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Extremely shy & genetically close : investigating neurobiological endophenotypes of social anxiety disorder

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Citation

Bas, J. M. (2020, January 14). *Extremely shy & genetically close : investigating neurobiological endophenotypes of social anxiety disorder*. Retrieved from https://hdl.handle.net/1887/82705

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Title: Extremely shy & genetically close : investigating neurobiological endophenotypes of social anxiety disorder
Issue Date: 2020-01-14

Part 5

Appendices

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Funding sources

All chapters

Janna Marie Bas-Hoogendam was funded by Leiden University Research Profile 'Health, Prevention and the Human Life Cycle' and the Institute of Psychology of Leiden University.

Chapter 4

Henk van Steenbergen was supported by a grant from the Netherlands Organization for Scientific Research (NWO) to Bernhard Hommel. Henk van Steenbergen, J. Nienke Pannekoek and Jean-Paul Fouche were partially supported by the EU 7th Frame Work Marie Curie Actions International Staff Exchange Scheme grant 'European and South African Research Network in Anxiety Disorders' (EUSARNAD). Jean-Paul Fouche is funded by the South African Medical Research Council National Health Scholarship. Münster (Jena) collaborators were partially supported by the Collaborative Research Center "Fear, Anxiety, and Anxiety disorders" in Münster, funded by the German Research Society (SFB/TRR-58, project C07 awarded to Thomas Straube) and by the Research Group "Person Perception" in Jena, funded by the German Research Society (grant number STR 987/6-1 to Thomas Straube). The infrastructure for the Netherlands Study of Depression and Anxiety (NESDA) was funded through the Geestkracht programme of the Netherlands Organization for Health Research and Development (ZonMw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, IQ Healthcare, Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos Institute)). Studies in Umea and Uppsala were supported by the Swedish Research Council and the Swedish Research Council for Health, Working Life and Welfare.

Acknowledgments

Chapters 2, 3, 5, 8-10

We are grateful to the Royal Dutch Academy of Sciences (KNAW) which enabled the organization of the Social Anxiety Conference, consisting of a two-day KNAW Academy Colloquium and a Master Class day (6 - 8 June 2011, Leiden, the Netherlands), and we thank the Lorentz Center (Leiden, the Netherlands) for their financial and practical support in organizing the workshop 'Endophenotypes of Social Anxiety Disorder: Can we detect them and are they useful in clinical practice?', which took place 14 - 18 December 2015 (https://www.lorentzcenter.nl/lc/web/2015/754/info.php3?wsid=754).

Chapter 4

We thank Tanja Kreuk (research intern, Leiden University) for her contribution to the visual inspection of the data, and the Anxiety Disorders Research Network of the European College of Psychopharmacology for its scientific and administrative support.

Chapters 5, 8 -10

We thank Anita Harrewijn, Melle J.W. van der Molen and Irene M. van Vliet for their contribution to the design and execution of the LFLSAD and their role in the recruitment of the families. Furthermore, we are grateful to several master students (Marjolein Barendse, Tanja Kreuk, Saskia van Leuverden, Farah Mesbahi, Eefje Poppelaars) and the support team of the Leiden Institute for Brain and Cognition (LIBC) who assisted in acquiring the MRI data.

Chapter 6

We thank Karina S. Blair (Boys Town National Research Hospital, Boys Town, NE, USA) and Melle J.W. van der Molen (Leiden University, Leiden, The Netherlands) for their assistance in developing the stories included in the SNPT-R, and Anne C. Miers (Leiden University, Leiden, The Netherlands) for her help in back translating the Dutch stories into English.

Chapter 7

We gratefully thank Tanja Kreuk who was involved in designing the study and data acquisition as part of her research master thesis project.

Chapter 10

We thank Renaud L. M. Tissier and Jeanine J. Houwing-Duistermaat for their statistical support and providing the analyses scripts.

