Shy parent, shy child ? : delineating psychophysiological endophenotypes of social anxiety disorder

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Chapter 7

Summary and general discussion

Summary

The goal of this dissertation was to delineate psychophysiological endophenotypes of social anxiety disorder (SAD). Studying endophenotypes could be seen as a first step in unraveling genetic mechanisms underlying psychiatric disorders, because endophenotypes are supposedly influenced by less genes than complex psychiatric disorders (Cannon & Keller, 2006; Glahn et al., 2007). In addition, endophenotypes could yield better understanding of the biological mechanisms underlying SAD (Glahn et al., 2007; Iacono et al., 2016; Miller & Rockstroh, 2013). Our Leiden Family Lab study on SAD focused on two criteria for endophenotypes: co-segregation with SAD within families and heritability. Patients with SAD participated with their partner and children, as well as their siblings with partner and children. This dissertation focused on EEG and heart rate measures during resting state, a social performance task and a social judgment paradigm. In the social performance task, participants watched and evaluated a speech of a female peer and then gave a speech in front of a video camera themselves. In the social judgment paradigm, participants received social acceptance or rejection feedback, after indicating their expectations about the upcoming feedback.

The *second chapter* gives an overview of the most frequently studied EEG measures of information processing biases in SAD. Studies on EEG spectral characteristics have shown that delta-beta correlation during anticipation of and recovery from a stressful social situation is a promising electrocortical marker, possibly reflecting the alleged imbalance between cortical and subcortical brain regions (Bishop, 2007; Bruhl et al., 2014; Cremers, Veer, Spinhoven, Rombouts, Yarkoni, et al., 2015; Miskovic & Schmidt, 2012). The event-related potential studies have shown information processing biases during early processing of faces (P1) and errors (error-related negativity; ERN). Increased P1 amplitude in response to faces possibly reflects hypervigilance to threatening stimuli (Bögels & Mansell, 2004; Clark & McManus, 2002; Heinrichs & Hofmann, 2001; Hirsch & Clark, 2004; Morrison & Heimberg, 2013), and increased ERN amplitude possibly reflects increased self-focused attention (Bögels & Mansell, 2004; Clark & McManus, 2002) or perfectionism (Clark & Wells, 1995).

The *third chapter* reports on the validation of our newly developed social performance task in high and low socially anxious females. High socially anxious females reported more nervousness and avoidance during the social performance task than low socially anxious females. We jointly examined frontal alpha asymmetry and delta-beta correlation in this task, and found that only negative delta-beta correlation during anticipation of and recovery from this stressful social situation was related to social anxiety. Increased negative delta-beta

correlation is interpreted to reflect the imbalance between cortical and subcortical regions as found in fMRI studies in SAD (Bruhl et al., 2014; Cremers, Veer, Spinhoven, Rombouts, Yarkoni, et al., 2015; Miskovic & Schmidt, 2012) or in anxiety more general (Bishop, 2007).

In the *fourth chapter* we investigate whether delta-beta correlation could also be seen as an endophenotype of SAD. We found that delta-low beta correlation co-segregated with (sub)clinical SAD within families and was heritable. So, delta-low beta correlation meets the second and third criteria for endophenotypes, and thus might be an endophenotype of SAD.

The *fifth chapter* focuses on heart rate variability during resting state and the social performance task as a candidate endophenotype of SAD. Heart rate variability did not co-segregate with SAD within families, but was heritable. So, heart rate variability did not meet the second criterion for endophenotypes. We suggest that heart rate variability might reflect a transdiagnostic genetic vulnerability for internalizing disorders, related to reduced flexibility due to impaired inhibition (Chalmers et al., 2014; Thayer & Lane, 2000) or generalized unsafety (Brosschot et al., 2016).

