi:10.1080/00223890903379332.
[180] Osman A, Barrios FX, Gutierrez PM, Kopper A, Merrifield T, Grittmann L. The Pain Catastrophizing Scale : Further Psychometric Evaluation with Adult Samples 2000;23.
[181] Norrholm S, Jovanovic T, Olin I, Sands L, Bradley B, Ressler K. Fear Extinction in Traumatized Civilians with Posttraumatic Stress Disorder : Relation to Symptom Severity. BPS 2011;69:556–63. doi:10.1016/j.biopsych.2010.09.013.
[182] Norrholm S, Glover E, Stevens J, Fani N, Galatzer-levy I, Bradley B, et al. Fear load : The psychophysiological over-expression of fear as an intermediate phenotype associated with trauma reactions. Int J Psychophysiol 2015;98:270–5. doi:10.1016/j.ijpsycho.2014.11.005.
[183] Kehle-Forbes SM, Meis LA, Spoont MR, Polusny MA. Treatment Initiation and Dropout From Prolonged

Exposure and Cognitive Processing Therapy in a VA Outpatient Clinic. Psychol Trauma Theory, Res Pract Policy 2016;8:107–14.
[184] Phelps E. Human emotion and memory: Interactions of the amygdala and hippocampal complex. Curr Opin Neurobiol 2004;14:198–202. doi:10.1016/j.conb.2004.03.015.
[185] Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR. Double Dissociation of Conditioning and Declarative Knowledge Relative to the Amygdala and Hippocampus in Humans. Science (80- ) 1995;269:1115–8.
[186] LaBar KS, LeDoux JE, Spencer DD, Phelps EA. Impaired fear conditioning following unilateral temporal lobectomy in humans. JNeurosci 1995;15:6846–55.
[187] Biggio F, Gorini G, Utzeri C, Olla P, Marrosu F, Mocchetti I, et al. Chronic vagus nerve stimulation induces neuronal plasticity in the rat hippocampus. Int J Neuropsychopharmacol 2009;12:1209–21. doi:10.1017/S1461145709000200.
[188] Revesz D, Tjernstrom M, Ben-Menachem E, Thorlin T. Effects of vagus nerve stimulation on rat hippocampal progenitor proliferation. Exp Neurol 2008;214:259–65. doi:10.1016/j.expneurol.2008.08.012.
[189] Laeng B, Sirois S, Gredeback G. Pupillometry: A Window to the Preconscious? Perspect Psychol Sci 2012;7:18–27. doi:10.1177/1745691611427305.
[190] Rohleder N, Nater UM, Wolf JM, Ehlert U, Kirschbaum C. Psychosocial stress-induced activation of salivary alpha-amylase: An indicator of sympathetic activity? Ann N Y Acad Sci 2004;1032:258–63. doi:10.1196/annals.1314.033.
[191] Bouton ME, King D a. Contextual control of the extinction of conditioned fear: tests for the associative value of the context. J Exp Psychol Anim Behav Process 1983;9:248–65. doi:10.1037/0097-7403.9.3.248.
[192] Thomas BL, Larsen N, Ayres JJB. Role of context similarity in ABA, ABC, and AAB renewal paradigms: Implications for theories of renewal and for treating human phobias. Learn Motiv 2003;34:410–36. doi:10.1016/S0023-9690(03)00037-7.
[193] Effting M, Kindt M. Contextual control of human fear associations in a renewal paradigm. Behav Res Ther 2007;45:2002–18. doi:10.1016/j.brat.2007.02.011.
[194] Sjouwerman R, Niehaus J, Lonsdorf TB. Contextual change after fear acquisition affects conditioned responding and the time course of extinction learning – Implications for renewal research. Front Behav Neurosci 2015;9:1–9. doi:10.3389/fnbeh.2015.00337.
[195] Bouton ME, Westbrook RF, Corcoran KA, Maren S. Contextual and Temporal Modulation of Extinction: Behavioral and Biological Mechanisms. Biol Psychiatry 2006;60:352–60. doi:10.1016/j.biopsych.2005.12.015.
[196] Burger AM, Verkuil B, Fenlon H, Thijs L, Cools L, Miller HC, et al. Mixed evidence for the potential of non-invasive transcutaneous vagal nerve stimulation to improve the extinction and retention of fear. Behav Res Ther 2017;97:64–74. doi:10.1016/j.brat.2017.07.005.
[197] Ben-Menachem E, Hamberger A, Hedner T, Hammond EJ, Uthman BM, Slater J, et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. Epilepsy Res 1995;20:221–7. doi:10.1016/0920-1211(94)00083-9.
[198] Makkar SR, Zhang SQ, Cranney J. Behavioral and neural analysis of GABA in the acquisition, consolidation, reconsolidation, and extinction of fear memory. Neuropsychopharmacology 2010;35:1625–52. doi:10.1038/npp.2010.53.
[199] Tully K, Bolshakov VY. Emotional enhancement of memory: how norepinephrine enables synaptic plasticity. Mol Brain 2010;3:1–9.
[200] Genheimer H, Andreatta M, Asan E, Pauli P. Reinstatement of contextual conditioned anxiety in virtual reality and the effects of transcutaneous vagus nerve stimulation in humans. Sci Rep 2017;7:17886. doi:10.1038/s41598-017-18183-3.
[201] Ho Y, Lipp O V. Faster acquisition of conditioned fear to fear-relevant than to nonfear-relevant conditional stimuli. Psychophysiology 2014;51:810–3. doi:10.1111/psyp.12223.
[202] Soeter M, Kindt M. Stimulation of the noradrenergic system during memory formation impairs extinction learning but not the disruption of reconsolidation. Neuropsychopharmacology 2012;37:1204–15. doi:10.1038/npp.2011.307.
[203] Gingras B, Marin MM, Fitch WT. Beyond intensity: Spectral features effectively predict music-induced subjective arousal. Q J Exp Psychol 2014;67:1428–46. doi:10.1080/17470218.2013.863954.
[204] Dean RT, Bailes F, Schubert E. Acoustic intensity causes perceived changes in arousal levels in music: An experimental investigation. PLoS One 2011;6:1–8. doi:10.1371/journal.pone.0018591.

