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SHORT REPORT

Plasticity during childhood and adolescence: innovative approaches to investigating neurocognitive development

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Abstract

Adolescence is a period of profound change, which holds substantial developmental milestones, but also unique challenges to the individual. In this opinion paper, we highlight the potential of combining two recently developed behavioural and neural training techniques (cognitive bias modification and functional magnetic neuroimaging-based neurofeedback) into a research approach that could help make the most of increased levels of plasticity during childhood and adolescence. We discuss how this powerful combination could be used to explore changing brain–behaviour relationships throughout development in the context of emotion processing, a cognitive domain that exhibits continuous development throughout the second decade of life. By targeting both behaviour and brain response, we would also be in an excellent position to define sensible time windows for enhancing plasticity, thereby allowing for targeted intervention approaches that can help improve emotion processing in both typically and atypically developing populations.

Development during adolescence

Adolescence is a life-period associated with profound changes in the social environment, physical growth and substantial hormonal changes (Blakemore, 2008). Adolescence is also a period of protracted brain maturation. This is reflected in both grey matter changes, such as synaptic pruning or synaptogenesis, and white matter changes due to ongoing myelination and fibre organization (Giedd, Blumenthal, Jeffries, Castellanos, Liu, Zijdenbos, Paus, Evans & Rapoport, 1999; Harris, Reynell & Attwell, 2011; Lebel & Beaulieu, 2011; Petanjek, Judas, Simic, Rasin, Uylings & Rakic, 2011). This plethora of neurobiological changes affects the functional responsiveness and processing abilities of the developing brain (Harris *et al.*, 2011). One attractive hypothesis is that brain changes occurring specifically during adolescence enable the considerable programme of cognitive development occurring at the same time, which enables the adolescent to think more rationally but also to acquire more sophisticated cognitive strategies for regulating responses to emotional and social stimuli (Blakemore, 2008; Goddings, Burnett Heyes, Bird, Viner & Blakemore, in press; Lau, Britton, Nelson, Angold, Ernst, Goldwin, Grillon, Leibenluft, Lissek, Norcross, Shiffrin & Pine, 2011; Scherf, Behrmann & Dahl, 2012).

With the increased availability of neuroimaging facilities for children and adolescents in the last decade, research has begun to explore how different factors drive development (Brown, Lugar, Coalson, Miezin, Petersen & Schlaggar, 2005; Church, Petersen & Schlaggar, 2010; Cohen Kadosh, 2011; Cohen Kadosh, Johnson, Dick, Cohen Kadosh & Blakemore, 2012a; Crone & Ridderinkhof, 2011; Goddings *et al.*, in press; Lu, Dapretto, O'Hare, Kan, McCourt, Thompson, Toga, Bookheimer & Sowell, 2009; Schlaggar, Brown, Lugar, Visscher, Miezin & Petersen, 2002; Shaw, Greenstein, Lerch, Clasen, Lenroot, Gogtay, Evans, Rapoport & Giedd, 2006). However, while the results have been most encouraging in that they have provided some insights into how a specific developmental factor, such as cortical

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development, can predict changes in cognitive abilities (e.g. Shaw *et al.*, 2006), they have also highlighted the significance of gaining greater understanding of the unfolding developmental programme. For example, it is not difficult to see how clearly defined developmental trajectories for emerging cognitive functions (and the different factors that shape them) could be used to compare typical and atypical development. Crucially, these comparisons could inform research on early biomarkers of atypical development (Beddington, Cooper, Field, Goswami, Huppert, Jenkins, Jones, Kirkwood, Sahakian & Thomas, 2008). We use the term *sensitive period* here to refer to developmental phases during which certain cognitive ability levels are continuing to mature (see Figure 1 for an example study on emotion categorization). Moreover, we would like to suggest that these typical developmental changes are based on greater plasticity in the underlying cognitive and brain levels and thus are sensitive to a range of endogenous and exogenous factors (Cohen Kadosh, 2011).