The *sixth chapter* describes whether behavioral and EEG measures in the social judgment paradigm could be seen as endophenotypes of SAD. Reaction time for acceptance-expectations, N1 amplitude in response to expected rejection feedback, and P3 amplitude in response to acceptance feedback met the two criteria for endophenotyps that we assessed (co-segregation and heritability). Reaction time for acceptance-expectations possibly reflects increased uncertainty or self-focused attention and vigilance during the social judgment paradigm (Van der Molen et al., 2014). Increased N1 amplitude possibly reflects hypervigilance to socially threatening stimuli (Bögels & Mansell, 2004; Clark & McManus, 2002; Heinrichs & Hofmann, 2001; Hirsch & Clark, 2004; Morrison & Heimberg, 2013), and increased P3 amplitude might reflect that positive feedback is more important for, and/or less expected by, participants with SAD (Ferdinand et al., 2012; Johnson, 1986; Rapee & Heimberg, 1997). Feedback-related negativity (FRN) and theta power were increased after unexpected rejection feedback compared to the other conditions in patients with SAD, but these measures were not heritable.

General discussion

This dissertation focused on three criteria for endophenotypes: association with SAD (*second chapter*), co-segregation with SAD within families, and heritability (*fourth, fifth* and *sixth chapter*). Delta-beta correlation, P1 and ERN meet the first criterion for endophenotypes. Delta-low beta correlation, reaction time, N1, and P3 meet the second and third criteria for endophenotypes. We have not assessed the fourth (non-affected versus general population) and fifth (state-independence) criteria for endophenotypes, so we have to be careful with concluding that these psychophysiological measures are endophenotypes of SAD. However, delta-beta correlation did not differ in patients with SAD between two visits approximately one week apart (Miskovic, Moscovitch, et al., 2011), which suggests stability over time and could be linked to the fifth criterion for endophenotypes (state-independence). Some studies have shown moderate to strong test-retest reliability for P1, N1, P3 and ERN amplitudes, albeit in different paradigms than employed in this dissertation (Cassidy, Robertson, & O'Connell, 2012; Hall et al., 2006; Polich, 2007; Weinberg & Hajcak, 2011). However, if the fifth criterion is interpreted as clearly distinctive states such as in bipolar disorder, this would not be applicable to SAD. To conclude, delta-beta correlation, N1 and P3 are candidate endophenotypes of SAD and future research should also study the other criteria for endophenotypes.

The results described in this dissertation also show which psychophysiological measures give less insight in the underlying mechanisms of SAD. First, frontal alpha asymmetry seems to be related to social anxiety or behavioral inhibition in children (Fox, Henderson, Rubin, Calkins, & Schmidt, 2001; Henderson et al., 2001; Henderson et al., 2004), but the findings in adults are mixed (see *chapter two*). Some early studies have found an effect of social anxiety on frontal alpha asymmetry (Davidson et al., 2000; Schmidt, Fox, Schulkin, & Gold, 1999), but more recent studies have only found an effect in specific conditions (Cole et al., 2012) or not at all (Beaton et al., 2008; Harrewijn et al., 2016). Also, when presenting the findings of this dissertation and talking to other researchers, it became clear that there are unpublished null findings on frontal alpha asymmetry as well. Inconsistencies in findings on frontal alpha asymmetry and SAD might be related to the role of comorbid depression (Thibodeau et al., 2006). Second, previous studies have reported mixed findings on heart rate variability in SAD (see *chapter five*). Decreased heart rate variability during resting state is related to different internalizing disorders, such as several anxiety disorders (Chalmers et al., 2014; B. H. Friedman, 2007; Pittig et al., 2013), and

depression (Kemp et al., 2012; Kemp et al., 2010). Therefore, we suggest in *chapter five* that heart rate variability is a transdiagnostic genetic vulnerability for internalizing disorders.

This dissertation aimed at delineating psychophysiological endophenotypes of SAD to gain more insight in the mechanisms underlying the development and maintenance of SAD. Information processing biases play an important role in the development and maintenance of SAD (Bögels & Mansell, 2004; Clark & McManus, 2002; Heinrichs & Hofmann, 2001; Hirsch & Clark, 2004; Morrison & Heimberg, 2013; Wong & Rapee, 2016), and the candidate endophenotypes in this dissertation might be reflective of these information processing biases. For example, early event-related potentials might be reflective of an early attention bias to socially threatening stimuli, and delta-beta correlation might be reflective of an interpretation bias during anticipation (Bögels & Mansell, 2004; Clark & McManus, 2002; Heinrichs & Hofmann, 2001; Hirsch & Clark, 2004; Morrison & Heimberg, 2013). Of course, future research is necessary to link these psychophysiological endophenotypes to information processing biases, and to use these psychophysiological endophenotypes in treatment to alleviate SAD symptoms. In the following paragraphs, I will discuss directions for future research and the clinical implications of research on psychophysiological endophenotypes.

