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# Mapping Prefrontal Cortex Functions in Human Infancy

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It has long been thought that the prefrontal cortex, as the seat of most higher brain functions, is functionally silent during most of infancy. This review highlights recent work concerned with the precise mapping (localization) of brain activation in human infants, providing evidence that prefrontal cortex exhibits functional activation much earlier than previously thought. A systematic evaluation of the activation patterns in these neuroimaging studies mainly based on functional near-infrared spectroscopy reveals that prefrontal cortex function can be broadly divided into two distinct anatomical clusters with different functional properties. One cluster of activations falls within the region of the medial prefrontal cortex and is mainly involved in affective processes; another cluster is located in lateral aspects of the prefrontal cortex and shows sensitivity to cognitive processes such as memory and attention. This distinction is in line with adult data and evolutionary models and may represent a developmentally continuous organization principle of prefrontal cortex function. All in all, this review is aimed at providing a synthesis of new findings that are emerging from the use of neuroimaging techniques with infants as well as at encouraging further theory-driven research to understand the developmental origins of prefrontal cortex function.

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In the course of evolution, humans have developed numerous higher cognitive skills such as language, reasoning, planning, and complex social behavior. It has been shown that the prefrontal cortex (PFC) can be seen as the neural substrate that underpins much of this higher cognition (Wood & Grafman, 2003). PFC refers to the regions of the cerebral cortex that are anterior to premotor cortex and the supplementary motor area (Zelazo & Müller, 2002). In humans, the PFC makes up approximately a quarter to a third of the cortex (Fuster, 2008). While the PFC in humans may not be disproportionately enlarged with respect to other brain regions when compared to our closest living relatives the great apes (Semendeferi, Lu, Schenker & Damasio, 2002), there have been suggestions that certain parts of the PFC possess a number of human-specific structural and functional properties that may underpin human-unique social and cognitive abilities (see Saxe, 2006).

Based on its neuroanatomical connections, the PFC can be broadly divided into two sections: (i) the medial PFC (mPFC) and (ii) the lateral aspects of the PFC (lPFC) (Fuster, 2008; Wood & Grafman, 2003). The mPFC includes the medial portions of Brodmann areas (BA) 9–12 and BA 25, and it has reciprocal connections with brain regions that are implicated in emotional processing (amygdala), memory (hippocampus), and higher-order sensory regions (temporal cortex). The lPFC includes the lateral portions of BA 9–12, BA 44, 45, and BA 46, and it has reciprocal connections with brain regions that are implicated in motor control (basal ganglia, premotor cortex, supplementary motor area), performance monitoring (cingulate cortex), and higher-order sensory processing (association areas, parietal cortex). Furthermore, lPFC and mPFC are reciprocally connected, allowing for information exchange and integration across these two broad sections of the PFC. Critically, the distinction between lPFC and mPFC in neuroanatomical terms maps onto general differences in brain function. Namely, while mPFC is thought to be mainly involved in processing, representing and integrating affective information, lPFC is thought to support cognitive control processes (Wood & Grafman, 2003). That it is of great importance to consider this distinction when thinking about PFC function is also reflected in evolutionary models according to which lPFC developed much later than mPFC and lPFC is considered to have evolved from motor regions of the brain (Fuster, 2008). Despite this distinction, it should be noted that mPFC and lPFC are parts of a coordinated system, and they normally work together in the service of guiding human behavior and decision-making.

In psychological research, the PFC has traditionally been studied as the neural system subserving executive control functions. Executive function (EF) can be understood as the collection of psychological processes that

are critical for controlling emotion, thought, and action (Zelazo & Müller, 2002). In the literature, PFC function and EF are often used interchangeably. While there might be some merit in conceptualizing the PFC as a control region of the brain, one should be cautious about simply equating PFC function with EF not least because some patients with PFC lesions are not impaired in their EF and other patients with lesions in regions other than the PFC show EF impairment (see Zelazo & Müller, 2002). More importantly, such a simple model fails to capture the organization of PFC (subsections with different connectivity) and the complexity of EF (different forms of control).

One basic distinction that has been particularly useful in thinking about EF and its relation to PFC function is a model that distinguishes between hot (mPFC) and cool (lPFC) EFs (Zelazo & Müller, 2002). The underlying idea is that any kind of problem a person is confronted with may differ in the degree to which it requires the regulation of affect and motivation. Zelazo and Müller (2002) argue that: "whereas cool EF is more likely to be elicited by relatively abstract, decontextualized problems, hot EF is required for problems that are characterized by high affective involvement or demand flexible appraisals of the affective significance of stimuli." (p.455) In many instances, the distinction between hot and cool EF may map very nicely onto the distinction between social and nonsocial contexts, because social behavior is very closely tied to emotion (Adolphs, 1999, 2001). However, there are many circumstances that are highly affectively charged that do not require a social interaction to take place or to be imagined. Conversely, there are many situations in which social behavior requires more calculated and cool executive control. Therefore, the distinction between hot and cool EF mainly rests on the affect induced in the individual by the specific situation and is less dependent on the domain (social versus nonsocial) in which a situation occurs. This functional distinction, which is based on the underlying neuroanatomy of the PFC, has been very fruitful in studying EF (Zelazo & Carlson, 2012).

