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A walk on the dark side: TMS over the right Inferior Frontal Gyrus (rIFG) disrupts behavioral responses to infant stimuli

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Abstract

Infant signals, including infant sounds and facial expressions, play a critical role in eliciting parental proximity and care. Processing of infant signals in the adulthood brain is likely to recruit emotional empathy neural circuits, including the inferior frontal gyrus (IFG). Here, we used transcranial magnetic stimulation (TMS) to test the role of right IFG (rIFG) in behavioral responses to infant signals. Specifically, a group of nulliparous women were asked to perform a handgrip dynamometer task and an Approach Avoidance Task (AAT) after receiving TMS over the right IFG or over a control site (vertex). Suppressing activity in the rIFG affected the modulation of handgrip force in response to infant crying. Moreover, the AAT showed that participants tend to avoid the sad infant face after Vertex stimulation, and this bias was counteracted by rIFG stimulation. Our results suggest a causal role of rIFG in sensitive responding towards sad infants and point to the rIFG as a critical node in the neural network underlying the innate releasing mechanism for feelings of love, affection and caring of sad infants.

Keywords: Infant Cry; Infant Faces; Repetitive Transcranial Magnetic Stimulation (rTMS); right Inferior Frontal Gyrus (rIFG)

Introduction

Infant signals elicit parental proximity and care and are essential for child survival. In particular, infant crying and emotional facial expressions are considered important ways to communicate infant needs to the parent. A key component of parents' ability to provide adequate care to the infant is empathy (Abraham, Raz, Zagoory-Sharon, & Feldman, 2017; Ainsworth, Blehar, Waters, & Wall, 1978; Stern, Borelli, & Smiley, 2015), defined as the ability to share and comprehend others' inner states (Zaki & Ochsner, 2012). In fact, empathy is postulated as one of the main components of sensitive parenting, as parents first have to interpret infant signals in an accurate way before they can select an adequate caregiving response (Ainsworth et al., 1978).

At the neural level, empathy relies on a basic emotional system that underlies the ability to share feelings, and a more cognitive system that supports understanding of the other's mental state (Zaki & Ochsner, 2012). Specifically, the emotional system relies on the embodied simulation function (Gallese, 2014), that allows individuals to form internal representations of the actions or emotions they perceive. This function is supported by a complex brain network, comprising of the anterior insula, the anterior cingulate cortex, and the inferior frontal gyrus (IFG). Several neuroimaging studies have shown that the emotional empathy system is involved in the perception of and response to infant signals. For example, the IFG seems to play a role both in the perception of infant emotional faces (Montoya et al., 2012) and infant sounds (Riem et al., 2011, 2012). Additional evidence for the role of the IFG in parenting processes comes from studies showing that reduced IFG reactivity to infant signals is associated with maternal depressive symptomatology and insensitive parenting (Laurent & Ablow, 2013). In particular, it seems that IFG de-activation is associated with less caregiving sensitivity (Musser, Kaiser-Laurent, & Ablow, 2012), that is, the ability to respond to infant's signals in a contingent and appropriate way. In addition, IFG activation in response to infant crying is sensitive to administration of oxytocin (Riem et al., 2011), a hormone involved in mother-infant bonding, the initiation of maternal care, responding to infant signals, and parenting behavior (Bakermans-Kranenburg, van IJzendoorn, Riem, Tops, & Alink, 2012; Weisman, Zagoory-Sharon, & Feldman, 2012). It is possible that decreased IFG activity hinders the activation of a process of empathic resonance in response to infant emotional states and therefore constitutes a risk for dysfunctional parenting at a behavioral level. In fact, a composite score of the integrity of the embodied simulation network (including IFG activity) measured in mothers during the first year of their infants' life predicted a variety of child outcomes during preschool (Abraham, Hendler, Zagoory-Sharon, & Feldman, 2016) and early school age (Abraham et al., 2017).