[205] Giustino TF, Maren S. Noradrenergic Modulation of Fear Conditioning and Extinction. Front Behav Neurosci 2018;12:1–20. doi:10.3389/fnbeh.2018.00043.
[206] Olatunji BO, Sawchuk CN. Development and Initial Validation of an Abbreviated Spider Phobia Questionnaire Using Item Response Theory. Behav Ther 2009;40:114–30. doi:10.1016/j.beth.2008.04.002.
[207] Cain CK, Blouin AM, Barad M. Adrenergic Transmission Facilitates Extinction of Conditional Fear in Mice. Learn Mem 2004;11:179–87. doi:10.1101/lm.71504.tional.
[208] Brosschot JF, Verkuil B, Thayer JF. Exposed to events that never happen: Generalized unsafety, the default stress response, and prolonged autonomic activity. Neurosci Biobehav Rev 2017;74:287–96. doi:10.1016/j.neubiorev.2016.07.019.
[209] Brosschot J, Verkuil B, Thayer J. The default response to uncertainty and the importance of perceived safety in anxiety and stress: An evolution-theoretical perspective. J Anxiety Disord 2015;41:22–34. doi:10.1016/j.janxdis.2016.04.012.
[210] Licursi de Alcântara AC, Salgado HC, Sassoli Fazan VP. Morphology and morphometry of the vagus nerve in male and female spontaneously hypertensive rats. Brain Res 2008;1197:170–80. doi:10.1016/j.brainres.2007.12.045.
[211] Moriyama H, Hayashi S, Inoue Y, Itoh M, Otsuka N. Sex differences in morphometric aspects of the peripheral nerves and related diseases. NeuroRehabilitation 2016;39:413–22. doi:10.3233/NRE-161372.
[212] Hammer N, Glätzner J, Feja C, Kühne C, Meixensberger J, Planitzer U, et al. Human vagus nerve branching in the cervical region. PLoS One 2015;10. doi:10.1371/journal.pone.0118006.
[213] Bangasser DA, Wiersielis KR, Khantsis S. Sex differences in the locus coeruleus-norepinephrine system and its regulation by stress. Brain Res 2016;1641:177–88. doi:10.1016/j.brainres.2015.11.021.
[214] Bangasser D, Zhang X, Garachh V, Hanhauser E, Valentino R. Structural Basis for Sex Differences in Emotional Arousal. Physiol Behav 2011;103:342–51. doi:10.1016/j.physbeh.2011.02.037.Sexual.
[215] Van Bockstaele EJ, Bajic D, Proudfit H, Valentino RJ. Topographic architecture of stress-related pathways targeting the noradrenergic locus coeruleus. Physiol Behav 2001;73:273–83. doi:10.1016/S0031-9384(01)00448-6.
[216] Twisk JWR. Applied Longitudinal Data Analysis for Epidemiology. Cambridge: Cambridge University Press; 2013. doi:10.1017/CBO9781139342834.
[217] Kindt M, Soeter M, Sevenster D. Disrupting Reconsolidation of Fear Memory in Humans by a Noradrenergic β-Blocker. J Vis Exp 2014:1–8. doi:10.3791/52151.
[218] Boucsein W, Fowles DC, Grimnes S, Ben-Shakhar G, Roth WT, Dawson ME, et al. Publication recommendations for electrodermal measurements. Psychophysiology 2012;49:1017–34. doi:10.1111/j.1469-8986.2012.01384.x.
[219] Behar E, Alcaine O, Zuellig AR, Borkovec TD. Screening for generalized anxiety disorder using the Penn State Worry Questionnaire: A receiver operating characteristic analysis. J Behav Ther Exp Psychiatry 2003;34:25–43. doi:10.1016/S0005-7916(03)00004-1.
[220] Klorman R, Weerts T, Hastings J, Melamed B, Lang P. Psychometric Description of Questionnaires. Behav Ther 1974;5:401–9.
[221] Nyenhuis DL, Stern RA, Yamamoto C, Luchetta T, Arruda JE. Standardization and validation of the Visual Analog Mood Scales. Clin Neuropsychol 1997;11:407–15. doi:10.1080/13854049708400470.
[222] Lonsdorf TB, Menz MM, Andreatta M, Fullana MA, Golkar A, Haaker J, et al. Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. Neurosci Biobehav Rev 2017;77:247–85. doi:10.1016/j.neubiorev.2017.02.026.
[223] Kunze AE, Arntz A, Kindt M. Journal of Behavior Therapy and Fear conditioning with film clips : A complex associative learning paradigm. J Behav Ther Exp Psychiatry 2015;47:42–50. doi:10.1016/j.jbtep.2014.11.007.
[224] Kindt M, Soeter M, Sevenster D. Disrupting Reconsolidation of Fear Memory in Humans by a Noradrenergic β-blocker. J Vis Exp 2014:1–8. doi:10.3791/52151.
[225] Feingold A. A Regression Framework for Effect Size Assessments in Longitudinal Modeling of Group Differences. Rev Gen Psychol 2013;17:111–21. doi:10.1037/a0030048.
[226] Morey RD, Rouder JN. BayesFactor (Version 0.9.10-2) 2015.
[227] JASP Team. JASP (Version 0.8.6) 2018.
[228] Rouder JN, Morey RD, Speckman PL, Province JM. Default Bayes factors for ANOVA designs. J Math Psychol 2012;56:356–74. doi:10.1016/j.jmp.2012.08.001.

