Anxiety disorders are a leading cause of morbidity and entail a lot of costs. Adolescence is characterized by social fears and poor emotion regulation abilities which together increase the likelihood of the emergence of anxiety disorders. This emotion dysregulation is potentially caused by the emotion regulating brain areas, such as the prefrontal cortex and temporal cortex, that are still undergoing developmental changes throughout late adolescence.

Recently, new approaches have used functional magnetic resonance imaging-based neurofeedback to help participants gain control over emotion regulation brain networks by receiving real-time feedback on their brain activity and to use effective emotion regulation abilities. In this review, we provide an overview of the developmental changes in the brain and the corresponding behavioural changes, and explore how these can be influenced during adolescence using neurofeedback. We conclude that recent studies show promising results that children and adolescents can self-regulate emotion regulation brain networks thereby supporting the development of effective emotion regulation abilities.

**ANXIETY DISORDERS DURING DEVELOPMENT**

Fear is a brief and automatic response towards a specific stimulus (e.g. spiders) that causes physiological reactions such as heightened heart rate and vigilance. The key brain region of fear is the amygdala which brings sensory information into context with the input coming from the cortical and subcortical regions. According to Pavlovian fear conditioning, when an aversive unconditional stimulus is constantly paired with a previously non-fearful stimulus, the non-fearful stimulus will after some time become a fearful conditional stimulus. Likewise, fear can be unlearned by presenting the conditional stimulus multiple times without the aversive unconditional stimulus, which is called fear extinction. Fear is the base of anxiety disorders and is often learned early in life.

Emotion regulation refers to a person modifying his/her emotional responses, a change which can either happen automatically or by using conscious strategies. Fully functional emotion regulation includes identifying the emotional valence, recognizing that emotion regulation is necessary, and choosing an appropriate strategy. It has been shown that emotion regulation strategies undergo significant changes throughout development, both qualitatively (i.e. with regards to which strategy is used predominantly) and quantitatively (i.e. how often a strategy
is employed). For example, a cross-sectional study by Zimmermann and Iwanski\(^{10}\) of participants between the ages of 11 and 50 years used a self-report questionnaire (Negative Emotion Regulation Inventory) to investigate the participants’ emotion regulation strategies and emotional experiences. The results showed that the range of emotion regulation strategies is very limited during adolescence in comparison to children (quantitative difference). In particular, social support seeking and adaptive emotion regulation decrease during this period, along with increased suppression of emotions in fear situations, and dysregulation of emotions in anger situation. These maladaptive strategies can lead to emotional instability and higher neuroticism,\(^{10}\) and further research has shown that adolescents use maladaptive emotion regulation strategies (qualitative difference), such as self-blame and rumination, and under-use reappraisal which, in turn, places them at higher risk for anxiety disorders.\(^9\) Children and adolescents are sensitive to social stress and bullying and this can have a great impact on mental health which can have long-lasting effects into adulthood.\(^{11}\) A reason for the great impact of social stress might be that fear extinction in adolescents is weakened and therefore they do not unlearn the fear and suffer longer from it. When fear persists for a longer period it can eventually develop into an anxiety disorder. In accordance with that, it has been shown that social exclusion, a form of social stress, can increase the likelihood of developing social anxiety in adolescence.\(^{11}\) In a longitudinal study by Van Oort et al.,\(^{12}\) young people were studied from the age of 10 to 12 years until the age of 14 to 18 years. Participants filled out a self-report questionnaire (Revised Child Anxiety and Depression Scale) that covers the symptoms of several anxiety disorders, obsessive-compulsive disorder, and depression. The results revealed that there is a decrease in anxiety symptoms during the transition from childhood to adolescence, but they increase again from middle to late adolescence. Furthermore, anxiety levels were consistently higher in females.\(^{12}\)

Why exactly the vulnerability for anxiety disorders is heightened in children and adolescents is still not clear, but one contributing factor could be a malfunction in threat learning and threat extinction learning. A study by Lau et al.\(^{13}\) showed that adults have better discrimination between safety and threat cues than adolescents. Accordingly, adolescents might confuse safe situations with threatening ones, and therefore are anxious more often which facilitates the likelihood of an anxiety disorder. This lack of discrimination may be due to ongoing maturation in the underlying brain networks and an age-specific change in brain network connectivity.\(^{14,16}\)

**BRAIN DEVELOPMENT DURING CHILDHOOD AND ADOLESCENCE**

The heightened vulnerability for anxiety disorders and emotion dysregulation during childhood and adolescence might be explained by the brain development during this time. The maturation of the brain is expressed by grey matter loss and starts in puberty. A longitudinal study by Gogtay et al.\(^{17}\) tested participants every 2 years for four scans in total to pinpoint developmental changes in brain function. The start of recruitment was at around the age of 10 years. The results revealed an increase in grey matter during childhood and a start of reduction in adolescence.\(^{17}\)