Curriculum vitae

Janna Marie Bas-Hoogendam was born on November 21, 1985 in Gouda, The Netherlands. In 2003, she graduated from Gymnasium Camphusianum in Gorinchem (cum laude / with honours) and started studying Medicine at the Erasmus Medical Center, Rotterdam. After finishing the Bachelor's phase (cum laude / with honours, 2004), she continued with the Master's phase of this study. During several research internships at the department of Psychiatry of the Erasmus Medical Center, she got acquainted with brain research and became more and more enthusiastic about the possibilities of neuroimaging, especially in relation to psychopathology. She wrote a review on the effect of antipsychotics on the blood-oxygen-level-dependent (BOLD) signal (published in revised form in *Current Pharmaceutical Design*) and decided to focus on brain research after her graduation. She was admitted to the prestige research master Neuroscience and Cognition at Utrecht University (2007). As part of this master, she completed an internship involving the combination of functional Magnetic Resonance Imaging (fMRI) and repetitive Transcranial Magnetic Stimulation (rTMS) at the Psychiatry department of the University Medical Center (UMC) Utrecht, and an internship concerning a magneto-encephalogram experiment in patients with Parkinson's disease and obsessive-compulsive disorder at the VU Medical Center in Amsterdam. In addition, she wrote a master's thesis on the physiological basis of the effects of rTMS on the brain, with a focus on synaptic plasticity (published as a review in *Brain Stimulation*).

She obtained her master's degree (cum laude / with honours) in 2009 and started working as a research assistant at the Psychiatry department of the UMC Utrecht on the BRain Imaging, Development & Genetics (BRIDGE) project. In this project, she investigated the structural and functional brain development of children (10 - 16 years of age) who were genetically at high risk for the development of schizophrenia and bipolar disorder. In 2012, she moved to the United Kingdom to work as a Marie Curie Early Stage Researcher at the Cognitive Neuroimaging Laboratory of the University of Birmingham within the Adaptive Brain Computations research program, a training network funded by the European Union.

In 2013, Janna Marie Bas-Hoogendam started her PhD project at the unit Developmental and Educational Psychology of the Institute of Psychology (Leiden University) and the department of Psychiatry of the Leiden University Medical Center (LUMC). This PhD project, embedded within the Leiden Family Lab study on Social Anxiety Disorder (LFLSAD) and supervised by prof. dr. P. Michiel Westenberg, prof. dr. Nic. J. A. van der Wee and dr. Henk van Steenbergen, aimed to determine endophenotypes of social anxiety disorder using structural and functional MRI. The results of this study are included in this thesis.

In addition to the data collection and analysis of the LFLSAD project, she was involved in the Netherlands Study of Depression and Anxiety (NESDA) and worked on a study on the neurobiological effects of cortisol on the brain, a collaboration between the departments of Psychiatry and Endocrinology (LUMC). Furthermore, Janna Marie was part-time

employed as a Junior staff-member at the Netherlands Organization for Scientific Research (NWO), the Hague (2015), and she was actively involved in teaching: she supervised Bachelor's and Master's theses, was coordinator and working group leader of Clinical Child and Adolescent Psychology and a mentor of first year's students of the International Bachelor in Psychology. She obtained her University Teaching Qualification in 2017.

Furthermore, Janna Marie Bas-Hoogendam is a coordinator of the ENIGMA-ANXIETY working group (since 2016) and associate faculty member of F1000prime (since 2017). Currently, Janna Marie is appointed as a researcher at the unit Developmental and Educational Psychology of the Institute of Psychology (Leiden University) and the department of Psychiatry (LUMC).

Janna Marie is married to Matthijs Bas and they have two sons: David (2016) and Manuel (2018).

Curriculum vitae (*Nederlands*)

Janna Marie Bas-Hoogendam is geboren op 21 November 1985 in Gouda. In 2003 behaalde ze haar diploma aan het Gymnasium Camphusianum in Gorinchem (*cum laude*) en in datzelfde jaar startte ze met de opleiding Geneeskunde aan het Erasmus Medisch Centrum, Rotterdam. Na het afronden van de propedeutische fase (*cum laude*, 2004), zette ze haar studie voort met de doctoraal fase van de opleiding. Tijdens meerdere onderzoeksstages bij de afdeling Psychiatrie van het Erasmus MC maakte ze kennis met hersenonderzoek, en werd daarbij steeds enthousiaster over de mogelijkheden van beeldvormende technieken om inzicht te krijgen in de neurobiologische basis van psychopathologie. Ze schreef een overzichtsartikel over het effect van antipsychotica op hersenactiviteit (in herziene vorm gepubliceerd in het wetenschappelijke tijdscrift *Current Pharmaceutical Design*) en besloot om zich na het afronden van haar doctoraal te richten op het doen van wetenschappelijk onderzoek naar het brein. Ze werd geselecteerd voor de prestige researchmaster Neuroscience and Cognition aan de Universiteit Utrecht (2007). Tijdens deze master rondde Janna Marie twee stages af. In de eerste stage, die plaatsvond op de afdeling Psychiatrie van het Universitair Medisch Centrum (UMC) Utrecht werkte ze mee aan een project waarin functionele Magnetische Resonantie Imaging (fMRI) gecombineerd werd met repetitieve Transcraniële Magnetische Stimulatie (rTMS); tijdens de tweede stage hield ze zich bezig met een magneto-encefalografie in patiënten met de ziekte van Parkinson en patiënten met een obsessieve-compulsieve dwangstoornis (VU Medisch Centrum, Amsterdam). Daarnaast schreef ze haar master scriptie over de fysiologische basis van de effecten van rTMS op het brein, waarbij ze zich met name richtte op synaptische plasticiteit. Deze scriptie werd in 2010 in het blad *Brain Stimulation* gepubliceerd.