Adolescence is a particularly interesting developmental period because novel factors become important during these times, as both the adolescent body and the social environment change substantially over a relatively short time period. Whether these factors are crucial or necessary for ensuring typical development remains to be determined. While there is some evidence for sensitive periods during language acquisition (Kuhl, Tsao & Liu, 2003) or basic face processing abilities (Le Grand, Mondloch & Maurer, 2004; Le Grand, Mondloch, Maurer & Brent, 2001) in earlier development, very little is known currently whether these periods also exist for more complex behaviours such as emotion processing and social cognition. New evidence that this may be the case was provided by a recent study in mice, which showed that social deprivation during pre-adolescence resulted in behavioural differences (i.e. sociability and working memory) and decreased myelination in the prefrontal cortex (Makinodan, Rosen, Ito & Corfas, 2012). The prefrontal cortex is a brain region in humans also known to be heavily involved in social interactions and understanding other people's mental states (Blakemore, 2008). Interestingly, another recent study found comparable *and* reversible effects in adult mice (Liu,

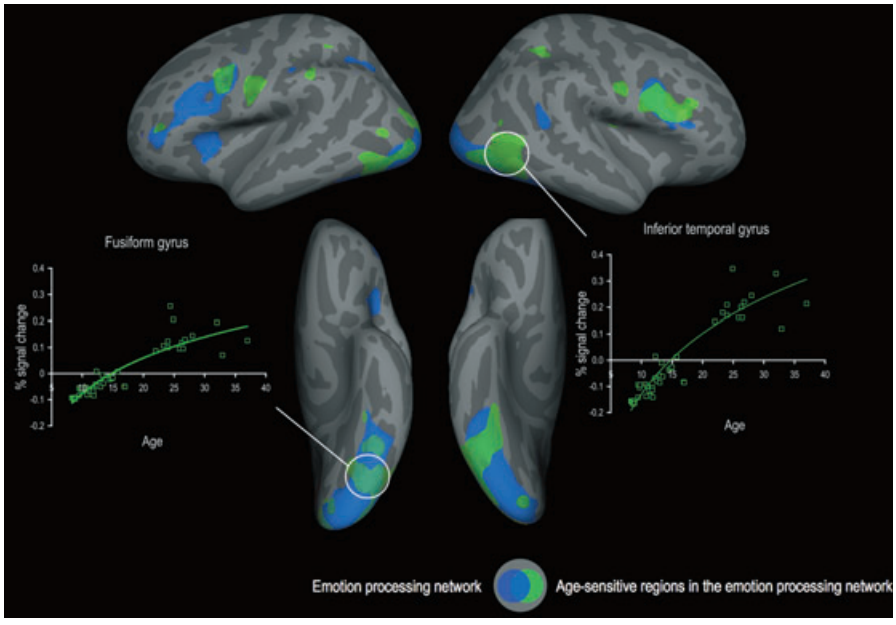

Figure 1 *Developmental changes in functional brain networks during childhood and adolescence. In this study, Cohen Kadosh and colleagues (2012) tested 48 participants aged 7–37 with a simple emotion categorization task and were able to show not only the general emotion processing network in the brain, but also highlight those brain regions that exhibit functional changes with age, but independent of task performance levels. Activation for the emotion network is shown in blue, and activation, whereas the age-sensitive sub-network is shown in green. For two selected brain regions, changes in activation are shown as a function of age. These age-sensitive brain regions might represent possible starting points for using a combination of cognitive bias modification and fMRI-based neurofeedback to influence emotion processing at earlier developmental stages. The maps are thresholded at uncorrected height-threshold of $p < .001$, and an extent-threshold of $p < .05$, corrected. Both hemispheres are shown in a lateral (top) and inferior (bottom) view. The right hemisphere is depicted on the right. Figure reprinted with permission from Cohen Kadosh et al. (2012a).*

Dietz, Deloyht, Pedre, Kelkar, Kaur, Vialou, Lobo, Dietz, Nestler, Dupree & Casaccia, 2012), which were observable even after relatively short periods of social isolation. Short periods of social isolation affected myelination only but did not result in overt behavioural effects. These findings led the authors to suggest that myelination levels might reflect plasticity in adults. It remains to be determined whether social deprivation might have similar effects during adolescence, or whether there are specific periods during which the effects of isolation are less reversible.