Although several studies point to a role of the IFG in mediating the appropriate response to infant signals, evidence has so far been only correlational, and it is unknown whether the IFG plays a causal role in empathic responses to infant signals. The aim of the present study is to test whether the IFG plays a causal role in empathic response to infant signals using Transcranial Magnetic Stimulation (TMS). We examined the effect of suppressing the right IFG (rIFG) activation on behavioral responses to infant crying and laughter sounds and happy and sad infant faces. We are interested in suppressing instead of exciting IFG since previous studies indicate that decreased IFG activity is involved in dysfunctional parenting behaviors (Laurent & Ablow, 2013; Musser et al., 2012). Therefore, we hypothesize a negative effect of suppressing rIFG activity on participants' behavioral response to infant stimuli in laboratory tasks. In particular, we examined whether suppressing activity in the rIFG affects handgrip force in response to infant crying and laughter, where an excessive grip force can be interpreted as an analogue of a harsh response to infant stimuli (Bakermans-Kranenburg et al., 2012; Compier-de Block et al., 2014). In addition, we measured approach and avoidant behavioral responses to happy and sad infant faces by means of the Approach-Avoidance Task. Using this task, a prior study demonstrated that participants are faster in avoiding (vs approaching) sad infants faces but not happy ones (De Carli, Riem, & Parolin, 2017). This tendency to avoid sad infants may be related to the fact that infant distress signals trigger feelings of shared distress in adults (Riem, van IJzendoorn, De Carli, Vingerhoets, & Bakermans-Kranenburg, 2017a), possibly through neural simulation mechanisms, which motivate an avoidant response in order to reduce negative emotionality.

If the IFG is critically involved in regulating empathic responses toward infants' signals, we hypothesize that suppressing its activity via TMS would lead to a less empathic response to infant signals, that is, to an increased handgrip force in response to infant crying and a reduced tendency to avoid sad infants.

Method

Participants

Eighteen female (under)graduate psychology students (mean age = 24.61, SD = 4.04) participated in the study. Inclusion criterion was nulliparity, in order to control for influences of experiences with own children. Moreover, all participants were screened for TMS eligibility and exclusion criteria (see supplemental material). The study was carried out in accordance with the recommendations of the Declaration of Helsinki and the approval of the local ethical committee. All subjects gave written informed consent in order to participate.

Procedure

Each subject took part in two TMS sessions in two subsequent weeks on the same weekday. In each session, participants first performed the handgrip-force task (baseline). Then TMS was administered, with the order of stimulation sites (rIFG or Vertex) counterbalanced across participants. No aversive effects or any uncomfortable feelings were reported by any participants. The post stimulation tasks started immediately after the end of the stimulation. In this post-TMS phase, participants always performed the handgrip task first and then the approach avoidance task. Handgrip force was administered before and after the stimulation, whereas the AAT was administered only after the stimulation because of time constraints. Although the AAT has been successfully used in similar within subjects procedure (De Carli et al., 2017), we decided to focus on handgrip force as the main outcome variable of interest, since multiple previous studies have demonstrated the validity of the handgrip paradigm (Bakermans-Kranenburg et al., 2012; Compier-de Block et al., 2014; Riem, De Carli, et al., 2017). The post-stimulation session lasted approximately 10 minutes in line with the lasting effect of repetitive TMS (Oliveri, Koch, Torriero, & Caltagirone, 2005). The whole session lasted approximately 50 minutes.