Taken together, a picture of PFC function emerges that is able to accommodate and to a certain degree unify what is known about neuroanatomy and connectivity of the PFC and EF. From a developmental perspective, a whole host of questions arises concerning the nature and ontogenetic roots of this functional organization (division) in PFC. While this model has been successfully applied to study EF in preschool age children (Zelazo & Carlson, 2012), we only know very little about PFC function in infancy. In particular, the main research focus on studying PFC function in infancy has been on lPFC and what one may call cool cognitive functions (Diamond, 1991, 2002), while mPFC functions have been greatly neglected. Furthermore, while there is a host of studies concerned

with infant PFC function using electroencephalographic measures (Bell & Cuevas, in press), EEG studies are limited in that they do not provide exact information regarding the location of brain activation (de Haan, 2007). Until recently, the use of neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS) to map (localize) cortical activation that can be readily used with human infants was relatively scarce. However, in the last decade, we have seen a strong increase especially in fNIRS research with infants (for a review see Lloyd-Fox, Blasi & Elwell, 2010), so that there are now a number of studies that have looked at PFC function during infancy but no review of this body of work is available (see Table 1 for an overview of those studies).

This review attempts to fill this gap by evaluating the existing data with a focus on the available fNIRS work on PFC function during infancy. The use of fNIRS permits the spatial localization of brain activation from cortical regions by measuring hemodynamic responses (Lloyd-Fox et al., 2010; Minagawa-Kawai, Mori, Hebden & Dupoux, 2008). Other neuroimaging techniques that are well established in adults are limited in their use with infants because of methodological concerns (Aslin & Mehler, 2005). For example, positron emission tomography (PET) exposes participants to radioisotopes, and fMRI requires the participant to remain very still and exposes them to a noisy environment. Although both PET and fMRI have been used with infants, this work is restricted to the study of sleeping, sedated or very young infants. The method of fNIRS is better suited for infant research because it can accommodate a good degree of movement from the infants, enabling them to sit upright on their parent's lap and behave relatively freely while watching or listening to certain stimuli. In addition, unlike PET and fMRI, fNIRS systems are portable. Finally, despite its inferior spatial resolution also in terms of obtaining responses from deeper (subcortical) brain structures, fNIRS, like fMRI, measures localized patterns of hemodynamic responses in cortical regions, thus allowing for a comparison of infant fNIRS data with adult fMRI data (see Strangman, Culver, Thompson & Boas, 2002 for evidence of a strong correlation between hemodynamic responses measured with fMRI and fNIRS).

The specific aim of the review is to assess under which conditions and when in development lPFC and mPFC engagement can be observed, and in particular, whether a pattern exists that follows the distinction between hot and cool functions introduced above. The following section will provide a review of the individual studies organized by topic. The emerging picture of PFC functions will then be critically evaluated in the discussion and a refined and extended model of PFC function based on prior work with

TABLE 1
Overview of studies on infant prefrontal cortex function

| *Age* | *Stimuli* | *PFC region involved in task* | *Imaging method* | *Publication* |
|---|---|---|---|---|
| Newborns | Olfactory (own mother's colostrum, vanilla essence, distilled water) | mPFC | fNIRS | Bartocci et al. (2000) |
| | Auditory (infant-directed speech, ADS) | mPFC | fNIRS | Saito, Aoyama et al. (2007) |
| | Auditory (emotive speech, monotone speech) | mPFC | fNIRS | Saito, Kondo et al. (2007) |
| | Auditory (syllable sequences with different repetition patterns) | lPFC (left) | fNIRS | Gervain et al. (2008) |
| 2 months | Visual (faces, diodes) | mPFC | PET | Tzourio-Mazoyer et al. (2002) |
| 3 months | Auditory (forward speech, backward speech) | lPFC (right) awake infants | fMRI | Dehaene-Lambertz et al. (2002) |
| | Auditory (beep cue predicts auditory event while infants were asleep) | lPFC | fNIRS | Nakano et al. (2008) |
| | Auditory (habituation to syllable sequences) | lPFC | fNIRS | Nakano et al. (2009) |
| | Visual (mobiles, checkerboards) | lPFC | fNIRS | Watanabe et al. (2008) |
| | Visual (mobiles presented with or without sound) | lPFC and mPFC | fNIRS | Watanabe et al. (2013) |
| 4 months | Visual (mutual gaze, averted gaze) | mPFC | fNIRS | Grossmann et al. (2008) |
| 5 months | Visual (triadic interaction, no referent, no eye contact) | lPFC (left) | fNIRS | Grossmann and Johnson (2010) |
| 4–13 months | Auditory (mother or stranger's voice, infant- or ADS) | mPFC and lPFC (left) | fNIRS | Naoi et al. (2012) |
| 5–13 months | Live interaction (object permanence test) | lPFC | fNIRS | Baird et al. (2002) |
| 9–12 months | Visual (video recording of own mother or unfamiliar female) | mPFC | fNIRS | Minagawa-Kawai et al. (2009) |