In general, the grey matter loss begins in the back of the brain and spreads towards the front. The last regions to fully develop at the end of adolescence are the temporal cortex and dorsolateral prefrontal cortex (PFC).\(^{17}\) This differential timing pattern, with key regions that have been linked to emotion regulation and anxiety disorders developing late in adolescence, might therefore be a reason for the high emergence of anxiety disorders and poor discrimination between safety and threat cues in adolescence.\(^{13}\)

Emotional behaviour in the brain is controlled by a network of regions that include the PFC and the amygdala, which exhibit both structural and functional connections.\(^{18,19}\) The functional negative coupling between the two regions has been suggested to reflect top-down PFC regulation of amygdala reactivity.\(^{20,21}\) Interestingly, this specific relationship is only established during adolescence, with younger children exhibiting more positive connectivity between the regions during emotion regulation tasks.\(^{14,22,23}\) This has been demonstrated in a cross-sectional study by Gee et al.\(^{14}\) in which they tested participants in their childhood through early adulthood and compared their amygdala reactivity towards fearful faces and their functional connectivity between the amygdala and medial PFC in general. In this case, functional connectivity means the temporal correlation between the time courses of the amygdala and the medial PFC. Accordingly, if activation in both brain regions increases, we will observe a positive connectivity pattern. If, however, activation patterns in both regions show opposite trends, whereby one region increases activation and the other brain region decreases its response, then we speak of a negative connectivity pattern. The findings indicated that the functional connectivity between amygdala and medial PFC is positive in early childhood, slightly negative towards adolescence, and highly negative in early adulthood. Furthermore, amygdala reactivity decreased with age.\(^{19}\) The positive functional connectivity between amygdala and medial PFC could be caused by poor regulation of the amygdala by the PFC and therefore the amygdala is overreactive which elicits emotional instability.

It has also been shown that the observed developmental change in the connectivity pattern goes along with the prolonged acquisition of effective emotional and attention control strategies.\(^{24,26}\) In our previous research, we showed that the neural networks that process emotional face

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**What this paper adds:**

- Functional magnetic resonance imaging-based neurofeedback can be used for brain self-regulation in development.
- The emotion regulation networks play a key role in treating social anxiety with neurofeedback.
expressions fine-tune continuously throughout childhood and adolescence, and that individual differences in trait anxiety affect how adolescents process emotional faces, and learn about threat and safety signals.

A study by McRae et al. attempted to connect brain activity with cognitive reappraisal ability in children, adolescents, and young adults. The participants viewed negative or neutral pictures and had to either look at the pictures or re-appraise their emotions in case of a negative picture. The results revealed that there was no difference in emotional reactivity when negative pictures were viewed, but that the ability to re-appraise the negative affect significantly increased with age. Moreover, the improved cognitive reappraisal with age was associated with higher activation of the ventrolateral PFC.

**USING NEUROFEEDBACK TO PINPOINT PLASTICITY IN THE DEVELOPING EMOTION REGULATION BRAIN NETWORKS**

Kohn et al. have proposed a three stage-model of emotion regulation in the brain. The first stage involves recognizing and evaluating a stimulus. The amygdala and ventral striatum are responsible for generating the emotion and passing on the information to the ventrolateral PFC, where the emotion is consciously perceived and evaluated. When there is a need for emotion regulation, the ventrolateral PFC will send a signal to the dorsolateral PFC in the second stage. Finally, premotor areas, angular gyrus, and superior temporal gyrus are stimulated to execute the regulation. This final stage may elicit activity in the ventral striatum and amygdala which in turn causes the generation of a new emotion. One possibility to influence this process of emotion regulation is by neurofeedback training. Neurofeedback utilizes the latest developments of real-time data processing and pattern analysis to train participants in the self-modulation of neural networks. One example of self-modulation of neural networks can be seen in Figure 1. The strength of this technique lies in its high spatial resolution (including the ability to probe deep subcortical structures and whole-brain coverage), as well as the extraction of information from distributed activation patterns, and the mapping of functionally connected networks. This is particularly critical in development when functional brain networks change significantly and the fine-tuning patterns for these functional networks differ for typically and atypically developing populations.

If implemented successfully, the neurofeedback approach holds much promise for brain-based intervention approaches that aim to influence and shape the emerging networks in the developing brain. That is, it allows us to target not only cortical and subcortical task-relevant regions, but it also offers the necessary flexibility to accommodate the frequent changes in brain network configurations that are typical for emerging networks. Hereby, it is important to choose an appropriate experimental design and intervention schedule for participants during their development.