Handgrip-force task

To measure the force used in response to different auditory stimuli a handgrip dynamometer was used (Bakermans-Kranenburg et al., 2012; Compier-de Block et al., 2014; Riem, De Carli, et al., 2017) (see supplemental material). Before the task, participants practiced squeezing the handgrip dynamometer at maximum and half strength and received feedback on their handgrip strength on a monitor. After the practice trials, participants did not receive feedback anymore. Then the real task started on a laptop. Participants were asked to squeeze the dynamometer four times at maximum strength and four times at 50% of their strength during two conditions: infant crying and infant laughter (randomized order). During each condition, the words "squeeze maximally" and subsequently "squeeze at half strength" were briefly presented on the screen. The infant laughter and crying sounds (duration of both sounds = 2 min) were taken from a previous study (2009). As outcome measure, for each trial the half-strength force was computed by dividing the half strength by the maximum strength, resulting in scores between 0 to 1 (Bakermans-Kranenburg et al., 2012; Riem, De Carli, et al., 2017). Excessive force is used when this value is > .50. Previous research has shown that this task is able to discriminate between neglectful, maltreating, and control mothers (Compier-de Block et al., 2014) and that handgrip force in response to infant crying as measured with this task is affected by intranasal administration of oxytocin, a hormone important for mother-infant bonding [12]. Thus, performance on this task does not only reflect individual differences in caregiving but has also been related to neurobiological mechanisms related to parenting.

Approach-avoidance task

The task (De Carli et al., 2017) consisted of two blocks of 80 trials in a randomized order. In one block, participants were instructed to push the joystick away when they saw a red dot on infants' forehead and to pull the joystick towards them when they did not see a red dot on infants' forehead. In the other block participants were instructed to pull the joystick towards them when they saw a red dot on infants' forehead and to push the joystick away when they did not see a red dot on infants' forehead. In each trial, after a fixation cross (500 ms), a picture of medium size (50 x 50 pixel) appeared. At this point the participant could push or pull the joystick and consequently the picture changed in size, giving the impression that the picture was pulled toward the participant (i.e. growing bigger) or pushed away (i.e. growing smaller). Images depicted either a happy or a sad infant. As outcome variable, a difference score for the latencies in approaching versus avoiding infant faces was computed. A score above 0 means that the participant was slower in approaching (vs avoiding) the stimulus, while a score below 0 means that the participant was faster in avoiding (vs approaching) the stimulus. Thus, a score above 0 reflects a tendency to avoid a stimulus, whereas a score below 0 reflects a tendency to approach the stimulus.

Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS was administered over the rIFG by means of a Magstim Rapid machine (Magstim Co Ltd, Whitland, UK) with a 70 mm butterfly coil. A fixed intensity of 60% of the maximum stimulator output was used, in line with prior studies (Ferrari et al., 2014). rIFG was localized by means of stereotaxic navigation on individual estimated magnetic resonance images (MRI) obtained through a 3D warping procedure fitting a high-resolution MRI template with the participant's scalp model and craniometric points (Softaxic, EMS, Bologna, Italy). Talairach coordinates for this site (x=-46, y=14, z=1) were obtained from a previous fMRI study investigating neural correlates of processing of infant crying (Riem et al., 2011). The Vertex, corresponding to the median point of the nasion–inion line, was used as a control area. For each of the sites stimulated, 900 pulses were applied at a frequency of 1 Hz (train duration 15 min). Previous studies have shown that rTMS at 1 Hz temporarily reduces the excitability of the stimulated cortex for a time window that outlasts the period of stimulation (Oliveri et al., 2005)

Data analysis

After checking outcome variables for outliers (more than 3 SD +/- individual means; no value excluded from the Approach Avoidance outcome variable and 4 trials excluded from the handgrip force task) multilevel linear models were performed. In each case, the most complete and conservative random part that allowed the model to converge was taken into consideration. Each model was controlled for atypical outliers in residuals (+/- 2.5 SD Baayen, Davidson, & Bates, 2008). The fixed effects were examined by a three-way interaction (sound [laugh vs cry] x time [pre vs post stimulation] x site of stimulation [rIFG vs Vertex]) for the handgrip task model and a two-way interaction (emotion [sad vs happy] x site of stimulation [rIFG vs Vertex]) for the approach-avoidance task model.

Results

Handgrip Task

Table 1 shows the descriptive statistics of the handgrip task.