PFC = prefrontal cortex; fNIRS = functional near-infrared spectroscopy; lPFC = lateral aspects of the PFC; mPFC = medial PFC; PET = positron emission tomography; ADS = adult-directed speech.

adults will be used to better understand infant PFC functions. Such a survey of the available data on infant PFC function is also important because there has been a long-held belief that PFC is functionally silent during childhood (see Zelazo & Müller, 2002; for a review). While this view has been changing in the last decades as a result of work showing that lPFC is functional at the end of the first year of life (Bell & Fox, 1992; Diamond, 2002), there still seems to be a prevailing view that PFC is functionally silent during most of the first year of life. Contrary to this view, this review will provide evidence from neuroimaging studies showing that PFC is functionally involved in a number of contexts from early in infancy.

## EMPIRICAL REVIEW

### Olfaction

Newborns enter the world with a number of behavioral biases that allow them to preferentially attend and respond to certain stimuli such as speech and faces (see Grossmann & Johnson, 2007). However, we are only beginning to understand what role prefrontal brain regions play in these early attempts of the newborn to respond to her environment and organize her perceptual experiences. It is interesting to note that one of the very first and pioneering fNIRS studies with infants looked at PFC responses in newborns to different olfactory stimuli (Bartocci et al., 2000). The perception of smells helps the newborn to navigate in the extrauterine world and is critical for the localization of and latching onto the nipple during breast-feeding. In Bartocci et al.'s study, newborns were presented with three different smells (mother's colostrum, vanilla, and as a control stimulus the smell of distilled water). As expected, the smell of distilled water did not activate mPFC. While the smell of vanilla resulted in an increased hemodynamic response in the left mPFC in all babies, the response in the left mPFC to the mother's colostrum decreased with age. This suggests that with experience a mPFC region that has been implicated in olfactory processing in adults (Sobel et al., 1998) becomes less responsive to a relevant olfactory cue that has been shown to help guide and motivate newborns' behavior during breast-feeding. Why the response decreases with age is not clear but one possibility suggested by the authors is that the critical odorous compound, which newborns are sensitive to, is more concentrated in the breast milk earlier on and reduces in concentration over the first few days or that the early milk contains a distinct substance that makes it smell different. Alternatively, an increased mPFC response to the mother's colostrum may play a greater role during the initial phase when the infant has to first learn to latch onto the breast, and this becomes less

important once this response is learned over the first few days. Regardless of the exact explanation, what is important for the current context is that already in newborns, parts of the mPFC cortex are sensitive to what is presumed to be an affectively loaded appetitive sensory cue.

## Speech and Language Processing

Saito, Aoyama et al. (2007) investigated PFC responses in the context of newborn infants' sensitivity to auditory stimulation. Specifically, they had newborns listen to their own mother's voice reading a story in infant-directed speech (IDS) compared with their mothers reading the same story in adult-directed speech (ADS). Prefrontal responses to IDS and ADS were measured compared with a baseline of white noise. IDS compared with ADS is characterized by a higher pitch, wider pitch range, and exaggerated pitch contours across cultures (Fernald, 1985, 1992). Infants are highly attuned to IDS, as shown in a preference for IDS over ADS (Cooper & Aslin, 1990). Using fNIRS, Saito, Aoyama et al. (2007) found that IDS when compared to ADS significantly increased mPFC responses, suggesting that newborn infants discriminate between these two forms of speech and dedicate increased mPFC-processing resources to IDS, which is of high affective relevance to the infant. In a follow-up study, Saito, Kondo et al. (2007) replicated this finding and showed that an increased mPFC can be obtained in response to nonmaternal emotional speech (synthesized unfamiliar female voice) when compared to monotone speech. This finding suggests that it is the emotional prosody that characterizes positive affect in speech that drives this effect on mPFC in newborns.

