Mapping the influence of social threat in the brain

In this thesis, research is presented with a strong focus on questions relating to how the brain responds when observing threat in others. All of the studies presented in this thesis were sampled from a healthy student population, in order to gain a fundamental understanding of automatic responses to social threat. Using various neuroimaging methods, we tried to investigate how such responses are represented in the brain. This research has given us an insight into at which level of the visual processing stream a distinction is made between neutral and emotional postures, as well as the involvement of action areas in emotion perception. In the case of sampling participants from the healthy population, we would consider automatic responses to social threat as adaptive and from an evolutionary viewpoint beneficial for survival. A fundamental understanding of triggering defensive actions can first of all give us insight into the differences with certain patient groups that would fail to show such responses, and secondly eventually provide insight in how to tailor treatment for these patient groups.

Automatic defensive responses to social threat; what if it goes wrong

As important as appropriate responses to social threat are, they are far from a given. Take the example of freezing behavior; freezing is a beneficial behavioural response which occurs whenever presented threat is ambiguous, which could stem for example from uncertainty of the intention of someone else or from observing threat at a distance (Blanchard, Hynd, Minke, Minemoto, & Blanchard, 2001). Freezing behavior allows for the scanning of the environment and making calculated decisions on how to proceed. Likewise, flight behaviour might be an optimal strategy when threat is close by and imminent. However, freeze and flight behaviours are not always the optimal defensive strategy when confronted with threat, and unnecessary or excessive freezing behaviour could be harmful rather than beneficial.

Excessive freezing and flight behaviour can be observed in anxiety disorders. Indeed, research has shown a positive correlation between the amount of freezing behaviour in response to aversive pictures and measured trait anxiety (Roelofs, Hagenaars & Stins, 2010), as well as a demonstrating a link between freezing behavior and subjective anxiety, panic, and other symptoms of anxiety (Schmidt, Richey, Zvolensky, & Maner, 2008). Similarly, one study presenting aversive pictures to either patients diagnosed with panic disorder, one of the six major anxiety disorders, or a group of control participants, showed heightened freezing responses in the patient group (Lopes et al., 2009). These are all examples of what is supposedly, from an evolutionary perspective, beneficial behavior leading to debilitating psychological disorders. When threat is misjudged to be omnipresent or inevitable, one might overexpress flight or freezing behavior, resulting for example in panic attacks or fear to leave the house.

At the other end of the spectrum we find fight behavior. If you are in an immediately threatening situation, one response strategy might be to *fight* rather than flee from the threat. This might prove to be the best strategy whenever the threat is deemed as defeatable, or if outrunning the threat seems unlikely. As goes for freeze or flight tendencies, fight can be an extremely beneficial response given the right circumstances. However, if fight behavior is too easily elicited, aggressive behavior might be observed. Specifically, psychopathy, a disorder which is associated with an increase in instrumental aggression (Glenn & Raine, 2009), has been linked to both increased fight tendencies, as well as reduced flight tendencies. Previous work has shown psychopathy patients fail to show avoidance tendencies towards angry faces that would normally be observed in healthy participants (von Borries, 2012).

Knowing that disorders such as anxiety and psychopathy might be partially explained through failure to show appropriate fight-flight-freeze responses to threat, how might this guide treatment plans? First of all, if we can establish a link between for example anxiety and symptoms rooted in avoidance of threat, treatment plans could be developed directly tackling the symptoms relating to this. For example, testosterone has been shown to facilitate social approach behaviours, and indeed administering testosterone to patients suffering from social anxiety disorders (SAD) increases approach tendencies towards presented angry faces (Dorien, Spinhoven & Roelofs, 2016). In a healthy female population, it has been demonstrated that testosterone administration biases the amygdala towards more threat approach (Radke et al., 2015). In psychopathic individuals it has been demonstrated that there is less down regulation of amygdala though dorslolateral prefrontal cortex when control of emotional actions is required, an effect which is particularly evident in psychopathic individuals with high levels of endogenous testosterone levels (Volman et al, 2016).

With respect to our own work, specifically referring to *Chapter 3*, we demonstrated that TMS stimulation over action related areas (inferior parietal lobule and ventral premotor cortex) has the ability to alter emotion specific amygdala responses in healthy participants. Given that the amygdala has been placed in the center of mediating motor responses to threat (LeDoux & Daw, 2018), it is of great interest for future research to explore whether such indirect mediation of amygdala could be beneficial for patient populations. This effect could be explored in two directions, firstly we demonstrated enhanced emotion sensitivity of the amygdala by means of an inhibitory protocol (continuous theta burst stimulation (cTBS)), something that could be of benefit in psychopathologies suffering from reduced emotion perception (e.g. psychopathy). On the other hand, it could be explored whether by use of excitatory protocols (such as intermittent theta burst stimulation (iTBS)) the reversed could be accomplished, i.e. reduced emotion sensitivity in the amygdala, something that could provide beneficial to patients suffering from anxiety disorders.