While understanding the driving factors of development is important in its own right, the main contribution of developmental research lies in the discovery of processes that may be amenable to intervention approaches. More specifically, a better understanding of when and possibly how these trajectories diverge could be useful for determining periods of increased plasticity (and time windows of increased sensitivity) in a specific cognitive domain. This would not only allow us to assess how improving cognitive functions affect brain development and vice versa, but, even more importantly, how we can use training and intervention techniques for far-reaching effects at the cognitive and functional and structural brain level (Jolles & Crone, 2012), thereby making the most of a period of profound plasticity, such as childhood and adolescence. It is important to point out that this research approach aims at a moving target, as the timing of these developmental trajectories may not always overlap. This leaves us with the special challenge to devise intervention techniques for emerging cognitive abilities, which are dependent on structural and functional brain networks that may have been established at an earlier stage. This is non-trivial, as research has shown for example that the majority of structural changes in the brain tend to peak either before or during mid-childhood (Giedd *et al.*, 1999; Petanjek *et al.*, 2011; Sowell, Thompson, Leonard, Welcome, Kan & Toga, 2004). This raises interesting questions about optimal timings (if these exist) of interventions – and whether these should be administered before or during these relevant neural changes.

A sensible starting point for training and intervention approaches would be emotion processing, as it has been shown that both emotion processing and regulation develop continuously throughout adolescence (Cohen Kadosh *et al.*, 2012a; Goddings *et al.*, in press; Guyer, Monk, McClure-Tone, Nelson, Roberson-Nay, Adler, Fromm, Leibenluft, Pine & Ernst, 2008; Monk, McClure, Nelson, Zarahn, Bilder, Leibenluft, Charney, Ernst & Pine, 2003; Thomas, De Bellis, Graham & LaBar, 2007; Waters, Henry, Mogg, Bradley & Pine, 2010; Waters, Mogg, Bradley & Pine, 2008). Emotion processing in this particular context refers to the identification and categorizing of emotional expressions in others in the first instance, as well as evaluating and regulating one's subsequent affective response. Prolonged acquisition periods, such as those observed for emotion processing, allow the individual to respond flexibly to changing environments. This is particularly important in light of the changing social environment and expectations that an adolescent faces. However, they also heighten vulnerability levels, in that they increase the time that an individual could be exposed to disruptive factors (Paus, Keshavan & Giedd, 2008). For emotion processing and regulation, it has been shown that approximately one in four adolescents exhibits increased levels of worries and anxiety. This is important, as there is evidence that adolescent anxiety is a major predictor for anxiety disorders in adulthood (Pine, 1999), thereby making adolescence a particularly sensitive period of plasticity for acquiring successful emotional coping strategies. Dual mismatch models have suggested that key difficulties in emotion regulation during adolescence may be owed to a developmental mismatch between earlier maturing limbic brain networks supporting emotional responses on the one hand, and slower developing prefrontal networks involved in cognitive control and inhibition on the other (Nelson, Leibenluft, McClure & Pine, 2005; Pfeifer & Allen, 2012; Pfeifer, Masten, Moore, Oswald, Mazziotta, Iacoboni & Dapretto, 2011). Similarly, it could be suggested that the observed difficulties in emotion regulation simply reflect the prolonged development of emotion processing in the limbic system itself. Targeting these emotion processing circuits would therefore be an intuitive starting point for exploring the effects of intervention on behavioural and neural plasticity during childhood and adolescence.

Changing emotion processing at the behavioural and brain levels

In recent years, two novel and promising intervention approaches have been pioneered that either (1) selectively target cognitive processing biases in children, adolescents and adults (i.e. cognitive or attentional bias modification (CBM/ABM)) or (2) modulate the brain response in the underlying supporting brain regions using real-time functional magnetic resonance imaging (fMRI)-based neurofeedback (NF).

Both ABM and CBM represent psychological intervention techniques which were developed based on principles of cognitive and affective neuroscience. ABM techniques modify a participant's automatic processing of affective stimuli and it can be used to train participants to systematically direct their attention away from