In a recent study (Naoi et al., 2012), infants 4–13 months of age were presented with IDS and ADS sentences spoken by their own mother or a female stranger and prefrontal and temporal cortex responses were measured using fNIRS. This study showed that while infants' temporal cortex discriminated between IDS and ADS regardless of speaker, PFC (mPFC and lPFC in the left hemisphere) was engaged only when the mother spoke with IDS. Together with the fNIRS data from newborns presented above, this suggests that prefrontal brain responses undergo change with development and become more finely tuned to the primary caregiver's voice. Indeed, Naoi et al. can show that prefrontal responses change within the age range tested (4–13 months) such that at 7–9 months of age infants' prefrontal brain activity is sensitive to their mothers' IDS, while younger (4–6 months) and older infants (10–13 months) do not show such an effect. The authors argue that this finding is consistent with behavioral work showing that at the age of 7–9 months infants show the strongest preferences for their primary caregivers and anxiety toward strangers.

Apart from emotional features of speech, fNIRS has also been used to examine newborns' sensitivity to speech structure. More specifically, Gervain, Macagno, Cogoi, Pena & Mehler (2008) assessed newborns' ability to detect repetitions in syllable sequences. In a first experiment, newborns listened to sequences containing immediate repetitions (e.g., "mubaba") compared with random sequences (e.g., "mubage"). Gervain et al. found that repetition sequences evoked greater responses in the left lPFC and that this repetition enhancement increased over the course of the experiment. In a second experiment, newborns listened to nonadjacent repetitions (e.g., "bamuba") compared with random sequences but did not show any evidence of discrimination. This indicates that infants are sensitive to immediate repetitions in the speech signal and that the lPFC in the left hemisphere, a region implicated in verbal working memory in adults (Jonides et al., 1997), may underpin this sensitivity critical for language learning. Note, though, that apart from the lPFC there were also differences observed in bilateral temporal cortices in both hemispheres, suggesting that a network of brain regions is involved in this repetition detection process.

Speech and language perception have also been examined in older infants. One very prominent example of speech perception research is the fMRI study by Dehaene-Lambertz, Dehaene and Hertz-Pannier (2002). In this study, awake and asleep 3-month-old infants were presented with normal (forward) and reversed (backward) speech. Irrespective of the alertness state, a region in the left angular gyrus (located in the posterior superior temporal and inferior parietal cortex) discriminated between forward and backward speech, showing a significantly increased activation to forward speech. This effect has been replicated in newborn infants using fNIRS and is seen only for the mother tongue (Sato et al., 2012). With respect to prefrontal functioning, Dehaene-Lambertz et al. (2002) found that similar to the angular gyrus finding, the right lPFC responded more strongly to forward speech. Importantly, unlike the angular gyrus, lPFC activation differed between forward and backward speech only when infants were awake but not when they were asleep. This effect of sleep on lPFC activation is in line with findings from a study using event-related brain potentials (ERPs) to study auditory processing in 2-month-olds that found a frontal negativity (mismatch response) only when infants were awake but not when they were in quiet sleep (Friederici, Friedrich & Weber, 2002).

In a more recent fNIRS study (Nakano et al., 2008), anticipatory brain activation in lPFC regions was observed in 3-month-old infants while asleep. More specifically, Nakano et al. (2008) presented infants with an auditory cue (beeps) that was either predictive of the following auditory

event (female voice) or did not have any predictive value. Only when the preceding beep was predictive, lPFC activity occurred preceding the onset of the female voice. This suggests that during sleep infants learn to implicitly associate a beep sound with a voice and increase lPFC activation in anticipation of the auditory event. This finding with sleeping infants appears to be in contrast to what Dehaene-Lambertz et al. (2002) reported concerning the absence of lPFC involvement during sleep. It seems important to consider here that there are different sleep states. In infants, quiet sleep (without rapid eye movements) can be distinguished from active sleep (with rapid eye movements) (Friederici et al., 2002). These sleep states have been shown to affect infant brain responses to auditory stimulation in such a way that active sleep brain responses during auditory tasks in many respects resemble brain responses when awake (Kushnerenko, 2003). It is possible that more infants were in active sleep during fNIRS testing than during fMRI testing, which could potentially have contributed to differences across studies. Moreover, the difference across studies may also have resulted from other factors, one being the different demands imposed on the cognitive system by the speech discrimination task when compared to the anticipation task. Specifically, implicit learning during sleep is a widespread phenomenon that can also be observed in sleeping rats (Coenen & Drinkenburg, 2002), although implicit learning in sleeping rats relies on the hippocampus not lPFC, while processing human speech and language and distinguishing it from other complex sounds may represent a more cognitively complex process and hence require the infant to be awake.

In any case, other work with sleeping infants supports the notion that lPFC plays a role in auditory working memory and learning. Specifically, Nakano et al. (2009) examined brain responses in 3-month-old asleep infants during an auditory habituation–dishabituation experiment using fNIRS. In this study, both temporal and prefrontal regions showed habituation effects (decrease in the hemodynamic response) but only regions in bilateral lPFC cortex were sensitive to novelty during the dishabituation phase, as seen in an increase in the hemodynamic response. This demonstrates that in young infants, the lPFC is involved in detecting auditory novelty, suggesting that it serves as a neural system instantiating the attentional orienting toward novelty, a mechanism that is considered pivotal for sensory learning.