The three-way interaction (sound x time x site of stimulation) was significant ($F(1,487.98) = 5.84$, $p = .02$) in predicting handgrip force. In addition, a significant two-way interaction time x site ($F(1,487.60) = 4.45$, $p = .035$) was found, see Figure 1. Subsequent analysis showed that the half-strength force in response to crying decreased between pre and post stimulation after the Vertex stimulation ($t(17) = 2.49$, $p = .02$, Cohen's $d = .59$) but not after rIFG stimulation. TMS did not affect handgrip force in response to infant laughter.

[Figure 1]

Approach Avoidance Task

Table 2 shows the descriptive statistics of the approach avoidance task.

A significant interaction between site of stimulation and type of emotion on the latency difference score (i.e., approach latency minus avoidance latency in response to the infant face) was found ($F(1,34.00) = 14.78$, $p < .001$), as shown in Figure 2. After Vertex stimulation, participants were significantly faster in avoiding (versus approaching) the sad infants ($t(17) = 4.50$, $p < .001$, Cohen's $d = 1.06$) but not the happy ones ($t(17) = 0.11$, $p = .92$, Cohen's $d = .03$). Critically, following rIFG stimulation, the difference in latency between approaching and avoiding sad infants disappeared ($t(17) = 0.34$, $p = .74$, Cohen's $d = .08$) and participants became faster in avoiding happy infants ($t(17) = 5.33$, $p < .001$, Cohen's $d = 1.26$). In addition, the latency scores after Vertex and rIFG stimulation differed significantly both in response to happy infant faces ($t(17) = -2.26$, $p = .037$, Cohen's $d = .53$) and to sad infant faces ($t(17) = 2.63$, $p = .02$, Cohen's $d = .62$).

[Figure 2]

Discussion

This study tested the possible causal role of rIFG in responding to infant signals, specifically infant facial expressions and infant crying and laughter sounds in nulliparous female participants. We used TMS in order to temporarily suppress activity in the rIFG functionality and examined whether this affected behavioral responses toward infant signals. We found that suppressing activity in rIFG by means of TMS resulted in increased handgrip force in response to infant crying sounds. In addition, participants showed a reduced bias to avoid sad infants after rIFG stimulation, possibly because TMS disrupts mentalization processes and feelings of shared distress. These results suggest a critical role of rIFG in empathic responses toward infant signals, in particular sad facial and vocal expressions. Our findings may indicate that IFG is important for processing and adequately responding to infants' negative emotions (Gallese, 2014).

Infant crying is an important attachment signal and at the same time an aversive stimulus, that on one hand elicits the caregiver to respond to infant's need but on the other hand is considered a powerful trigger of abuse (Soltis, 2004). In fact, excessive handgrip force as measured with the dynamometer has been found to discriminate between maltreating and non-maltreating mothers in response to infant crying as well as infant laughing (Compier-de Block et al., 2014). In our study with nulliparous females, rIFG functionality seems necessary to control the use of force in response to infant crying but not laughing. We suggest that rIFG activity has a buffering effect on the use of excessive force in response to infant crying, while it does not seem to affect the behavioral response to infant laughing. This was unexpected, considering that the rIFG is activated during laugh perception (Riem et al., 2012) as well as cry perception (Riem et al., 2011). However, this result is consistent with the effects of a study in which intranasal oxytocin administration decreased the use of excessive handgrip force in response to infant cry, but not in response to infant laughter (Bakermans-Kranenburg et al., 2012). Since oxytocin alters rIFG functionality in response to infant crying and laughing (Riem et al., 2011, 2012), it is possible that a change in rIFG activation (an increase in case of oxytocin administration or a decrease in case of TMS stimulation) is insufficient to solely determine modulation of behavioral responses to infant laughter. The excessive force used by maltreating mothers in response to infant laughter could be driven by altered functionality of other neural networks, such as the reward system (Kringelbach, Stark, Alexander, Bornstein, & Stein, 2016). It is tempting to suggest that rIFG plays a more important role behavioral responses to negative infant sounds, such as crying. This suggestion is supported by the role of rIFG within the mirror and emotional empathy networks that rely on this area for emotional recognition and contagion (Kilner, Neal, Weiskopf, Friston, & Frith, 2009; Shamay-Tsoory, 2011). Responses to infant crying may depend more on the functionality of this area, consistent with the idea that in order to respond in a sensitive way to infant needs, an adult needs to attune to the infant's emotional state (Ainsworth et al., 1978; Winnicott, 1960). rIFG decreased functionality may lower the ability to empathize with the crying infant and therefore lead to excessive handgrip force. However, previous studies suggested that oxytocin was effective only on non-maltreated individuals' responses, consistent with other findings on the role of early experience in behavioral and brain responses to infant stimuli (De Carli et al., 2017; Riem, De Carli, et al., 2017; Riem, van IJzendoorn, De Carli, Vingerhoets, & Bakermans-Kranenburg, 2017b). Future studies should address a possible differential role of rIFG depending on childhood caregiving experiences in the perspective of the intergenerational transmission of parenting (De Carli et al., 2018).