potentially threat-inducing stimuli, such as emotional faces or words (Bar-Haim, 2010). For most ABM designs, a variant of the dot-probe task is used. The dot-probe task requires participants to process two stimuli (a neutral and a threatening stimulus), which are then replaced by a target stimulus in the screen location of one of the emotional stimuli (MacLeod, Mathews & Tata, 1986). A faster orientation response towards dots that are replacing threatening stimuli is taken to signify an attention bias towards threat, whereas the opposite pattern signifies avoidance of threat. ABM techniques have been used in both adults and pediatric populations. For example, Eldar and colleagues (Eldar, Apter, Lotan, Edgar, Naim, Fox, Pine & Bar-Haim, 2011) found that ABM training could successfully reduce anxiety levels in clinically anxious children and adolescents (aged 8–14 years). CBM techniques modify the automatic, emotional assessment of stimuli, such as ambiguous sentences or situations (MacLeod & Holmes, 2011). In the study by Lothmann and colleagues (Lothmann, Holmes, Chan & Lau, 2011), typically developing 13–17-year-olds were presented with incomplete scenarios, which had to be resolved by completing the last word (e.g. 'it is the first day of the term. Your new teacher asks everyone to stand up and introduce themselves. After you have finished, you guess the others thought you sounded … cl-v-r.'; see also, for more examples). They found that following a training session during which the participants saw either mostly positively or negatively resolving scenarios, participants were more likely to endorse either positive or negative attributions of novel situations as a function of training group. While training did not directly alter mood, those who had been trained to adopt more positive interpretations reported feeling less anxious under emotional provocation (Lau, Belli & Chopra, 2012). In a more recent study, this training paradigm successfully challenged negative interpretations of clinically anxious youths, although with only a single session of training mood effects were not found (Fu, Du, Au & Lau, in press). These examples show the impressive plasticity of attentional processing strategies and highlight the translational potential for clinical and especially pediatric clinical populations (Eldar *et al*., 2011; Fu *et al*., in press; Hakamata, Lissek, Bar-Haim, Britton, Fox, Leibenluft, Ernst & Pine, 2010; Lang, Blackwell, Harmer, Davison & Holmes, 2011).

For self-regulation at the brain level, NF is a newly emerging technique that utilizes the latest developments of real-time data processing and pattern analysis in order to train participants in the self-modulation of neural networks. In NF studies, participants are presented with real-time brain activation in specific regions of interest, usually via a simplified visualization, such as a thermometer. This thermometer receives online updates on actual brain responses, albeit with a delay of a couple of seconds, and participants are instructed that blue values indicate low activation levels and red values indicate high activation levels (see Figure 2). With NF, participants can be trained to reliably regulate their online brain response with high spatial precision (deCharms, 2007; deCharms, Maeda, Glover, Ludlow, Pauly, Soneji, Gabrieli & Mackey, 2005; Johnston, Boehm, Healy, Goebel & Linden, 2010; Weiskopf, Mathiak, Bock, Scharnowski, Veit, Grodd, Goebel & Birbaumer, 2004a; Weiskopf, Scharnowski, Veit, Goebel, Birbaumer & Mathias, 2004b), and participants learn to regulate their brain responses within a training time of 15–30 minutes. Whether this amount of training will be sufficient in the case of minor participants remains to be determined, but we are currently investigating this question with a group of children. For both typical adults and clinical populations (e.g. deCharms *et al*., 2005; Johnston *et al*., 2010), success rates have been quite high (most participants learn to regulate their brain response within one or two sessions), which might be due

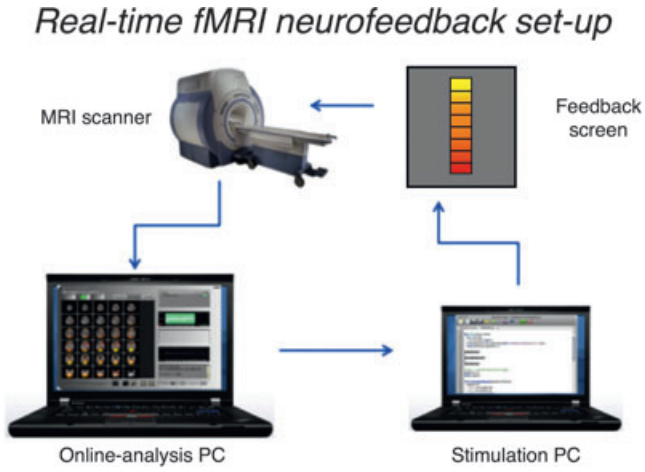

Figure 2 *Experimental set-up in real-time fMRI neurofeedback experiments. Following a simple localizer run, participants are instructed to up- or downregulate their brain response in specific regions of interest. These brain regions may differ for each participant. The online analysis allows the experimenter to conduct a live analysis of the brain activation in those regions of interest and to display the response level in a simplified thermometer display via the stimulation computer. The thermometer is updated every 2 seconds. Most participants will learn to control their brain regions within a short training session of 15–20 minutes and reliable effects can be secured and continuously improved in 2–3 10-minute test sessions (e.g. Johnston et al., 2010). Figure modified with permission from Esmail & Linden (in press).*