## Object Processing

More evidence for the notion that lPFC plays a critical role in attentional orienting also comes from fNIRS work on visual processing in infancy.

Watanabe, Homae, Nakano and Taga (2008) found that 3-month-old infants showed increased lPFC responses to videos showing moving objects of a mobile than when presented with checkerboard reversal patterns. The authors suggest that the increased lPFC response to colorful mobiles reflects increased attention and a visual preference for this stimulus. However, what underpins this visual preference for mobiles remains unclear. There seem to be at least two factors that may be reflected in the increased lPFC response to mobiles: (i) enhanced visual complexity in object number, shape, color, and motion, and (ii) potential familiarity with mobiles which are commonly placed over cribs or changing tables at home (mobiles are very powerful in attracting and maintaining infants' attention). More work is needed to clarify what visual properties of objects such as mobiles attract infants' attention and engage lPFC. While these questions remain open, Watanabe et al. (2013) conducted a follow-up study in which they extended the prior work by showing that presenting a sound that accompanied the visual presentation of the mobile resulted in activation of mPFC. On the basis of this finding, the authors argue that mPFC activation may reflect increased affective processing during multisensory stimulation.

One fNIRS study that has systematically looked at infants' object processing and PFC functioning is the work by Baird et al. (2002). This study investigated the role of lPFC in 5- to 12-month-old infants' ability to hold objects in working memory when the objects were hidden under a piece of cloth (object permanence test). The results demonstrated that infants that reliably searched for the object (i.e., showed object permanence) showed increased lPFC activation during the occlusion phase, while this activation of lPFC was absent in infants that did not search for the object (did not show object permanence). This finding is in line with developmental data from work with nonhuman primates (Diamond & Goldman-Rakic, 1989) and human infants (Bell & Fox, 1992) implicating lPFC in the emergence of object permanence and working memory.

## Face and Gaze Processing

Another important area of research is the work on the perception of social visual stimuli. The human face provides the infant with a wealth of socially and affectively relevant information. To respond to faces is considered an important adaptation in social animals. From birth, human infants preferentially attend to faces (Johnson & Morton, 1991). One study that has looked at the brain areas involved in face processing is the work by Tzourio-Mazoyer et al. (2002), who presented 2-month-old infants with a face or an array of colored diodes used as a control stimu-

lus, while measuring brain activity using PET (note that although PET is not commonly used with infants due to the fact that it exposes infants to small amounts of radiation, the six infants scanned in this study were tested in an intensive care unit as part of a clinical follow-up). The results of this study revealed that, like adults, 2-month-olds activated core face-processing regions such as the right inferior temporal gyrus and bilateral superior temporal gyrus. More important for the purpose of the current review, when viewing faces compared with the visual control stimulus infants activated regions within the mPFC in the right hemisphere. This suggests that already at this young age, infants recruit parts of the so-called extended face-processing network that are considered to be crucial in assigning social and affective significance to faces (Haxby, Hoffman & Gobbini, 2000).

An important social signal encoded in faces is eye gaze. The detection and monitoring of eye gaze direction is essential for effective social learning and communication among humans (Csibra & Gergely, 2009). Eye contact is considered to be one of the most powerful modes of establishing a communicative link between humans (Kampe, Frith & Frith, 2003). In an fNIRS study, 4-month-old infants watched two kinds of dynamic scenarios in which a face either established eye contact or averted its gaze followed by a smile (Grossmann et al., 2008). The results revealed that, similar to what is known from adults (Kampe et al., 2003; Pelphrey, Viola & McCarthy, 2004), processing eye contact activates not only superior temporal cortex implicated in processing information from biological motion cues but also the mPFC important for social and affective communication. A further experiment measuring electrical brain responses (high-frequency bursts in the 40 Hz range) showed that only a smile that was preceded by eye contact evoked increased PFC responses in 4-month-old infants (Grossmann et al., 2008).

That smiling at an infant while making eye contact is a powerful socio-affective cue triggering mPFC activation has also been shown in another study (Minagawa-Kawai et al., 2009), in which 9- to 12-month-old infants were presented with videos of either their own mother or a female stranger smiling at them or looking neutrally (without positive affect) at them. Smiling at the infants evoked greater activity in mPFC regardless of the familiarity with the face. However, mPFC activity was significantly greater in response to the own mother smiling when compared to the female stranger smiling. This demonstrates that infants' mPFC responses are tuned to affective cues from the primary caregiver, suggesting that mPFC is involved in social-communicative processes that are of vital importance for attachment between caregiver and infant. It is interesting to note that in the same study mothers showed very similar mPFC response when

looking at their own infants' smiling, indicative of a neural mechanism shared by caregivers and infants.