Na het behalen van haar masterdiploma (*cum laude*) in 2009 werkte Janna Marie een aantal jaar als onderzoeksassistent op de afdeling psychiatrie van het UMC Utrecht aan het *BRain Imaging, Development & Genetics* (BRIDGE) onderzoek. In dit project onderzocht ze de structurele en functionele ontwikkeling van de hersenen in kinderen (10 - 16 jaar oud) die een hoog genetisch risico hadden voor het ontwikkelen van schizofrenie of een bipolaire stoornis. In 2012 verhuisde ze naar het Verenigd Koninkijk om daar als een *Marie Curie Early Stage Researcher* te werken bij het *Cognitive Neuroimaging Laboratory* van de Universiteit van Birmingham, in het kader van het *Adaptive Brain Computations* onderzoeksprogramma (financieel mogelijk gemaakt door de Europese Unie).

In 2013 begon Janna Marie Bas-Hoogendam met haar promotieonderzoek bij de afdeling Ontwikkelings- en onderwijspsychologie (Instituut Psychologie, Universiteit Leiden) en de afdeling Psychiatrie (Leiden Universitair Medisch Centrum, LUMC), onder begeleiding van prof. dr. P. Michiel Westenberg, prof. dr. Nic. J. A. van der Wee en dr. Henk van Steenbergen. Het project was onderdeel van de Leidse Familiestudie naar Sociale Angststoornis (LFLSAD) en was erop gericht om endofenotypes van sociale angststoornis vast te stellen

met behulp van structurele en functionele MRI. De resultaten van het onderzoek zijn in dit proefschrift beschreven.

Naast het verzamelen en analyseren van de onderzoeksgegevens van de LFLSAD was Janna Marie betrokken bij de Nederlandse Studie naar Depressie en Angst (NESDA), en werkte ze aan een onderzoek naar de neurobiologische effecten van cortisol op het brein, een samenwerking tussen de afdelingen Psychiatrie en Endocrinologie van het LUMC. Verder werkte ze parttime als Junior Beleidsmedewerker bij de Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO; Den Haag; 2015) en vervulde ze diverse onderwijstaken. Ze begeleidde studenten bij het schrijven van hun bachelor- en masterscripties, was coördinator en werkgroepdocent van het vak *Clinical Child and Adolescent Psychology* en mentor van eerstejaarsstudenten van de *International Bachelor in Psychology*. Ze behaalde haar Basiskwalificatie Onderwijs in 2017.

Verder is Janna Marie sinds 2016 coördinator van de ENIGMA-ANXIETY werkgroep en *associate faculty member* van de website F1000prime (sinds 2017). Momenteel is Janna Marie werkzaam als onderzoeker bij de afdeling Ontwikkelings- en onderwijspsychologie (Instituut Psychologie, Universiteit Leiden) en de afdeling Psychiatrie (LUMC).

Janna Marie is getrouwd met Matthijs Bas en samen hebben ze twee zoons: David (2016) en Manuel (2018).

List of publications

Papers in peer-reviewed journals

Janna Marie Bas-Hoogendam, Henk van Steenbergen, Jennifer U. Blackford, Renaud L.M. Tissier, Nic. J.A. van der Wee, P. Michiel Westenberg (2019b). Impaired neural habituation to neutral faces in families genetically enriched for Social Anxiety Disorder. *Depression & Anxiety* (available online, in press).

Janna Marie Bas-Hoogendam, Henk van Steenbergen, Renaud L.M. Tissier, Nic. J.A. van der Wee, P. Michiel Westenberg (2019a). Altered neurobiological processing of unintentional social norm violations: a multiplex, multigenerational fMRI study on social anxiety endophenotypes. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (available online, in press).