During neurofeedback training, participants learn to gain control over specific brain areas by receiving feedback on their brain activity. Participants are either encouraged to find a strategy to influence their brain activity on their own by trial and error or they get an instruction by the experimenter beforehand (e.g., ‘Think of happy things’). In anxiety disorders where emotion regulation seems to be dysfunctional, the PFC and amygdala can be targeted for neurofeedback training. During the training, brain activity is recorded by an fMRI or an electroencephalogram and the participant receives visual or audible feedback about his/her brain activity in a real-time setting. The participant learns to influence his/her brain activity either by trial and error or is taught certain strategies beforehand. (See Paret et al. for more information on the different neurofeedback research designs and approaches.) After some training, the participant becomes aware of the activity within the target areas and can change the activity consciously. Ideally, successful self-regulation of brain activity will turn into behavioural changes. As anxiety disorders are mostly associated with disrupted functional connectivity between the PFC and amygdala and not their separate activity levels, neurofeedback with real-time fMRI is advantageous, because of its high spatial resolution.

Several studies have demonstrated that neurofeedback training can be an effective method for reducing anxiety symptoms. For example, in Scheinost et al., patients with contamination anxiety performed neurofeedback training. They learned to self-regulate their orbitofrontal cortex which led to lower limbic circuitry connectivity and higher dorsolateral PFC connectivity. At the same time, contamination anxiety symptoms decreased, and the change persisted for several days. Another study by Zilverstand et al. achieved an improvement of symptoms in spider phobia by training participants to down-regulate their insula activity via neurofeedback. Moreover, the study proved that neurofeedback training was more effective than cognitive appraisal without giving feedback on brain activity. Further, Kimmig et al. conducted a near-infrared spectroscopy neurofeedback study in patients with social anxiety disorder. Throughout 15 training sessions, the participants learned to voluntarily regulate their dorsolateral PFC either up or down over a course of 6 to 8 weeks. After the training, the participants showed lower symptom severity. Recently, a study by Zhao et al. examined a subclinical sample with high levels of anxiety and conducted three sessions of neurofeedback training. During the training, they received feedback on their functional connectivity between the ventrolateral PFC and amygdala, while in the sham condition the participants got feedback on their functional connectivity between the amygdala and motor cortex. Unlike the sham group, the active group increased the functional connectivity and their anxiety levels significantly decreased.

With regards to the developing brain, our research group was the first to show that children and adolescents can be taught to regulate activity in emotion regulation...
One of the key findings was that the self-regulation effects were not limited to the neurofeedback target region but had also a differential effect on the overall emotion regulation brain network. This showcases the suitability of this approach to affect and modulate the underlying networks in the developing brain. In a second study, we then used functional connectivity-based neurofeedback to directly modulate emotion regulation network connectivity in females aged 14 to 17 years. Specifically, we were able to successfully train participants to modulate the functional coupling of the PFC and the amygdala towards a more negative connectivity pattern, which resembles the connectivity pattern found in the mature brain and away from the positive connectivity patterns that predominates in

Figure 1: Results from a previous neurofeedback study by Cohen Kadosh et al., where children and adolescents aged 7–17 years were training to upregulate activity in the anterior insula, a key emotion regulation region using positive imagery. Granger causality analysis was then used to assess the effective connectivity in the emotion regulation network as a function of percent signal change in the bilateral insula during the up-regulation condition (a) and the down-regulation condition (b). All arrows indicate significant correlations, whereas the red arrows indicate significant differences in amygdala–insula regulation. Reprinted from Cohen Kadosh et al. with permission from Elsevier. lAMY, left amygdala; lINS, left insula; rINS, right insula; IPL, left inferior parietal lobule; MCC, mid cingulate cortex; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute template; Pre, precentral sulcus; SMA, supplementary motor area.
younger children and anxious adults.\textsuperscript{21} We also found several brain–behaviour correlations. For example, we found that trait anxiety levels were positively correlated with initial functional connectivity, with lower trait anxiety levels predicting more negative functional connectivity. This result is in line with the finding that lower levels of PFC–amygdala functional connectivity can predict anxiety levels in anxious participants. We further extended this finding by showing that baseline state anxiety levels were negatively correlated with neurofeedback-related change (i.e. the lower the baseline state anxiety, the higher the neurofeedback-related change in functional connectivity throughout the training). This suggests that neurofeedback success could be increased if participants, and especially those with high levels of state anxiety, are relaxed and comfortable during the intervention. Further studies are now needed to pinpoint the specific characteristics of the relationship at the brain and behavioural level, and the longevity of these effects across time and sex.\textsuperscript{38,39}

**CONCLUSION**

Anxiety disorders are one of the most common mental disorders and often emerge in late childhood or adolescence.\textsuperscript{49} They are associated with emotional dysregulation that is most likely related to dysfunctional functional connectivity between the PFC and amygdala.\textsuperscript{50} As key emotion regulation brain regions such as the PFC develop continuously into late adolescence and early adulthood, this maturational change is also likely to be reflected in emotion regulation abilities. Here we have provided some first evidence of how neurofeedback can be successfully used to help children and adolescents to learn to self-regulate key emotion regulation brain networks, and to support the development of effective emotion regulation abilities.

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