Eye gaze also plays an important role in directing and coordinating attention during triadic interactions between self, other, and the environment. During a typical triadic interaction, a person may establish eye contact with another person and then direct that person's gaze to an object or event. The psychological process by which two people share attention toward the same object or event is called joint attention. In a recent study, fNIRS was used to localize infant prefrontal brain responses during triadic social interactions (Grossmann & Johnson, 2010). Infants watched an adult's face in the middle of the screen with an object either to the left or to the right side of the face. In the joint attention condition, the adult raised her eyebrows and smiled while holding eye contact with the infant, then shifted her eyes toward the object, then shifted her eyes back to the infant, and finally turned her head toward the object. In the first control condition, the no referent condition, the person behaved exactly the same as in the joint attention condition, except that she looked and turned toward the side where there was no object. In the second control condition, the no eye contact condition, the person looked at the object without establishing any eye contact with the infant (the person looked down with her eyes closed before shifting her eyes toward the object). The results showed that by the age of 5 months, infants are sensitive to triadic interactions and, like adults, they recruit a specific prefrontal region localized in left lPFC only when engaged in joint attention with another person but not during the control conditions (Schilbach et al., 2010). This raises the question why, in comparison with the other studies using face and gaze stimuli that showed mPFC involvement (see above), this study shows an effect on lPFC function. One possibility is that while gaze cues might play an important role in this study, the affective component, in particular the mutual engagement with a social partner through eye contact was controlled for in one of the control conditions (no referent condition). Thus, if the affective component is controlled for then the specific cognitive structure (representations of self-other-object) that is required during triadic interaction may become primary. This might be why lPFC involvement was observed during the triadic interactions in Grossmann and Johnson's (2010) study.

## DISCUSSION

This review of the available neuroimaging work on infant PFC function from various domains (olfaction, speech and language, object, and face–

gaze processing) has revealed systematic differences with respect to which subsection of the PFC is involved. Specifically, we have seen that while mPFC is mainly associated with affective processes, lPFC is mostly involved in cognitive processes (memory and attention). To a certain degree, this functional distinction also maps onto the difference between social (face and gaze) and nonsocial information (language and object) processing. This might have to do with the fact that social cognition and interaction is inherently and tightly linked to emotional processes (Adolphs, 1999, 2001). However, the social versus nonsocial distinction falls short of explaining why in the studies by Watanabe et al. (2008, 2013) on object processing (nonsocial tasks), the pairing of a visually presented mobile with a sound would evoke a response in the mPFC, while presenting the same stimulus only visually would not. Similarly, in the work on joint attention (Grossmann & Johnson, 2010), which clearly falls in the social domain, a specific lPFC response was observed. Therefore, the distinction between mPFC and lPFC function is best described by a division of labor into affective and cognitive processes, respectively.

This distinction is also in line with various models of adult PFC function (Fuster, 2008) and models of EF in childhood (Zelazo & Müller, 2002). Even within one research area, such as the work presented on speech and language processing in infants, there appear to be fairly clear distinctions as to when mPFC and lPFC become involved. More specifically, while some aspects of language, namely prosodic processing of infant-directed and in particular emotive speech evokes mPFC activation (Saito, Aoyama et al., 2007; Saito, Kondo et al., 2007), processing other aspects of speech and language such as linguistic structure, predictability, and novelty result in differential activation of lPFC (Gervain et al., 2008; Nakano et al., 2008, 2009). This suggests that even within one domain of cognitive functioning such as language processing, there is functional specialization within PFC depending on the features of language that are being processed.

Given this distinction between lPFC and mPFC involvement as evident in this review, it is interesting to note that to date there has not been any study testing differential functional involvement of these two sections of the PFC directly with the same group of infants. Based on what we have seen in this review, it would be predicted that, for example, when infants were habituated to faces averting their gaze and then presented with a face showing eye contact or a face showing another individual during dishabituation, then for the same infant, seeing eye contact should result in mPFC activation while seeing a novel face should result in lPFC activation. This is because the social-affective aspect of the face would presumably be represented in mPFC, whereas novelty would evoke activation of the lPFC.

Similarly, in the auditory domain, if infants were habituated to a sentence read in ADS and then presented with the same sentence in IDS or a novel sentence in ADS, then hearing IDS should result in mPFC activation, while hearing a novel sentence in ADS should result in lPFC. It is important to test this prediction in future studies because an experimental design of this kind would allow us to directly examine whether and when this distinction in PFC function emerges.