Janna Marie Bas-Hoogendam (2019). Commentary: Gray Matter Structural Alterations in Social Anxiety Disorder: a Voxel-Based Meta-Analysis. *Front. Psychiatry* 10:1.

Janna Marie Bas-Hoogendam, Henk van Steenbergen, Renaud L.M. Tissier, Jeanine J. Houwing-Duistermaat, P. Michiel Westenberg, Nic J.A. van der Wee (2018b). Subcortical brain volumes, cortical thickness and cortical surface area in families genetically enriched for social anxiety disorder – a multiplex multigenerational neuroimaging study. *EBioMedicine, 36,* 410-428

Janna Marie Bas-Hoogendam, Anita Harrewijn, Renaud L.M. Tissier, Melle J.W. van der Molen, Henk van Steenbergen, Irene M. Van Vliet, Catrien G. Reichart, Jeanine J. Houwing-Duistermaat, P. Eline Slagboom, Nic J.A. van der Wee, P. Michiel Westenberg (2018a). The Leiden Family Lab study on Social Anxiety Disorder: a multiplex, multigenerational family study on neurocognitive endophenotypes. *International Journal of Methods in Psychiatric Research*: e1616.

Janna Marie Bas-Hoogendam, Henk van Steenbergen, Nic J.A. van der Wee, P. Michiel Westenberg (2018c). Not intended, still embarrassed: social anxiety modulates the experience of unintentional social norm violations. *European Psychiatry*, *52*, 15-21.

Janna Marie Bas-Hoogendam*, Henk van Steenbergen* , J. Nienke Pannekoek, Jean-Paul Fouche, Christine Lochner, Coenraad J. Hattingh, Karin Roelofs, Tomas Furmark, Kristoffer N.T. Månsson, Andreas Frick, Jonas Engman, Carl-Johan Boraxbekk, Per Carlbring, Gerhard Andersson, Mats Fredrikson , Thomas Straube, Jutta Peterburs, Heide Klumpp, K. Luan Phan, Henk R. Cremers, Dick J. Veltman, Marie-José van Tol, Dan J. Stein, Nic

J.A. van der Wee (2017a). Voxel-Based Morphometry Multi-Center Mega-Analysis of Brain Structure in Social Anxiety Disorder. *NeuroImage: Clinical, 16*, 678-688. (*: shared first authorship)

Janna Marie Bas-Hoogendam, Henk van Steenbergen, Tanja Kreuk, Nic J.A. van der Wee, P. Michiel Westenberg (2017b). How embarrassing! The behavioral and neural correlates of processing social norm violations. *PLOS ONE, 12 (4)*, e0176326.

Janna Marie Bas-Hoogendam, Jennifer U. Blackford, Annette B. Brühl, Karina S. Blair, Nic J.A. van der Wee, P. Michiel Westenberg (2016). Neurobiological Candidate Endophenotypes of Social Anxiety Disorder. *Neuroscience and Biobehavioral Reviews* , *71*, 362-378.

Janna Marie Bas-Hoogendam*, Cornelie D. Andela*, Steven J.A. van der Werff, J. Nienke Pannekoek, Henk van Steenbergen, Onno C. Meijer, Mark A. van Buchem, Serge A.R.B. Rombouts, Roos C. van der Mast, Nienke R. Biermasz, Nic J.A. van der Wee, Alberto M. Pereira (2015). Altered neural processing of emotional faces in remitted Cushing's disease. *Psychoneuroendocrinology* 59, 134–146. (*: shared first authorship)

Matthijs Vink, Bram B. Zandbelt, Thomas Gladwin, Manon Hillegers, **Janna Marie Hoogendam**, Wery P.M. van den Wildenberg, Stefan Du Plessis, René S Kahn (2014). Frontostriatal activity and connectivity increase during proactive inhibition across adolescence and early adulthood. *Human Brain Mapping 35 (9)*, 4415-4427.

Matthijs Vink, Jolanda M. Derks, **Janna Marie Hoogendam**, Manon Hillegers, René S. Kahn (2014). Functional differences in emotion processing during adolescence and early adulthood. *NeuroImage 91*, pp 70-76.

Janna Marie Hoogendam, René S. Kahn, Manon H.J. Hillegers, Mariët van Buuren, Matthijs Vink (2013). Different developmental trajectories for anticipation and receipt of reward during adolescence. *Developmental Cognitive Neuroscience 6*, 113-124.