to the fact that in some studies NF regions are defined individually for each participant and great care is taken to ensure that participants try out different strategies to find the one that works for them. There are currently no effect sizes available, and because of the relative novelty of the method, no evidence is available about how long the effects last.

Another issue, which is of course critical for all neuroimaging studies, concerns the suitability of using the fMRI signal to discern individual differences in functional brain organization. Previous research has shown that retest reliability tends to be middling to low, depending on the specific index chosen, with slightly higher rates for intra-subject reliability as opposed to between-subject reliability (see Bennett & Miller, 2010, for a recent review). A variety of factors, such as scanner system noise, physical noise introduced by the subject in the scanner environment, as well as subject-dependent variations in cognitive processing strategy and affective state, all contribute to lowering retest reliability. Moreover, substantial structural change, as observed during childhood and adolescence might exacerbate these measurement problems. In addition, there is some evidence that reliability might vary across brain regions. A recent study assessed reliability for brain regions supporting the processing of emotional faces in adolescents and found that retest reliability decreased significantly from occipital to frontal brain regions and was particularly poor for the amygdala (van den Bulk, Koolschijn, Meens, van Lang, van der Wee, Rombouts, Vermeiren & Crone, in press). While these issues are known and are relevant for all neuroimaging research, they require a particularly cautious approach for choosing reliable and effective target areas for NF in pediatric populations.

We also have only very limited information about the potential mechanisms of successful self-regulation or its behavioural effects. FMRI-based NF seems to affect the functional connectivity of the regulated area, which is defined on the basis of the correlation between this area and other parts of the brain (Rota, Handjaras, Sitaram, Birbaumer & Dogil, 2011). For example, up-regulation of amygdala activity was associated with increased functional connectivity with frontal areas (Zotev, Krueger, Phillips, Alvarez, Simmons, Bellgowan, Drevets & Bodurka, 2011), but further work is certainly needed to assess the specificity and sustainability of any changes to the functional architecture of brain networks brought about by NF. It is an attractive speculation that any positive behavioural effects of NF are accompanied by changes in neural plasticity. There are several ways to address this issue experimentally. The best-established procedures are probably available for the motor cortex, and one pilot study of NF in stroke has used TMS (transcranial magnetic stimulation)-based plasticity measures to assess its neuroplastic effects (Sitaram, Veit, Stevens, Caria, Gerloff, Birbaumer & Hummel, 2012). We expect that more mechanistic work of this nature will be incorporated into future studies of the feasibility and behavioural or clinical effects of NF. Work with paired-pulse TMS, in particular, combined with behavioural and perceptual tests will also reveal how fine grained any temporal effects of NF-based learning will be. This is perhaps of less relevance to its potential effects on the cognitive appraisal of emotions, which is relatively slow (e.g. in the second range, which corresponds to the timescale of the haemodynamic delay) (Silvers, McRae, Gabrieli, Gross, Remy & Ochsner, 2012), but may be crucial for any effects on fast perceptual processes. However, recent data on grating discrimination after NF training of directional patterns of activity in visual cortex (Shibata, Watanabe, Sasaki & Kawato, 2011) are promising for a potential role of NF in perceptual learning protocols as well.