One issue that seems particularly pertinent for a better understanding of the development of PFC function is that only very few of the reviewed studies have examined infant PFC function across different ages. Obviously, this is critical to assess whether and how PFC functions change during infancy. For both lPFC and mPFC, there is evidence that functional changes occur during infancy. Baird et al. (2002) showed that lPFC involvement changes between 5 and 12 months of age as the ability to hold objects in working memory (object permanence test) emerges. From the study, it is not clear at what age the increased lPFC involvement emerged, making it difficult to evaluate when the reported changes in lPFC function occur and how this relates to other behavioral and EEG studies. Naoi et al. (2012) found that mPFC activity changes such that at 7–9 months of age infants' prefrontal brain activity is sensitive to their mothers' IDS, while younger and older infants do not show such an effect. However, while the authors argue that this finding is consistent with behavioral work showing at the age of 7–9 months infants show the strongest preferences for their primary caregivers and anxiety toward strangers, there is no behavioral criterion as in Baird et al. (2002) work that could be used to verify this conjecture. This points to the general problem in neuroimaging work of a lack of data on how brain function relates to actual behavioral performance. While it is valuable to include behavioral variables to study brain–behavior relationships during infant development, such behavioral measures are not always available. In fact, this might be precisely why infancy researchers resort to neuroimaging, because it provides a unique window into the infant mind by bypassing infants' limited behavioral repertoire. After this general discussion, the following sections will deal with a number of important remaining issues that arise from the review of the empirical work presented here.

## Connectivity

As alluded to in the introduction, the division into mPFC and lPFC is largely based on its neuroanatomical connections and what we know about human adult and monkey brain anatomy (Fuster, 2008; Wood & Grafman, 2003), with the mPFC being reciprocally connected to brain regions

that are implicated in emotional processing (amygdala), memory (hippocampus), and higher-order sensory regions (temporal cortex), and the lPFC being reciprocally connected with brain regions that are implicated in motor control (basal ganglia, premotor cortex, supplementary motor area), performance monitoring (cingulate cortex), and higher-order sensory processing (association areas, parietal cortex). To gain a better and more complete picture of PFC function in infancy, it is vital to understand how PFC connectivity develops during the first year of life. However, the studies presented here do not provide any insights into how structural and functional connectivity changes for the PFC functions studied. More generally speaking, one important aspect to consider is that while we have observed activation of individual PFC regions during infancy, we do not know whether the activity of these regions is coordinated into functional networks as seen in adults. In other words, we are still in the dark about how PFC function in terms of cortical networks develops. Here, I would like to briefly outline some emerging evidence that speaks to this important issue (for a more extensive discussion of the development of functional cortical networks and the role of PFC, see Johnson, Grossmann & Cohen Kadosh, 2009).

As seen in this review, PFC may be activated from early on in infancy but at that point may not be functionally connected with more posterior regions of cortex, and thus play little role in selectively activating ('controlling') posterior regions due to a lack of myelination of the relevant long-range connections (fiber tracts) (Johnson et al., 2009). In line with this, there is work using resting-state fMRI with infants indicating that some of the functional connections between certain parts of PFC and posterior cortical regions known in adults are not yet developed in infants (Fransson et al., 2007). Furthermore, evidence from resting-state studies testing infants across various ages shows that this long-range integration of cortical activity emerges throughout the first few years of life (Fransson, Aden, Blennow & Lagercrantz, 2011; Homae et al., 2010) and that the so-called cortical hubs within the PFC, that is PFC regions that are heavily connected to other cortical regions, can be first identified at the end of the first year of life and then become progressively more complex and adult-like during development (Gao et al., 2009). The relevance that these changes in resting-state activity during infancy have for infants' brain function while actively involved in one of the functional experimental tasks reviewed here is unclear and requires attention in future work.

Another important issue to consider in this context is the relationship of learning and PFC functional connectivity. Specifically, in adults prefrontal regions have been shown to be required more when learning a task

or acquiring a new skill, than once it is acquired (see e.g., Sigman et al., 2005). This may explain the observation from a number of developmental fMRI studies that there is a general migration of activity during childhood from greater activity in PFC than in temporal cortex to the reverse pattern in adulthood (see Johnson et al., 2009 for a review). This supports the notion that a great deal of what makes up development is learning. Based on these findings, it is possible that once PFC has learned to select the appropriate pattern of posterior regional activation to succeed in a given task, cortical activity will tend to migrate to these posterior regions and decrease in PFC itself. However, as alluded to in the discussion on the resting-state findings, this pattern of PFC and posterior cortex relationship might be complicated by the fact that long-range connectivity is limited at least in younger infants.