Directions for future research

Studying endophenotypes could be seen as a first step in unraveling genetic mechanisms underlying psychiatric disorders, because endophenotypes are proposed to be related to fewer genes than complex psychiatric disorders such as SAD (Cannon & Keller, 2006; Glahn et al., 2007). Future research should investigate the genes that are related to psychophysiological endophenotypes, and whether these genes are also related to SAD. This use of endophenotypes has been criticized in recent studies, as endophenotypes are also influenced by many genes (Flint et al., 2014; Iacono et al., 2016). Nevertheless, endophenotypes could yield a better understanding in the biological mechanisms underlying SAD (Glahn et al., 2007; Iacono et al., 2016; Miller & Rockstroh, 2013) and could help in interpreting genetic findings (De Geus, 2010; Flint et al., 2014). Below, I discuss how psychophysiological endophenotypes of SAD might be used in future studies to provide more insight on information processing biases and their role in the maintenance and development of SAD.

So far, research has focused on psychophysiological measures of separate information processing biases. However, it would be interesting to investigate how these psychophysiological measures influence each other. For example, it might be possible that

hypervigilance (as reflected in early event-related potentials) influences later processing of socially threatening stimuli (as reflected in later event-related potentials). EEG is the ideal method to study this, because of the high temporal resolution (Amodio et al., 2014; M. X. Cohen, 2011; Ibanez et al., 2012; Luck, 2005). Moreover, it is proposed that these information processing biases in SAD have formed a persistent cycle: they are triggered by social situations, repeated within the situation, and carried forward over time during anticipation (Clark & McManus, 2002; Morrison & Heimberg, 2013). This persistent cycle plays an important role in the maintenance of SAD, but has only scarcely been studied. Few studies have focused on the influence of anticipation on later processing in healthy participants. Anticipation of public speaking enhanced early processing of negative faces (Wieser et al., 2010). However, anticipation of receiving social evaluative feedback (as measured by the stimulus preceding negativity) did not influence processing of this feedback as measured by the FRN and P3 (Van der Molen et al., 2014). This is an interesting line of research to continue, as anticipation might have an increased effect in patients with SAD.

Another important area for future research is investigating the link between psychophysiological endophenotypes and behavior. A promising line of research on the ERN has focused on post-error slowing, which is the tendency of people to respond slower after they have made an error on the previous trial (Danielmeier & Ullsperger, 2011; Gehring & Fencsik, 2001). Only one study has investigated this in SAD and found no difference between participants with and without SAD (Endrass et al., 2014), but this should be confirmed in future studies. Extending this line of research to other candidate psychophysiological endophenotypes might yield promising information. For example, it should be studied how patients with SAD interact with people, after the hypervigilant reaction to faces. They might try to use safety behaviors, such as avoiding eye contact, to hide their extreme initial reaction towards this person (Clark & Wells, 1995; Wells et al., 1995). Furthermore, it should also be studied how decreased delta-beta correlation during anticipation of a stressful social situation influences subsequent behavior. Most participants were nervous during our social performance task, but it might be the case that nervous behavior during the speech is most apparent in participants with increased delta-beta correlation during anticipation. The relation between psychophysiological endophenotypes and behavior might play an important role in the maintenance of SAD.

Psychophysiological endophenotypes of SAD might reflect a genetic vulnerability for developing SAD. However, not everyone with this genetic vulnerability will eventually develop the disorder. An important next step is to study which persons with this genetic

vulnerability will develop SAD, and which persons will not. Many factors play a role in the development of SAD, such as temperament, cognitive factors, peer relationships, parenting, adverse life events and cultural variables (Spence & Rapee, 2016). It should be investigated how these factors interact with endophenotypes. Gender should also be taken into account in future studies, as there might be gender differences in psychophysiological endophenotypes or factors interacting with these endophenotypes. Besides studying which factors increase the risk for developing SAD in persons with a certain endophenotype, future longitudinal studies should also investigate which factors protect persons with a certain endophenotype from developing SAD.