[229] Dymond S, Dunsmoor JE, Vervliet B, Roche B, Hermans D. Fear Generalization in Humans: Systematic Review and Implications for Anxiety Disorder Research. Behav Ther 2015;46:561–82. doi:10.1016/j.beth.2014.10.001.
[230] Yassa MA, Stark CEL. Pattern separation in the hippocampus. Trends Neurosci 2011;34:515–25. doi:10.1016/j.tins.2011.06.006.Pattern.
[231] Besnard A, Sahay A. Adult Hippocampal Neurogenesis, Fear Generalization, and Stress. Neuropsychopharmacology 2016;41:24–44. doi:10.1038/npp.2015.167.
[232] Neunuebel JP, Knierim JJ. CA3 Retrieves Coherent Representations from Degraded Input: Direct Evidence for CA3 Pattern Completion and Dentate Gyrus Pattern Separation. Neuron 2014;81:416–27. doi:10.1016/j.neuron.2013.11.017.CA3.
[233] Maren S, Aharonov G, Fanselow MS. Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. Behav Brain Res 1997;88:261–74. doi:10.1016/S0166-4328(97)00088-0.
[234] Antoniadis EA, McDonald RJ. Amygdala, hippocampus and discriminative fear conditioning to context. Behav Brain Res 2000;108:1–19. doi:10.1016/S0166-4328(99)00121-7.
[235] Frankland PW, Cestari V, Filipkowski RK, McDonald RJ, Silva AJ. The dorsal hippocampus is essential for context discrimination but not for contextual conditioning. Behav Neurosci 1998;112:863–74.
[236] Gilbert PE, Kesner RP, Lee I. Dissociating hippocampal subregions: A double dissociation between dentate gyrus and CA1. Hippocampus 2001;11:626–36. doi:10.1002/hipo.1077.
[237] McHugh TJ, Jones MW, Quinn JJ, Balthasar N, Coppari R, Elmquist JK, et al. Dentate Gyrus NMDA Receptors Mediate Rapid Pattern Separation in the Hippocampal Network. Science (80- ) 2007;317:94–9. doi:10.1126/science.1140263.
[238] Bakker A, Kirwan CB, Miller M, Stark CEL. Pattern Separation in the Human Hippocampal CA3 and Dentate Gyrus. Science (80- ) 2010;319:1640–2. doi:10.1126/science.1152882.Pattern.
[239] Lissek S, Bradford DE, Alvarez RP, Burton P, Espensen-sturges T, Reynolds RC, et al. Neural substrates of classically conditioned fear-generalization in humans : a parametric fMRI study. Scan 2014;9:1134–42. doi:10.1093/scan/nst096.
[240] Burger AM, Van Diest I, van der Does W, Hysaj M, Thayer JF, Brosschot JF, et al. Transcutaneous vagus nerve stimulation and extinction of prepared fear: A conceptual non-replication. Sci Rep 2018;8:11471. doi:10.1038/s41598-018-29561-w.
[241] Segal SK, Stark SM, Kattan D, Stark CE, Yassa MA. Norepinephrine-mediated emotional arousal facilitates subsequent pattern separation. Neurobiol Learn Mem 2012;97:465–9. doi:10.1016/j.nlm.2012.03.010.
[242] Revesz D, Tjernstrom M, Ben-Menachem E, Thorlin T. Effects of vagus nerve stimulation on rat hippocampal progenitor proliferation. Exp Neurol 2008;214:259–65. doi:10.1016/j.expneurol.2008.08.012.
[243] Gebhardt N, Bär KJ, Boettger MK, Grecksch G, Keilhoff G, Reichart R, et al. Vagus nerve stimulation ameliorated deficits in one-way active avoidance learning and stimulated hippocampal neurogenesis in bulbectomized rats. Brain Stimul 2013;6:78–83. doi:10.1016/j.brs.2012.01.009.
[244] Davis M. Neural systems involved in fear and anxiety measured with fear-potentiated startle. Am Psychol 2006;61:741–56. doi:10.1037/0003-066X.61.8.741.
[245] Davis M, Falls WA, Campeau S, Kim M. Fear-potentiated startle: a neural and pharmacological analysis. [Review]. Behav Brain Res 1993;58:175–98.
[246] Lissek S, Biggs AL, Rabin SJ, Cornwell BR, Alvarez RP, Pine DS, et al. Generalization of conditioned fear-potentiated startle in humans: Experimental validation and clinical relevance. Behav Res Ther 2008;46:678–87. doi:10.1016/j.brat.2008.02.005.
[247] Vanbrabant K, Boddez Y, Verduyn P, Mestdagh M, Hermans D, Raes F. A new approach for modeling generalization gradients: a case for hierarchical models. Front Psychol 2015;6:652. doi:10.3389/fpsyg.2015.00652.
[248] Grady AK, Bowen KH, Hyde AT, Totsch SK, Knight DC. Effect of continuous and partial reinforcement on the acquisition and extinction of human conditioned fear. Behav Neurosci 2016;130:36–43. doi:10.1037/bne0000121.
[249] Bos MGN, Beckers T, Kindt M. The effects of noradrenergic blockade on extinction in humans. Biol Psychol 2012;89:598–605. doi:10.1016/j.biopsycho.2012.01.007.
[250] LeDoux JE. Coming to terms with fear. Proc Natl Acad Sci 2014;111:2871–8. doi:10.1073/pnas.1400335111.
[251] Hamm AO, Vaitl D, Lang PJ. Fear conditioning, meaning, and belongingness: A selective association analysis. J Abnorm Psychol 1989;98:395–406. doi:10.1037/0021-843X.98.4.395.