Bram B. Zandbelt, Mirjam Bloemendaal, **Janna Marie Hoogendam**, René S. Kahn, Matthijs Vink (2013). Transcranial magnetic stimulation and functional MRI reveal cortical and subcortical interactions during stop-signal response inhibition. *Journal of Cognitive Neuroscience, 25 (2)*, 157-174.

N.M.J. van Veelen, M. Vink, N.F. Ramsey, M. van Buuren, **J.M. Hoogendam**, R.S. Kahn (2011). Prefrontal lobe dysfunction predicts treatment response in medication-naive first-episode schizophrenia. *Schizophrenia Research 129 (2-3*), 156-162.

N.M.J. van Veelen, M. Vink, N.F. Ramsey, I.E.C. Sommer, M. van Buuren, **J.M. Hoogendam**, R.S. Kahn (2011). Reduced language lateralization in first-episode medication-naive schizophrenia. *Schizophrenia Research 127 (1-3),* 195-201.

C.H. Röder, **J.M. Hoogendam**, F.M. van der Veen (2010). FMRI, antipsychotics and schizophrenia. Influence of different antipsychotics on BOLD-signal. *Current Pharmaceutical Design 16 (18)*, 2012-2025.

J.M. Hoogendam, G.M.J.Ramakers, V.Di Lazzaro (2010). Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimulation 3 (2)*, 95-118.

Papers under review

Paul Thompson, Neda Jahanshad, Christopher R. K. Ching, Lauren E. Salminen, Sophia I. Thomopoulos, Joanna Bright, Bernhard T. Baune, …., **Janna Marie Bas-Hoogendam**, …, Nic J. A. van der Wee, Ysbrand D. van der Werf, Theo G. M. van Erp, PhD, Neeltje E. M. van Haren, Daan van Rooij, Laura S. van Velzen, Ilya M. Veer, Dick J. Veltman, Julio E. Villalon-Reina, Henrik Walter, Christopher D. Whelan, Elisabeth A. Wilde, Mojtaba Zarei, and Vladimir Zelman, for the ENIGMA Consortium (2019). *ENIGMA and Global Neuroscience: A Decade of Large-Scale Studies of the Brain in Health and Disease across 43 Countries.* ***PsyArXiv.*** *July 4.*

Janna Marie Bas-Hoogendam, Henk van Steenbergen, Nic. J.A. van der Wee, P. Michiel Westenberg (under review). Amygdala hyperreactivity to faces conditioned with a social-evaluative meaning – a multiplex, multigenerational fMRI study on social anxiety endophentoypes.

Laura S. van Velzen, Marie-José van Tol, Martijn P. van den Heuvel, **Janna Marie Bas-Hoogendam**, Nic J. A. van der Wee, Dick J. Veltman, Brenda W. J. H. Penninx, Lianne Schmaal (in revision). Multimodal graph theoretical brain networks and the 9-year cumulative disease load of depression and anxiety.

Book chapters

Janna Marie Bas-Hoogendam, Eline F. Roelofs, P. Michiel Westenberg, Nic J. A. van der Wee. Pathogenesis of SAD; chapter in 'The American Psychiatric Association Textbook of Anxiety, Trauma and OCD related Disorders', edited by Naomi Simon, Eric Hollander, Barbara O. Rothbaum, and Dan J. Stein (2019, in press).

Dick J. Veltman, **Janna Marie Bas-Hoogendam**, Nic J. A. van der Wee en Odile A. van den Heuvel. Het angstige brein: beeldvormend onderzoek; hoofdstuk in 'Handboek angst- en

dwangstoornissen', onder redactie van Ton van Balkom, Désirée Oosterbaan, Saka Visser en Irene van Vliet. Uitgeverij de Tijdstroom (2018).

Conference abstracts *(selection)*

Janna Marie Bas-Hoogendam, Henk van Steenbergen, Nic J.A. van der Wee, P. Michiel Westenberg (2019). Neuroimaging results from the Leiden Family Lab study on Social Anxiety Disorder: a multiplex, multigenerational endophenotype study. *Journal of Neural Transmission* (in press).

Janna Marie Bas-Hoogendam, Henk van Steenbergen, Nic J.A. van der Wee, P. Michiel Westenberg (2019). Social conditioning of neutral faces in families genetically enriched for social anxiety disorder. *European Neuropsychopharmacology* (in press). ***WINNER TRAVEL AWARD 32nd ECNP Congress (2019), and selected for 'Poster Jam Session: Anxiety and stress related disorders' dedicated to four high-scoring posters.***

Laura van Velzen, Marie-José van Tol, Martijn van den Heuvel, **Janna Marie Bas-Hoogendam**, Nic van der Wee, Dick Veltman, Brenda Penninx, Lianne Schmaal (2019). Multimodal Graph Theoretical Brain Networks and the 9-Year Cumulative Disease Load of Depression and Anxiety. *Biological Psychiatry 85 (10),* S264.