Future longitudinal studies should also investigate how these psychophysiological endophenotypes develop over time. As described in *chapter two*, only the ERN has been studied in both adults and children. The other psychophysiological endophenotypes could also be compared between adults and children, preferably in a longitudinal design. Furthermore, endophenotypes might affect the development of SAD differently across the lifespan. For example, Haller et al. (2014) propose that normal development in brain regions associated with emotional and social processes increases information processing biases in attention, interpretation and expectations. This puts adolescents at increased risk for developing SAD (Haller et al., 2014). Furthermore, adolescents become more focused on peers instead of their parents (Blakemore & Mills, 2014; R. W. Larson & Richards, 1991; R. W. Larson, Richards, Moneta, Holmbeck, & Duckett, 1996), and react more intensely to social rejection (Gunther Moor et al., 2014; Sebastian, Viding, Williams, & Blakemore, 2010). So, normal development might enhance information processing biases, which might lead to SAD in certain adolescents.

Clinical implications

The ultimate goal of this research on psychophysiological endophenotypes of SAD is to gain more insight in the underlying mechanisms of this disorder, and to eventually improve early detection and intervention. These insights can be used to focus treatment on the most important underlying mechanisms of SAD. For example, if it turns out that aberrant early processing of socially threatening stimuli is most important for maintaining SAD, it might help to focus treatment on alleviating this initial reaction. Furthermore, endophenotypes might eventually predict which treatment works best for which patient, as not all treatments might be equally effective for all patients with SAD. For example, patients with

psychophysiological endophenotypes related to attention biases (such as early event-related potentials) might need a different treatment than patients with psychophysiological endophenotypes related to interpretation biases (such as delta-beta correlation during anticipation). Although EEG research on predicting treatment response in anxiety disorders is only in its infancy (Lueken et al., 2016), some recent studies have found promising results. That is, P1 amplitude in response to faces might be a predictor of treatment outcome and N2 and LPP amplitudes in response to faces might be predictors of treatment response in anxiety disorders (Bunford et al., 2017; Hum et al., 2013).

Second, endophenotypes might play a role in early detection of SAD and the development of preventive interventions. If we could assess delta-beta correlation during anticipation, or N1/P3 amplitudes in the social judgment paradigm in children before they have developed SAD, it might be easier to intervene. Interestingly, children with a parent with SAD showed increased delta-beta correlation during resting state, compared to children without a parent with SAD (Miskovic, Campbell, et al., 2011). Insight in the factors that influence the development of SAD in children with a genetic vulnerability will help in the development of preventive interventions. Endophenotype research is not only useful for clinical settings, but might even be useful for school settings. School is a very stressful environment for children with SAD, due to the many interactions with peers and teachers. It should be investigated how teachers could encourage children with a genetic vulnerability for SAD to interact with peers and to gain positive experiences.

Conclusion

The goal of this dissertation was to delineate psychophysiological endophenotypes of SAD. Delta-beta correlation during anticipation of a stressful social situation, and N1 and P3 amplitude in the social judgment paradigm are candidate endophenotypes of SAD. Future research should continue this promising line of endophenotype research in three different directions. First, it should be investigated how these endophenotypes maintain SAD by studying their influence on later processing stages and subsequent behavior. Second, it should be studied which factors influence the development of SAD in persons with this genetic vulnerability and how endophenotypes develop over time. Third, it should be investigated how the endophenotypes could be best used in treatment, for example by giving more insight in the patho-etiology of SAD, and by improving early detection and preventive interventions.

Socially anxious parents were motivated to participate in our family study because they recognized their own anxiety in their children and did not want their children to develop the same problems as they were having. In addition, many participants came from the other end of the country and had to drive three hours (with young children on the back seat) to participate in our study. This nicely illustrates how motivated these family members were to do something for their relative with social anxiety disorder. These examples underline the importance of research on SAD and the need for future studies on factors that might help alleviating SAD.