Interestingly, interfering with rIFG activity did not only disrupt typical responses toward expressions of distress but also induced a tendency to avoid happy faces. One explanation is that the inhibition of emotional empathy through suppressed rIFG activity may disrupt functional connectivity with reward areas (e.g. nucleus accumbens Cauda et al., 2011) that encode the rewarding value of happy children faces (Kringelbach et al., 2016).

Some limitations must be acknowledged. First, despite the within-subject design that increases statistical power (van IJzendoorn & Bakermans-Kranenburg, 2016), the sample size is small and does not allow to test the moderating role of individuals' childhood experiences or other characteristics. Second, we selected nulliparous women, but it is known that both gender and parental status (Kringelbach et al., 2016; Maupin, Rutherford, Landi, Potenza, & Mayes, 2018; Rigo et al., 2017) have different processes associated with responses to infants stimuli. More research is needed to study the causal role of rIFG in real parenting behaviors and more realistic settings. Third, the stimulation site was localized on estimated MRIs, as widely used in TMS research (Carducci & Brusco, 2012). However, participants' individualized MRIs would have better controlled for anatomical variability in rIFG localization. Also, despite the use of fixed intensity stimulation is a common procedure in TMS studies (Campana, Cowey, Casco, Oudsen, & Walsh, 2007), it could potentially result in suboptimal stimulation of rIFG. Future investigations adopting an MRI-guided TMS approach and individualized TMS intensity represent a future development that will help to clarify and strengthen the current results. In addition, the approach avoidance task was always administered after the stimulation and the order of the task was not counterbalanced across participants to avoid an additional factor reducing power. As a check, we compared our results after the Vertex Stimulation with results from a previous study (De Carli et al., 2017). Results were consistent, suggesting that they are reliable and likely not influenced by the handgrip task.

In sum, this study provides the first empirical evidence for a causal role of rIFG in the responses to infant crying sounds and infant emotional facial expressions. rIFG activity seems to represent an important buffer preventing the use of excessive force in response to infant crying and affecting the approach avoidance tendencies toward sad infant faces. Together with the correlational evidences of diminished activation of IFG in depressed (Laurent & Ablow, 2013) and insensitive mothers (Musser et al., 2012), our results suggest that empathy-related processes rely on rIFG activation. IFG less-than-optimal functionality disrupts the ability to respond empathically to infant signals (Ainsworth et al., 1978).

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Tables

Table 1. Descriptive statistics of the handgrip task.