[252] Struyf D, Zaman J, Hermans D, Vervliet B. Gradients of fear: How perception influences fear generalization. Behav Res Ther 2017;93:116–22. doi:10.1016/j.brat.2017.04.001.
[253] Maren S. Nature and causes of the immediate extinction deficit: A brief review. Neurobiol Learn Mem 2014;113:19–24. doi:10.1016/j.nlm.2013.10.012.
[254] Chang C -h., Maren S. Early extinction after fear conditioning yields a context-independent and short-term suppression of conditional freezing in rats. Learn Mem 2009;16:62–8. doi:10.1101/lm.1085009.
[255] Panayiotou G, van Oyen Witvliet C, Robinson JD, Vrana SR. Modulation of the Startle Reflex By Valence and Arousal. Biol Psychol 2012;87:226–33. doi:10.1016/j.biopsycho.2011.03.001.A.
[256] Engineer ND, Riley JR, Seale JD, Vrana W a, Shetake J a, Sudanagunta SP, et al. Reversing pathological neural activity using targeted plasticity. Nature 2011;470:101–4. doi:10.1038/nature09656.
[257] Meyers EC, Solorzano BR, James J, Ganzer PD, Lai ES, Rennaker RL, et al. Vagus nerve stimulation enhances stable plasticity and generalization of stroke recovery. Stroke 2018;49:710–7. doi:10.1161/STROKEAHA.117.019202.
[258] Vanneste S, Martin J, Rennaker RL, Kilgard MP. Pairing sound with vagus nerve stimulation modulates cortical synchrony and phase coherence in tinnitus: An exploratory retrospective study. Sci Rep 2017;7:17345. doi:10.1038/s41598-017-17750-y.
[259] Borland MS, Engineer CT, Vrana WA, Moreno NA, Engineer ND, Vanneste S, et al. The Interval Between VNS-Tone Pairings Determines the Extent of Cortical Map Plasticity. Neuroscience 2018;369:76–86. doi:10.1016/j.neuroscience.2017.11.004.
[260] Tyler R, Cacace A, Stocking C, Tarver B, Engineer N, Martin J, et al. Vagus Nerve Stimulation Paired with Tones for the Treatment of Tinnitus: A Prospective Randomized Double-blind Controlled Pilot Study in Humans. Sci Rep 2017;7:1–11. doi:10.1038/s41598-017-12178-w.
[261] Clancy J a, Mary D a, Witte KK, Greenwood JP, Deuchars S a, Deuchars J. Non-invasive Vagus Nerve Stimulation in Healthy Humans Reduces Sympathetic Nerve Activity. Brain Stimul 2014. doi:10.1016/j.brs.2014.07.031.
[262] Badran BW, Mithoefer OJ, Summer CE, LaBate NT, Glusman CE, Badran AW, et al. Short trains of transcutaneous auricular vagus nerve stimulation (taVNS) have parameter-specific effects on heart rate. Brain Stimul 2018;11:699–708. doi:10.1016/j.brs.2018.04.004.
[263] Couck M De, Cserjesi R, Caers R, Zijlstra WP, Widjaja D, Wolf N, et al. Effects of short and prolonged transcutaneous vagus nerve stimulation on heart rate variability in healthy subjects. Auton Neurosci Basic Clin 2017;203:88–96. doi:10.1016/j.autneu.2016.11.003.
[264] Yoo PB, Liu H, Hincapie JG, Ruble SB, Hamann JJ, Grill WM. Modulation of heart rate by temporally patterned vagus nerve stimulation in the anesthetized dog. Physiol Rep 2016;4:1–10. doi:10.14814/phy2.12689.
[265] Michl LC, McLaughlin KA, Shepherd K, Nolen-Hoeksema S. Rumination as a mechanism linking stressful life events to symptoms of depression and anxiety: longitudinal evidence in early adolescents and adults. J Abnorm Psychol 2013;122:339–52. doi:10.1037/a0031994.
[266] Olatunji BO, Wolitzky-Taylor KB, Sawchuk CN, Ciesielski BG. Worry and the anxiety disorders: A meta-analytic synthesis of specificity to GAD. Appl Prev Psychol 2010;14:1–24. doi:10.1016/j.appsy.2011.03.001.
[267] Haller H, Cramer H, Lauche R, Gass F, Dobos GJ. The prevalence and burden of subthreshold generalized anxiety disorder: a systematic review. BMC Psychiatry 2014;14:128. doi:10.1186/1471-244X-14-128.
[268] Hunot V, Churchill R, Silva de LM, Teixeira V. Psychological therapies for generalised anxiety disorder. Cochrane Database Syst Rev 2007:CD001848. doi:10.1002/14651858.CD001848.pub4.www.cochranelibrary.com.
[269] Rodriguez BF, Weisberg RB, Pagano ME, Bruce SE, Spencer M a, Culpepper L, et al. Characteristics and predictors of full and partial recovery from generalized anxiety disorder in primary care patients. J Nerv Ment Dis 2006;194:91–7. doi:10.1097/01.nmd.0000198140.02154.32.
[270] Yakunina N, Kim SS, Nam E-C. Optimization of Transcutaneous Vagus Nerve Stimulation Using Functional MRI. Neuromodulation Technol Neural Interface 2016;2016. doi:10.1111/ner.12541.
[271] Fischer R, Ventura-Bort C, Hamm A, Weymar M. Transcutaneous vagus nerve stimulation (tVNS) enhances conflict-triggered adjustment of cognitive control. Cogn Affect Behav Neurosci 2018:1–14. doi:10.3758/s13415-018-0596-2.
[272] Steenbergen L, Sellaro R, Stock AK, Verkuil B, Beste C, Colzato LS. Transcutaneous vagus nerve stimulation (tVNS) enhances response selection during action cascading processes. Eur Neuropsychopharmacol 2015;25:773–8. doi:10.1016/j.euroneuro.2015.03.015.