In relation to the topic of this article, NF has proven particularly useful for up- or down-regulating the brain regions involved in emotional responses (Johnston *et al.*, 2010; Johnston, Linden, Healy, Goebel, Habes & Boehm, 2011; Zotev *et al.*, 2011), a finding that is of relevance to research on adolescent emotion regulation. Johnston *et al.* (2010) used affective pictures to first localize emotion networks in adults. They then used NF techniques in subsequent runs and found activation increases during periods of up-regulation in the precuneus and medial prefrontal cortex and, with increasing training success, in the ventral striatum (Johnston *et al.*, 2010). Zotev and colleagues taught adults to successfully up-regulate their left amygdala in an NF experiment and they also observed significant increases in functional connectivity between different regions of the amygdala network comprising also the right medial frontal polar cortex, the bilateral dorsomedial prefrontal cortex, the left anterior cingulate cortex, and bilateral superior frontal gyri. The latter finding is important, as it shows that NF not only affected brain responses within a specific brain region (i.e. the left amygdala), but also the processing flow within a larger network of regions, thereby highlighting the potential of using NF to affect activity within the whole brain. In clinical pilot studies, NF has shown some preliminary success in reducing pain in patients with fibromyalgia (deCharms *et al.*, 2005), improving motor fluency in Parkinson's disease (Subramanian, Hindle, Johnston, Roberts, Husain, Goebel & Linden, 2011) or alleviating depression (Linden, Habes, Johnston, Linden, Tatineni, Subramanian, Sorger, Healy & Goebel, 2012; Esmail & Linden, in press).

The NF studies reviewed above have used comparable approaches to demonstrate the effectiveness and feasibility of using NF in both healthy and clinical populations. However, they varied in one crucial aspect, namely, whether participants were given explicit instructions as to which strategy they should use to regulate their brain responses. That is, participants in most studies were instructed to figure out an effective regulation strategy on their own, with only some patient studies suggesting the use of positive mental imagery (deCharms *et al.*, 2005). It is not difficult to see therefore how much more powerful NF could be in combination with an established cognitive regulation strategy, such as CBM. We therefore think that the obvious next step would be to combine CBM and NF to improve functioning during periods of exceptional plasticity, i.e. during childhood and adolescence (Figure 3). The combination of CBM-NF could not only further our understanding of how CBM affects emotion regulation at the cognitive level, but also of their joint effects on neural plasticity (by using real-time fMRI), thereby shedding light on brain–behaviour relationships during development.

We believe the benefits from such a combined approach to be multifold (see also Box 1 for further thoughts): *first*, it will provide important insights into the amenability of developmental trajectories in a specific cognitive domain, such as emotion processing. Moreover, a better understanding of the simultaneous changes in behaviour and brain functions will inform research on learning and training in general and across the entire lifespan, thus being of interest to research on development and mature functions alike. *Second*, it could help with identifying sensitive developmental windows during which intervention approaches would prove most effective. The combination of CBM/NF could be used, for example, to establish a window of enhanced activation in the learning-relevant networks during which the acquisition of cognitive strategies is particularly effective. Alternatively, it could be used to determine time windows during which intervention approaches would be ineffective or even disruptive, having an adverse effect on development (Jolles & Crone, 2012). It may very well be, for example, that attempts to improve or enhance cognitive functioning in a specific domain, e.g. emotion processing relies on several subprocesses that develop at different speeds, thereby rendering intervention at a suboptimal time pointless. Such a finding would also help with understanding the timing of different developmental trajectories, as suggested by the developmental mismatch models of adolescence reviewed above. With regard to adolescence, it would be interesting to see, for example, whether boosting cognitive control by selectively targeting specific brain circuits could to some extent guide earlier maturing emotion perception.