Site of Stimulation	Sound	Pre/Post	Handgrip Force Ratio			
			M	SD	Min	Max
Vertex Stimulation	Cry	Pre	0.687	0.146	0.416	0.901
	Cry	Post	0.650	0.170	0.330	0.855
	Laugh	Pre	0.672	0.176	0.300	0.886
	Laugh	Post	0.650	0.156	0.374	0.849
IFG Stimulation	Cry	Pre	0.668	0.213	0.265	0.919
	Cry	Post	0.685	0.188	0.394	0.912
	Laugh	Pre	0.696	0.189	0.352	0.921
	Laugh	Post	0.670	0.241	0.238	0.963

Table 2. Descriptive statistics of the approach avoidance task.

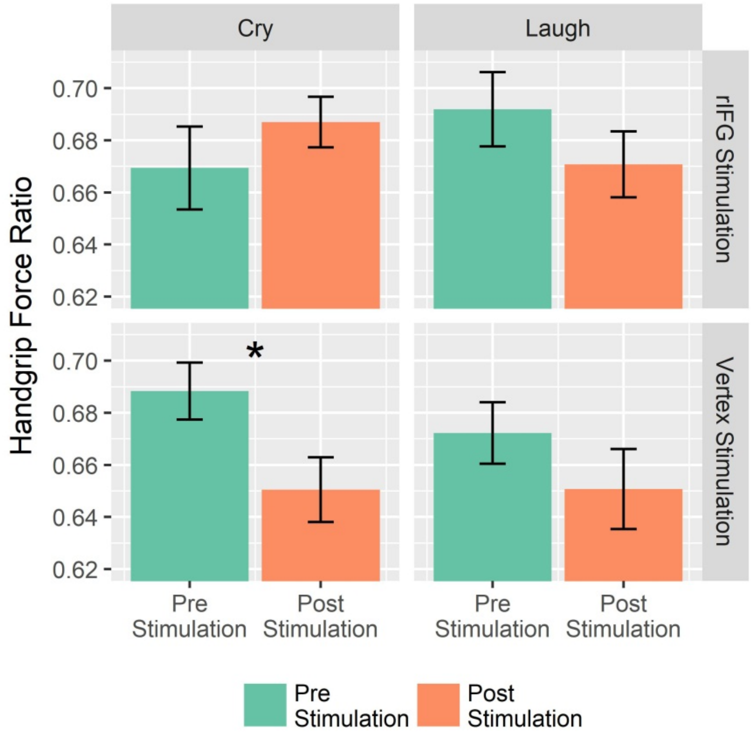
Site of Stimulation	Infant Stimuli	Approach-Avoidance Latency			
		M	SD	Min	Max
Vertex Stimulation	Happy	0.002	0.087	-0.255	0.124
	Sad	0.053	0.05	-0.083	0.145
IFG Stimulation	Happy	0.06	0.048	-0.019	0.137
	Sad	0.005	0.068	-0.161	0.154

Figure Captions

Figure 1. Average handgrip force ratio (Half Strength/Maximum Strength) during the Crying and Laughter sounds. Upper panels show the effects of the rIFG stimulation, while lower panels represent the Vertex (control) stimulation. Left panels show the effect in response to infant crying, while right panels show the effect in response to infant laughter. Higher scores reflect the use of more excessive force. Error-bars represent standard errors of the mean. * = $p < .05$.

Figure 2. Differences in latency between approaching and avoiding the happy and sad infant faces (Approach Latency minus Avoidance Latency). Left panel shows the effects of the rIFG stimulation, while the right panel represents the Vertex (control) stimulation. Values above 0 mean that participants are faster in avoiding (vs approaching) the stimulus and, thus, reflect a tendency to avoid the stimulus. Error-bars represent standard errors of the mean. * = $p < .05$.

Figure 1



Cry
Laugh
rIFG Stimulation
Vertex Stimulation
Handgrip Force Ratio
0.70
0.68
0.66
0.64
0.62
*
Pre Stimulation
Post Stimulation

Figure 2


rIFG Stimulation
Vertex Stimulation
*
*
0.06
0.03
0.00
Approach-Avoidance
Happy
Sad
Happy
Sad
Infant Face
Happy
Sad