[273] Hirsch CR, Hayes S, Mathews A. Looking on the bright side: accessing benign meanings reduces worry. J Abnorm Psychol 2009;118:44–54. doi:10.1037/a0013473.
[274] Hayes S, Hirsch CR, Krebs G, Mathews A. The effects of modifying interpretation bias on worry in generalized anxiety disorder. Behav Res Ther 2010;48:171–8. doi:10.1016/j.brat.2009.10.006.
[275] Borkovec TD, Robinson E, Pruzinsky T, DePree JA. Preliminary exploration of worry: some characteristics and processes. Behav Res Ther 1983;21:9–16.
[276] Yoo PB, Lubock NB, Hincapie JG, Ruble SB, Hamann JJ, Grill WM. High-resolution measurement of electrically-evoked vagus nerve activity in the anesthetized dog. J Neural Eng 2013;10:026003. doi:10.1088/1741-2560/10/2/026003.
[277] Verkuil B, Brosschot J. The online version of the Dutch Penn State Worry Questionnaire : Factor structure , predictive validity and reliability. J Anxiety Disord 2012;26:844–8. doi:10.1016/j.janxdis.2012.08.002.
[278] Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder. Arch Intern Med 2006;166:1092. doi:10.1001/archinte.166.10.1092.
[279] Löwe B, Decker O, Müller S, Brähler E, Schellberg D, Herzog W, et al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. Med Care 2008;46:266–74. doi:10.1097/MLR.0b013e318160d093.
[280] Derryberry D, Reed MA. Anxiety-related attentional biases and their regulation by attentional control. J Abnorm Psychol 2002;111:225–36. doi:10.1037/0021-843X.111.2.225.
[281] Judah MR, Grant DM, Mills AC, Lechner W V. Factor structure and validation of the attentional control scale. Cogn Emot 2014;28:433–51. doi:10.1080/02699931.2013.835254.
[282] Just N, Alloy LB. The response styles theory of depression: tests and an extension of the theory. J Abnorm Psychol 1997;106:221–9. doi:10.1037/0021-843X.106.2.221.
[283] Penttila J, Helminen a, Jartti T, Kuusela T. Time domain, geometrical and frequency domain analysis of cardiac vagal outflow: effects of various {…}. Clin Physiol 2001;1:365–76.
[284] Hill L, Siebenbrock A, Sollers J, Thayer J. Are all measures created equal? Heart rate variability and respiration. Biomed Sci Instrum 2009;45:71–6.
[285] Reyes del Paso GA, Langewitz W, Mulder LJM, van Roon A, Duschek S. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a reanalysis of previous studies. Psychophysiology 2013;50:477–87. doi:10.1111/psyp.12027.
[286] Schoofs H, Hermans D, Raes F. Brooding and reflection as subtypes of rumination: Evidence from confirmatory factor analysis in nonclinical samples using the dutch Ruminative Response Scale. J Psychopathol Behav Assess 2010;32:609–17. doi:10.1007/s10862-010-9182-9.
[287] Fajkowska M, Derryberry D. Psychometric properties of Attentional Control Scale: The preliminary study on a Polish sample. Polish Psychol Bull 2010;41:1–7. doi:10.2478/s10059-010-0001-7.
[288] Hallion LS, Tolin DF, Assaf M, Goethe J, Diefenbach GJ. Cognitive Control in Generalized Anxiety Disorder: Relation of Inhibition Impairments to Worry and Anxiety Severity. Cognit Ther Res 2017;41:610–8. doi:10.1007/s10608-017-9832-2.
[289] Servaas MN, Riese H, Ormel J, Aleman A. The Neural Correlates of Worry in Association with Individual Differences in Neuroticism. Hum Brain Mapp 2014;35:4303–15. doi:10.1002/hbm.22476.
[290] Krebs G, Hirsch CR, Mathews A. The effect of attention modification with explicit vs . minimal instructions on worry. Behav Res Ther 2010;48:251–6. doi:10.1016/j.brat.2009.10.009.
[291] Ventura-Bort C, Wirkner J, Genheimer H, Wendt J, Hamm AO, Weymar M. Effects of transcutaneous vagus nerve stimulation (tVNS) on the P300 and alpha-amylase level: A pilot study. Front Hum Neurosci 2018;12:202. doi:10.3389/FNHUM.2018.00202.
[292] Ng GA, Brack KE, Coote JH. Effects of Direct Sympathetic and Vagus Nerve Stimulation on the Physiology of the Whole Heart - A Novel Model of Isolated Langendorff Perfused Rabbit Heart with Intact Dual Autonomic Innervation. Exp Physiol 2001;86:319–29. doi:10.1113/eph8602146.
[293] Ottaviani C, Thayer J, Verkuil B, Lonigro A, Medea B, Couyoumdjian A, et al. Physiological Concomitants of Perseverative Cognition: A Systematic Review and Meta-Analysis. Psychol Bull 2016;142:231–59. doi:10.1037/bul0000036.
[294] Jepma M, Nieuwenhuis S. Pupil diameter predicts changes in the exploration-exploitation trade-off: evidence for the adaptive gain theory. J Cogn Neurosci 2011;23:1587–96. doi:10.1162/jocn.2010.21548.
[295] Nieuwenhuis S, Aston-Jones G, Cohen JD. Decision making, the P3, and the locus coeruleus-norepinephrine system. Psychol Bull 2005;131:510–32. doi:10.1037/0033-2909.131.4.510.
[296] Badran BW, Dowdle LT, Mithoefer OJ, LaBate NT, Coatsworth J, Brown JC, et al. Neurophysiologic

effects of transcutaneous auricular vagus nerve stimulation (taVNS) via electrical stimulation of the tragus: A concurrent taVNS/fMRI study and review. Brain Stimul 2018. doi:10.1016/j.brs.2017.12.009.
[297] Fay T. Observations and resijlts from intracranial section of the glossopharyngeus and vagus nerves in man. J Neurol Neurosurg Psychiatry 1927;S1-8:110–23. doi:10.1136/jnnp.s1-8.30.110.
[298] Sherrington C. Experiments in examination of the peripheral distribution of fibers of the posterior roots of some spinal nerves - part II. Philos Trans R Soc London Ser B 1897:49–185. doi:doi:10.1086/303379.
[299] Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. J Inflamm Res 2018;11:203–13. doi:10.2147/JIR.S163248.
[300] Rong P, Liu J, Wang L, Liu R, Fang J, Zhao J, et al. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: A nonrandomized controlled pilot study. J Affect Disord 2016;195:172–9. doi:10.1016/j.jad.2016.02.031.
[301] Jin Y, Kong J. Transcutaneous vagus nerve stimulation: A promising method for treatment of autism spectrum disorders. Front Neurosci 2017;10:1–7. doi:10.3389/fnins.2016.00609.
[302] Redgrave JN, Moore L, Oyekunle T, Ebrahim M, Falidas K, Snowdon N, et al. Transcutaneous Auricular Vagus Nerve Stimulation with Concurrent Upper Limb Repetitive Task Practice for Poststroke Motor Recovery: A Pilot Study. J Stroke Cerebrovasc Dis 2018;27:1998–2005. doi:10.1016/j.jstrokecerebrovasdis.2018.02.056.
[303] Aihua L, Lu S, Liping L, Xiuru W, Hua L, Yuping W. A controlled trial of transcutaneous vagus nerve stimulation for the treatment of pharmacoresistant epilepsy. Epilepsy Behav 2014;39:105–10. doi:10.1016/j.yebeh.2014.08.005.
[304] Raedt R, Clinckers R, Mollet L, Vonck K, El Tahry R, Wyckhuys T, et al. Increased hippocampal noradrenaline is a biomarker for efficacy of vagus nerve stimulation in a limbic seizure model. J Neurochem 2011;117:461–9. doi:10.1111/j.1471-4159.2011.07214.x.
[305] Roosevelt RW, Smith DC, Clough RW, Jensen R a, Browning R a. Increased extracellular concentrations of norepinephrine in cortex and hippocampus following vagus nerve stimulation in the rat. Brain Res 2006;1119:124–32. doi:10.1016/j.brainres.2006.08.048.
[306] Verguts T, Notebaert W. Adaptation by binding: a learning account of cognitive control. Trends Cogn Sci 2009;13:252–7. doi:10.1016/j.tics.2009.02.007.
[307] Samuels E, Szabadi E. Functional Neuroanatomy of the Noradrenergic Locus Coeruleus: Its Roles in the Regulation of Arousal and Autonomic Function Part I: Principles of Functional Organisation. Curr Neuropharmacol 2008;6:235–53. doi:10.2174/157015908785777229.
[308] Joshi S, Li Y, Kalwani RM, Gold JI. Relationships between Pupil Diameter and Neuronal Activity in the Locus Coeruleus, Colliculi, and Cingulate Cortex. Neuron 2016;89:221–34. doi:10.1016/j.neuron.2015.11.028.
[309] Rajkowski J, Kubiak P, Aston-Jones G. Correlations between locus coeruleus (LC) neural activity, pupil diameter and behavior in monkey support a role of LC in attention. Soc Neurosc Abstr 1993;19:974.
[310] Phillips MA, Szabadi E, Bradshaw CM. Comparison of the effects of clonidine and yohimbine on pupillary diameter at different illumination levels. Br J Clin Pharmacol 2000;50:65–8. doi:10.1046/j.1365-2125.2000.00225.x.
[311] Hou RH, Freeman C, Langley RW, Szabadi E, Bradshaw CM. Does modafinil activate the locus coeruleus in man? Comparison of modafinil and clonidine on arousal and autonomic functions in human volunteers. Psychopharmacology (Berl) 2005;181:537–49. doi:10.1007/s00213-005-0013-8.
[312] Hou RH, Langley RW, Szabadi E, Bradshaw CM. Comparison of diphenhydramine and modafinil on arousal and autonomic functions in healthy volunteers. J Psychopharmacol 2007;21:567–78. doi:10.1177/0269881106071022.
[313] Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci 2005;28:403–50. doi:10.1146/annurev.neuro.28.061604.135709.
[314] Gilzenrat MS, Nieuwenhuis S, Cohen JD. Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. Cogn Affect Behav Neurosci 2010;10:252–69. doi:10.3758/CABN.10.2.252.Pupil.
[315] Bianca R, Komisaruk BR. Pupil dilatation in response to vagal afferent electrical stimulation is mediated by inhibition of parasympathetic outflow in the rat. Brain Res 2007;1177:29–36. doi:10.1016/j.brainres.2007.06.104.
[316] Nieuwenhuis S, Gilzenrat MS, Holmes BD, Cohen JD. The role of the locus coeruleus in mediating the attentional blink: a neurocomputational theory. J Exp Psychol Gen 2005;134:291–307. doi:10.1037/0096-3445.134.3.291.