Nynke A. Groenewold, **Janna Marie Bas-Hoogendam**, Alyssa R. Amod, Laura van Velzen, Moji Aghajani, Courtney A. Filippi, Andrea L. Gold, Christopher R.K. Ching, Karin Roelofs, Tomas Furmark, Kristoffer N.T. Månsson, Thomas Straube, Jutta Peterburs, Heide Klumpp, K. Luan Phan, Christine Lochner, Alexander Doruyter, Jesus Pujol, Narcis Cardoner, Laura Blanco-Hinojo, Katja Beesdo-Baum, Kevin Hilbert, Benjamin Kreifelts, Michael Erb, Qi-yong Gong, Su Lui, Jair C. Soares, Mon-Ju Wu, P. Michiel Westenberg, Dominik Grotegerd, Elisabeth J. Leehr, Udo Dannlowski, Peter Zwanzger, Dick J. Veltman, Daniel S. Pine, Neda Jahanshad, Paul M. Thompson, Dan J. Stein, and Nic J.A. van der Wee, on behalf of the ENIGMA-Anxiety Working Group (2018). Subcortical volumes in Social Anxiety Disorder: Preliminary Results from ENIGMA-Anxiety. *Biological Psychiatry 83 (9),* S247-S248.

Janna Marie Bas-Hoogendam, Henk van Steenbergen, Nic J.A. van der Wee, P. Michiel Westenberg (2017); Subcortical brain volumes as endophenotypes of social anxiety disorder – preliminary findings from the Leiden Family Study on Social Anxiety Disorder. *Journal of Neural Transmission 124 (10),* 1300. ***WINNER TRAVEL AWARD WASAD Congress (2017).***

Janna Marie Bas-Hoogendam, Henk van Steenbergen, Nic J.A. van der Wee, P. Michiel Westenberg (2017); Subcortical brain volumes as endophenotypes of social anxiety disorder

– preliminary findings from the Leiden Family Study on Social Anxiety Disorder. *European Neuropsychopharmacology 27 (4),* s1021.

Janna Marie Bas-Hoogendam, Henk van Steenbergen, J. Nienke Pannekoek, Jean-Paul Fouche, Christine Lochner, Coenraad J. Hattingh, Henk R. Cremers, Tomas Furmark, Kristoffer N.T. Månsson, Andreas Frick, Jonas Engman, Carl-Johan Boraxbekk, Per Carlbring, Gerhard Andersson, Mats Fredrikson, Thomas Straube, Jutta Peterburs, Heide Klumpp, K. Luan Phan, Karin Roelofs, Dan J. Stein, Nic J.A. van der Wee (2017). Sample size matters: A voxel-based morphometry multi-center mega-analysis of gray matter volume in Social Anxiety Disorder. *Biological Psychiatry 81 (10),* S7-S8.

Janna Marie Bas-Hoogendam, Henk van Steenbergen, Nic J.A. van der Wee, P. Michiel Westenberg (2017). Social norm processing as an endophenotype of social anxiety disorder - a family study in two generations. *European Neuropsychopharmacology 27*, S49-S50. ***WINNER TRAVEL AWARD ECNP Workshop on Neuropsychopharmacology for Junior Scientists in Europe (2017).***

Janna Marie Bas-Hoogendam, Henk van Steenbergen, P. Michiel Westenberg, Nic J.A. van der Wee (2015). Social conditioning of neutral faces: A pilot-study on brain functioning in social anxiety patients and their unaffected first-degree relatives. *European Neuropsychopharmacology 25*, S573-S574. ***WINNER TRAVEL AWARD 28th ECNP Congress (2015).***

Patients with social anxiety disorder (SAD) are 'extremely shy': they are afraid of a negative evaluation and avoid social situations as much as possible, with negative influences on their lives. SAD runs in families: being 'genetically close' to a patient with SAD substantially increases the risk to develop the disorder.

The studies summarized in this thesis aim to broaden our knowledge of this genetic vulnerability to SAD. Using MRI scans from the unique Leiden Family Lab study on Social Anxiety Disorder, we demonstrate that alterations in the structure and function of the brain are genetically linked to the disorder. These results offer novel insights in the neurobiological pathways leading to SAD.