Optimization of Transcranial Magnetic Stimulation to increase clinical efficiency

A second major theme in this thesis concerns the use of non-invasive brain stimulation, and how the use of this methodology can be improved. One feature avenue of improving efficiency of non-invasive brain stimulation is by individualizing the stimulation paramters. In this thesis we had a particular interest in the variability observed in outcome measures related typically obtained in brain stimulation studies. Specifically, *Chapter 5* looked into some sources that may underlie variability that is observed when measuring Motor Evoked Potentials (MEPs) elicited with Transcranial Magnetic Stimulation (TMS). In this study we sought to understand whether the frequency and phase of an entraining transcranial alternating current stimulation (tACS) signal was applied at certain individualized frequencies. We found this to be the case when looking at the phase of an individualized beta signal entrainment. How can findings such as these be relevant in a broader perspective?

Importantly, TMS has proven of great value as a tool in cognitive neuroscience, but by now has proven itself equally indispensable within clinical settings (Lefaucheur et al, 2014, Wassermann & Lisanby, 2001). The clinical relevance of TMS has been first and most convincingly demonstrated in the treatment of depression. In 2008 the application of repetitive TMS (rTMS) was approved by the U.S. Food and Drug Administration for the treatment of depression, particularly for patients who failed to benefit from medication. Last year, *Zorgverzekeraars Nederland* deemed rTMS treatment for depression as scientifically proven to be beneficial, and in the near future Dutch health insurance will start covering the treatment costs. This treatment consists of applying a high frequency protocol (10Hz) over the left dorsolateral prefrontal cortex daily, for the duration of 4-6 weeks. One great advantage of rTMS treatment is that side effects are relatively few, mostly relating to discomfort of the stimulation, whereas beneficial effects can last up to several months after the treatment has ended. Response rates to rTMS treatment are typically between 40-45% (Fitzgerald, Hoy, Anderson & Daskalakis, 2016).

Whereas these results are undoubtedly solid and a promising result, there is certainly room for improvement. This mainly becomes apparent when looking at the application of TMS treatment in other psychological or neurological disorders, for which either treatment success is low, or results of effectiveness are altogether lacking. Whereas there is now sufficient evidence for definite efficacy for the use of rTMS in the treatment of depression and pain, evidence for motor stroke and schizophrenia is still a more mixed, and efficiency for treatment of auditory hallucinations and tinnitus seems probable but is not yet irrefutably present (Lefaucheur et al., 2014).

These mixed or altogether lacking findings could of course directly result from lack of effectiveness of TMS treatment for these particular disorders. However, given all the earlier mentioned benefits that TMS as a treatment method has, it is worthwhile exploring if the lack of evidence results from the fact that in these cases a 'one size fits all' approach is not fitting. Specifically, as we showed in *Chapter 5*, variability of brain stimulation can be both explored and explained by oscillatory activity in the brain. This holds true for externally entrained oscillations, something which our data provides evidence for, but also holds true for intrinsic neuronal oscillations. Together, current data stemming from fundamental research, could and is being used to tailor brain stimulation treatment. Of particular interest for the future is moving towards individualized brain stimulation.

This idea of individualized brain stimulation for treatment is by no means a far-fetched idea reserved for a distant future (Thut et al., 2018). As a matter of fact, the amount of research on the topic is ever increasing, and just last month Nature news reported on the matter. In an article titled 'Brain-stimulation trials get personal to lift depression', it is outlined that variability in the effectiveness of brain stimulation treatment likely resulting from differences both within and between individuals. Most importantly an individual's current brain state and brain activity could be driving such differences. At the moment, two different trials trying to implement this knowledge in treatment for depression are running; one team at Monash university in Australia is specifically interested in the potential of using electroencephalography (EEG) in the online guiding of the stimulation frequencies used in tACS. Another team in Tübingen, Germany, is applying a similar methodology, however with an interest in TMS. This group recently already demonstrated in a healthy sample the potential of reducing variability online using EEG-triggered TMS, demonstrating efficacy both for Motor Evoked Potentials, as well as rTMS (Zrenner, Desideri, Belardinelli & Ziemann, 2018).

The next step will be to apply this novel methodology to patient groups and see if indeed brain stimulation treatment can be optimized by means of individualized parameters. By applying brain stimulation in sync with ongoing intrinsic neuronal oscillations of the patient, and thus taking into account the current brain state of the patient, might radically change treatment efficacy. Additionally, efficacy of TMS treatment for disorders for which so far evidence was either weak, or lacking might be demonstrated.

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