[317] Zylberberg A, Oliva M, Sigman M. Pupil dilation: A fingerprint of temporal selection during the "Attentional Blink." Front Psychol 2012;3:1–6. doi:10.3389/fpsyg.2012.00316.
[318] Usher M, Cohen JD, Servan-Schreiber D, Rajkowski J, Aston-Jones G. The Role of Locus Coeruleus in the Regulation of Cognitive Performance. Science (80- ) 1999;283:549–54. doi:10.1126/science.283.5401.549.
[319] De Martino B, Strange B a., Dolan RJ. Noradrenergic neuromodulation of human attention for emotional and neutral stimuli. Psychopharmacology (Berl) 2008;197:127–36. doi:10.1007/s00213-007-1015-5.
[320] Nieuwenhuis S, Van Nieuwpoort IC, Veltman DJ, Drent ML. Effects of the noradrenergic agonist clonidine on temporal and spatial attention. Psychopharmacology (Berl) 2007;193:261–9. doi:10.1007/s00213-007-0770-7.
[321] Brown SBRE, Slagter HA, Van Noorden MS, Giltay EJ, Van Der Wee NJA, Nieuwenhuis S. Effects of clonidine and scopolamine on multiple target detection in rapid serial visual presentation. Psychopharmacology (Berl) 2016;233:341–50. doi:10.1007/s00213-015-4111-y.
[322] Burger AM, Van der Does W, Thayer JF, Brosschot JF, Verkuil B. Transcutaneous vagus nerve stimulation reduces spontaneous but not induced negative thought intrusions in high worriers. Biol Psychol 2019;142:80–9. doi:10.1016/j.biopsycho.2019.01.014.
[323] Steinhauer SR, Siegle GJ, Condray R, Pless M. Sympathetic and parasympathetic innervation of pupillary dilation during sustained processing. Int J Psychophysiol 2004;52:77–86. doi:10.1016/j.ijpsycho.2003.12.005.
[324] Kret ME, Sjak-Shie EE. Preprocessing pupil size data: Guidelines and code. Behav Res Methods 2018:1–7. doi:10.3758/s13428-018-1075-y.
[325] Warton DI, Francis. The arcsine is asinine: the analysis of proportions in ecology. Ecology 2011;92:3–10.
[326] Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8. University of Florida, Gainesville, FL: 2008.
[327] de Oca BM, Villa M, Cervantes M, Welbourne T. Emotional Modulation of the Attentional Blink by Pleasant and Unpleasant Pictures. J Gen Psychol 2012;139:289–314. doi:10.1080/00221309.2012.708681.
[328] Teufel HJ, Wehrhahn C. Evidence for the contribution of S cones to the detection of flicker brightness and red-green. J Opt Soc Am A Opt Image Sci Vis 2000;17:994–1006. doi:10.1364/JOSAA.17.000994.
[329] Fox E, Russo R, Dutton K. Attentional bias for threat: Evidence for delayed disengagement from emotional faces. Cogn Emot 2002;16:355–79. doi:10.1080/02699930143000527.
[330] Stefanopoulou E, Hirsch CR, Hayes S, Adlam A, Coker S. Are attentional control resources reduced by worry in generalized anxiety disorder? J Abnorm Psychol 2014;123:330–5. doi:10.1037/a0036343.
[331] Wierda SM, van Rijn H, Taatgen NA, Martens S. Pupil dilation deconvolution reveals the dynamics of attention at high temporal resolution. Proc Natl Acad Sci U S A 2012;109:8456–60. doi:10.1073/pnas.1201858109.
[332] Nunan D, Sandercock GRH, Brodie DA. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. PACE - Pacing Clin Electrophysiol 2010;33:1407–17. doi:10.1111/j.1540-8159.2010.02841.x.
[333] Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003;54:573–83. doi:10.1016.
[334] Calvo MG, Lundqvist D. Facial expressions of emotion (KDEF): Identification under different display-duration conditions. Behav Res Methods 2008;40:109–15. doi:10.3758/BRM.40.1.109.
[335] Müsch K, Engel AK, Schneider TR. On the blink: The importance of target-distractor similarity in eliciting an attentional blink with faces. PLoS One 2012;7. doi:10.1371/journal.pone.0041257.
[336] De Taeye L, Vonck K, van Bochove M, Boon P, Van Roost D, Mollet L, et al. The P3 Event-Related Potential is a Biomarker for the Efficacy of Vagus Nerve Stimulation in Patients with Epilepsy. Neurotherapeutics 2014;11:612–22. doi:10.1007/s13311-014-0272-3.
[337] Yerkes RM, Dodson JD. The relation of strength of stimulus to rapidity of habit-formation. J Comp Neurol Psychol 1908;18:459–82. doi:10.1002/cne.920180503.
[338] Ellrich J. Transcutaneous vagus nerve stimulation. Eur Neurol Rev 2011;6:254–6.
[339] Brosschot JF, Verkuil B, Thayer JF. Generalized unsafety theory of stress: Unsafe environments and conditions, and the default stress response. Int J Environ Res Public Health 2018;15:1–35. doi:10.3390/ijerph15030464.
[340] Lawrence AJ, Watkins D, Jarrott B. Visualization of beta-adrenoceptor binding sites on human inferior