### Neurotransmitters

A further point to reflect on concerning the distinction between mPFC and lPFC is that these two sections of PFC are also different with respect to the neurotransmitter systems that play a primary role within these regions. There is evidence that the serotonergic system is particularly important for mPFC functions (e.g., Heinz et al., 2004), while the dopaminergic system is important for lPFC functions (e.g., Diamond, 2002). This differentiation in terms of neurotransmitter systems is consistent with the functional distinction between mPFC and lPFC discussed throughout this review. Namely, serotonin has been shown to play a major role in emotional processing and social behavior (Canli & Lesch, 2007), whereas dopamine is involved in working memory and cognitive control (Goldberg & Weinberger, 2004). The effect of genetic variation within these neurotransmitter systems on PFC function has been extensively studied in adults (Meyer-Lindenberg & Weinberger, 2006). There are only very few extant studies investigating genetic association effects on PFC function in infancy, most of which have used behavioral measures to examine PFC function (Diamond, 2002; Holmboe et al., 2010). However, so far, there has not been any work that has directly looked at genetic variation in neurotransmitter systems and its association with PFC activity using fNIRS or fMRI in infants. Taking this step is a further important aspect of elucidating developing PFC function especially when it comes to understanding individual differences in PFC function. That the investigation of genetic variation in the serotonergic and dopaminergic system is useful in understanding individual differences in infant brain functioning has been shown in recent work using ERPs (Grossmann et al., 2011).

## Selectivity

A further issue that arises from this review is that the fNIRS studies that make up the majority of the work discussed here differ a great deal with respect to the coverage of cortical regions and the spatial resolution within each region. This affects the conclusions that can be drawn concerning the selectivity of localized prefrontal brain responses. Specifically, due to NIRS systems constraints, some of the older fNIRS studies only used very few channels (corresponding to one small cortical region) from which hemodynamic responses were sampled. For example, Bartocci et al. (2000) measured from only two channels and Baird et al. (2002) measured from only four channels and then collapsed data across those channels. Although there might have been theoretical reasons as to why certain brain regions were targeted, not sampling brain responses from other regions (also outside PFC) may point to a much higher degree of selectivity in the brain responses than warranted. Now that whole-head fNIRS systems have become available a much more precise mapping of infant brain function has been achieved (e.g., Watanabe et al., 2013). Nonetheless, whole-head fNIRS systems are very cost intensive and may thus not be easily available. In these cases, the imaging protocol should be that a few channels are also used to measure activity from a control region, that is, a region for which no functional differentiation or a different response pattern is predicted.

Relatedly, the fNIRS data presented here did not allow for an assessment of the depth at which the source of given PFC activation is located (more superficial or deeper aspects of the PFC) (see Correia et al., 2012; for fNIRS methodology that allows for the measurement of depth-dependent hemodynamic responses in infants) . This question is of particular relevance to our understanding of infant mPFC function and linking it to adult mPFC function. Specifically, from the fNIRS data available it is not clear whether the functional differences described in infants stem from more superficial parts of mPFC or from regions localized deeper in the orbital and medial aspects of mPFC where much of the adult fMRI work has localized affective processing (see, Roy, Shohamy & Wagner, 2012 for review). Thus far, it is mainly the functional similarity in infant and adult mPFC responses that render it likely that the adult and infant neuroimaging results represent comparable brain processes.

## Emotion versus Cognition

A final point for discussion is the degree to which *affective* and *cognitive* functions that we have assigned to mPFC and lPFC, respectively, are

separable in this way and whether there is not a need for integration of these processes. This issue goes back to a general discussion of the degree to which emotion and cognition need to be considered as distinct (Bell & Wolfe, 2004; Pessoa, 2008), a question that is beyond the scope of this article. As far as models of PFC function are concerned, there has been a recent proposal according to which the most anterior portion of PFC, namely the fronto-polar cortex or BA 10, might play an important role in manipulating and integrating affective information from mPFC and cognitive information from lPFC (Koechlin & Hyafil, 2007). To extend a model of infant PFC function in this form might be very useful, providing a more powerful platform for thinking about developing PFC function by allowing for the integration of emotional and cognitive processes in the service of decision-making and social behavior.

## CONCLUSION

In summary, this review has shown that the distinction in mPFC and lPFC functions can be observed from early in development and may thus represent a hard-wired and developmentally continuous organization principle of PFC function. Moreover, we have seen that to better understand developing PFC function, it is important to integrate information from functional neuroimaging studies with what is currently known about PFC connectivity, neurotransmitter systems, and behavioral development. Wood and Grafman (2003) argued that the merit of any theory of PFC function should be evaluated according to a number of criteria such as whether the theory is explicit about the (kind of) information that is stored in the PFC and whether the theory consistent with the structure, connectivity, and neurophysiology of the PFC. An additional criterion that should be added to the list of criteria is how well the theory lives up to what we know about the development of PFC function. It is my hope that this review of the neuroimaging data available on localizing infant PFC function contributes to a better understanding of this developmental dimension of PFC function and can ultimately help shape theoretical accounts.

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