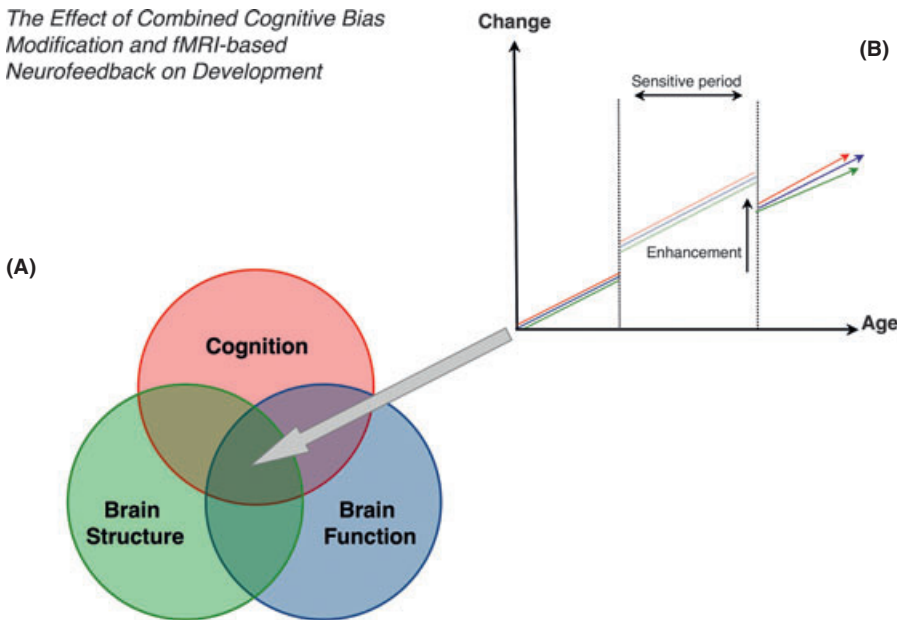

Figure 3 *Possible effects of cognitive bias modification (CBM) and fMRI-based neurofeedback (fMRI-NF) intervention approaches on development.* ***A:*** *The different interacting factors that shape development.* ***B:*** *The combination of CBM and fMRI-NF can be used to define sensitive periods during which the enhancement of the behavioural and neural bases of learning is particularly effective. Moreover, it could be used to influence and possibly enhance learning and development in typically and atypically developing populations.*

Box 1.
Using CBM and NF in pediatric populations: Food for thought

Are there sensitive periods during which the use of combined CBM and NF is most effective? Similarly, are there time windows when it is most aversive?

Could this approach be useful for identifying early biomarkers of atypical development in children at risk of developmental disorders?

What does successful NF reflect: improvements in the functional response of specific brain regions, of the connectivity between multiple brain regions? Or does NF lead to changes in the underlying brain structure?

How do these changes affect neurotransmitter concentration in the targeted brain regions?

How do these changes differ from typical, age-appropriate changes that come along with everyday exposure and brain maturation?

Third, it is exciting to think that we could have to hand effective tools to shape response strategies during childhood and adolescence and possibly avert maladaptive response patterns, especially in populations at risk of developing psychological disorder. Given that the particular strength of ABM/CBM lies in the little interventive effort needed to achieve impressive effects, one could easily imagine that once instructions have been given, these designs could be self-administered at home, possibly using a mobile phone applet. CBM could thus aid the transfer of the self-regulation strategies learnt in the NF sessions into real-life situations. The latter assumption runs in line with cognitive behavioural therapy approaches, but this time, cognitive strategies are additionally strengthened by the increased response from underlying brain networks. While it is currently not yet possible to answer conclusively how NF will eventually guide training programmes, it nevertheless represents an exciting and potent research approach that can provide great insight into plasticity and developmental changes of particular abilities. There is increasing support for neural factors to be considered correlates of behaviour – and in the case of disorders, as biomarkers, i.e. features that developmentally precede the behavioural phenotype. Here, we are suggesting that we could pre-empt the manifestation of a behavioural disorder by exploring whether these developmental neural precursors can be changed. In addition, the increased spatial resolution that fMRI-based NF provides over more conventional EEG-based NF will allow us to determine where a particular stimulus is processed in the brain and to focus intervention approaches with increased precision. This approach can also accommodate individual differences that are due to differences in age, gender or ability level and that are reflected in the activation of slightly different brain regions. FMRI-based NF allows the possibility to make individually tailored target areas which, presumably, once targeted are more amenable to change. Also, understanding which brain regions are implicated in a behavioural disorder, and which regions are amenable to change, may be important from a preventative perspective.

Finally, given the increasing interest in looking not only at the impaired side of the spectrum of atypical development, but also the enhanced, exceptional side, another use of combined CBM and NF would be to achieve cognitive enhancement by improving functioning within the typical range and beyond or even just reinstituting functioning through compensatory networks. Needless to say, the latter suggestion would require thorough social and ethical discourse and consent (Cohen Kadosh, Levy, O'Shea, Shea & Savulescu, 2012b).

To conclude, the proposed approach of combining CBM with NF has much potential to open new vistas to conducting research on brain development. In addition, we hope that a better understanding of the underlying developmental trajectories and the amenability of brain–behaviour relationships to intervention approaches as provided by the techniques discussed above could contribute to developing effective intervention approaches that both target atypical development and contribute to cognitive enhancement.

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