vagal ganglia and their axonal transport along the rat vagus nerve. J Hypertens 1995;13:631–5. doi:10.1097/00004872-199506000-00009.
[341] Alpers GW, Abelson JL, Wilhelm FH, Roth WT. Salivary cortisol response during exposure treatment in driving phobics. Psychosom Med 2003;65:679–87. doi:10.1097/01.PSY.0000073872.85623.0C.
[342] Beste C, Steenbergen L, Sellaro R, Grigoriadou S, Zhang R, Chmielewski W, et al. Effects of Concomitant Stimulation of the GABAergic and Norepinephrine System on Inhibitory Control – A Study Using Transcutaneous Vagus Nerve Stimulation. Brain Stimul 2016;9:811–8. doi:10.1016/j.brs.2016.07.004.
[343] Dietrich S, Smith J, Scherzinger C, Hofmann-Preiss K, Freitag T, Eisenkolb A, et al. [A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI]. Biomed Tech (Berl) 2008;53:104–11. doi:10.1515/BMT.2008.022.
[344] Aarts AA, Anderson JE, Anderson CJ, Attridge PR, Attwood A, Axt J, et al. Estimating the reproducibility of psychological science. Science (80- ) 2015;349:aac4716-aac4716. doi:10.1126/science.aac4716.
[345] Vasey MW, Thayer JF. The Continuing Problem of False Positives in Repeated Measures ANOVA in Psychophysiology: A Multivariate Solution. Psychophysiology 1987;24:479–86. doi:10.1111/j.1469-8986.1987.tb00324.x.
[346] Ugrinowitsch C, Fellingham GW, Ricard MD. Limitations of ordinary least squares models in analyzing repeated measures data. Med Sci Sports Exerc 2004;36:2144–8. doi:10.1249/01.MSS.0000147580.40591.75.
[347] Kuehl RO. Design of Experiments: Statistical Principles of Research Design and Analysis. 2nd ed. Pacific Grove: Duxbury Press; 2000.
[348] Goadsby PJ, de Coo IF, Silver N, Tyagi A, Ahmed F, Gaul C, et al. Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: A randomized, double-blind, sham-controlled ACT2 study. Cephalalgia 2017;0:333102417744362. doi:10.1177/0333102417744362.
[349] Straube A, Ellrich J, Eren O, Blum B, Ruscheweyh R. Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): a randomized, monocentric clinical trial. J Headache Pain 2015;16:543. doi:10.1186/s10194-015-0543-3.
[350] Tso AR, Marin J, Goadsby PJ. Noninvasive Vagus Nerve Stimulation for Treatment of Indomethacin-Sensitive Headaches. JAMA Neurol 2017;74:1266. doi:10.1001/jamaneurol.2017.2122.
[351] Stefan H, Kreiselmeyer G, Kerling F, Kurzbuch K, Rauch C, Heers M, et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: A proof of concept trial. Epilepsia 2012;53:115–8. doi:10.1111/j.1528-1167.2012.03492.x.
[352] Li S, Zhai X, Rong P, McCabe MF, Zhao J, Ben H, et al. Transcutaneous auricular vagus nerve stimulation triggers melatonin secretion and is antidepressive in zucker diabetic fatty rats. PLoS One 2014;9:1–6. doi:10.1371/journal.pone.0111100.
[353] Huang F, Dong J, Kong J, Wang H, Meng H, Spaeth RB, et al. Effect of transcutaneous auricular vagus nerve stimulation on impaired glucose tolerance: A pilot randomized study. BMC Complement Altern Med 2014;14:1–8. doi:10.1186/1472-6882-14-203.
[354] Busch V, Zeman F, Heckel A, Menne F, Ellrich J, Eichhammer P. The effect of transcutaneous vagus nerve stimulation on pain perception--an experimental study. Brain Stimul 2013;6:202–9. doi:10.1016/j.brs.2012.04.006.
[355] Napadow V, Edwards RR, Cahalan CM, Mensing G, Kim J, Maeda Y, et al. Evoked Pain Analgesia in Chronic Pelvic Pain Patients Using Respiratory-Gated Auricular Vagal Afferent Nerve Stimulation. Pain Med 2012:777–89.
[356] Ylikoski J, Lehtimäki J, Pirvola U, Mäkitie A, Aarnisalo A, Hyvärinen P, et al. Non-invasive vagus nerve stimulation reduces sympathetic preponderance in patients with tinnitus. Acta Otolaryngol 2017;137:426–31. doi:10.1080/00016489.2016.1269197.
[357] Lehtimäki J, Hyvärinen P, Ylikoski M, Bergholm M, Mäkelä JP, Aarnisalo A, et al. Transcutaneous vagus nerve stimulation in tinnitus: A pilot study. Acta Otolaryngol 2013;133:378–82. doi:10.3109/00016489.2012.750736.
[358] Yigit E, Dursun E, Omeroglu E, Sunter AV, Edizer DT, Terzi S, et al. The course of lower cranial nerves within the neck: a cadaveric dissection study. Eur Arch Oto-Rhino-Laryngology 2018;275:2541–8. doi:10.1007/s00405-018-5091-4.
[359] Brown C, Gayzik F, Stitzel J. Characterization of the carotid and adjacent anatomy using non-contrast CT for biomechanical model development. Biomed Sci Instrum 2007;43:330–5.
[360] Puts N, Edden R. In vivo magnetic spectroscopy of GABA: a methodological review. Prog Nucl Magn Reson Spectrosc 2012;60:29–41. doi:10.1016/j.pnmrs.2011.06.001.In.
[361] Capone F, Assenza G, Di Pino G, Musumeci G, Ranieri F, Florio L, et al. The effect of transcutaneous

vagus nerve stimulation on cortical excitability. J Neural Transm 2015;122:679–85. doi:10.1007/s00702-014-1299-7.
[362] Keute M, Ruhnau P, Heinze HJ, Zaehle T. Behavioral and electrophysiological evidence for GABAergic modulation through transcutaneous vagus nerve stimulation. Clin Neurophysiol 2018;129:1789–95. doi:10.1016/j.clinph.2018.05.026.
[363] Neese SL, Sherill LK, Tan AA, Roosevelt RW, Browning RA, Smith DC, et al. Vagus nerve stimulation may protect GABAergic neurons following traumatic brain injury in rats: An immunocytochemical study. Brain Res 2007;1128:157–63. doi:10.1016/j.brainres.2006.09.073.
[364] Button KS, Ioannidis JPA, Mokrysz C, Nosek BA, Flint J, Robinson ESJ, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci 2013;14:365–76. doi:10.1038/nrn3475.
[365] Dhanani A, Lee SY, Phothilimthana PM, Pardos Z. A comparison of error metrics for learning model parameters in Bayesian knowledge tracing. CEUR Workshop Proc 2014;1183:153–4.

# Dankwoord (Acknowledgements)

Ik heb enorm genoten van de jaren waarin ik heb kunnen werken aan mijn promotieonderzoek, en dat is grotendeels te danken aan de mensen die ik om me heen heb gehad. Een aantal van hen wil ik hier in het bijzonder bedanken.

Willem, bedankt voor alle kansen die je me hebt geboden, en je betrokkenheid in het onderzoek. Jouw kritische geest en no-nonsense manier van schrijven is zichtbaar in elk hoofdstuk van dit proefschrift en hebben mij veel geleerd.

Jos, ik ben trots om me een 'kleinzoon' in jouw onderzoek-stamboom te mogen noemen. Jouw affiniteit met onderzoek en het enthousiasme dat jij kan laten wanneer je aan het brainstormen bent, waarbij het ene onderwerp naadloos verbonden wordt met het volgende, is echt een bron van inspiratie voor mij.

Bart, een betere begeleider had ik me niet kunnen wensen. Je enthousiasme, positieve houding en open instelling hebben mij van begin af aan geïnspireerd en gaven mij het vertrouwen om ook met eigen ideeën te komen. Ik heb in de afgelopen jaren heel veel van je geleerd, niet alleen over hoe ik onderzoek zou willen doen, maar ook over wat voor persoon ik als onderzoeker zou willen zijn.

Julian, thank you so much for the great collaboration, and for all the interesting discussions over the years.

Lieve collega's in Leiden, wat heb ik het toch onwijs naar mijn zin gehad met jullie. De gezellige borrels, sportieve initiatieven, spontane gesprekken en koffieafspraken, ik had het niet willen missen. Met name de lunch crew wil ik bedanken - Bart, Sanne, Charlotte, Stefanie, Dana, Loes, Lisanne, Dianne, en Mirjam -, omdat jullie mij altijd een goede reden gaven om een half uurtje mijn ogen van het scherm af te halen om even te kunnen lachen. Sanne, jou wil ik in het bijzonder bedanken: ik heb echt onwijs veel lol gehad met jou als kamergenoot. Bedankt voor alle mooie gesprekken, stomme grapjes, en goede adviezen.

I would also really like to thank all my colleagues in the Health Psychology group in Leuven, for being so welcoming during the semester I visited you. I feel right at home in your group, and feel incredibly thankful that you gave me the chance to stay with you as a postdoc. In het bijzonder wil ik Ilse bedanken – bedankt dat je van begin af aan open stond om samen te werken, en dat je mij zo veel kansen hebt willen bieden. Martina, thanks for being my 'Team tVNS' buddy and for all the interesting discussions.

Astrid, Edin, Niels, Roel, Roel, en Vincent - beste leden van het MHG, bedankt voor de vele jaren mooie vriendschap. Woensdagavond-gastenavond was onmisbaar tijdens mijn promotie. Het feit dat ik door jullie onstilbare behoefte aan Woo-Ping nooit meer iets bij de Chinees wil bestellen neem ik op de koop toe.

Vincent en Ferdi, bedankt voor alle goede gesprekken en adviezen over statistiek, programmeren, en onderzoek. Ik zou niemand liever aan mijn zijde willen hebben tijdens mijn promotie.

Liebe Eltern, vielen Dank für die Freiheit und für die wertvolle Unterstützung, die Ihr Stephan und mir im Laufe unserer Leben geboten habt. Ohne Euch hätte ich den langen Weg, der zu diesem Moment geführt hat, niemals geschafft. Lieber Stephan – beste Burger Brother - vielen Dank das du immer für mich da gewesen bist. Ob du nun in Deutschland, Schottland, Burundi, Pakistan, oder Belgien wohnst, du bist mir immer nahe.

Ook mijn schoonfamilie wil ik heel erg bedanken. Reina, Rob, Peter, Arjenne, Tom, Eef, en Dennis: jullie zijn voor mij echt als een tweede familie geworden, en dat is mij heel dierbaar.

Lieve Marjolein, in de afgelopen jaren heb jij altijd voor me klaargestaan en hebt me de steun en rust geboden die ik nodig had. Zonder jou waren deze jaren niet zo kleurrijk geweest. Wat ben ik blij dat ik samen me jou door het leven mag gaan.