FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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The effects of intranasal oxytocin on the neural circuitry of social cognition

ARTIGO DE REVISÃO

ÁREA CIENTÍFICA DE PSIQUIATRIA

Trabalho realizado sob a orientação de:

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MARÇO/2018

FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

The effects of intranasal oxytocin on the neural circuitry of social cognition

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Abstract

Oxytocin (OXT) has multiple functions in the human body, both peripherally, as a hormone, and centrally, as a neuropeptide. OXT plays an important role in social behavior and cognition, which justifies the increasing interest it has been receiving lately. This effect on social cognition appears to be due to the biding of the OXT to specific brain areas that still haven't been fully explored. We conducted a systematic review, using placebo-controlled studies that used functional magnetic resonance imaging (fMRI) to investigate the influence of intranasal OXT on the human brain, during social cognitive tasks. We identified 16 studies that met our inclusion criteria. The results show that oxytocin had influence in the activity of several brain areas: the amygdala, mainly in the processing of facial emotion and social scenes and in associative learning; the insula, which was implicated in tasks requiring empathy and altruism; cingulate cortex, activated during the anticipation of social reward/punishment; the caudate nucleus and putamen, both very active during cooperation tasks; the temporal and frontal lobes and their different regions, implicated, in a way or another, in every type of task the hippocampus. They also revealed that gender and type of task lead to significant variations in the activity of those brain structures.

Keywords: oxytocin; social cognition; social behavior; fMRI; brain activity; brain imaging; neural circuits.

Resumo

A oxitocina (OXT) tem múltiplas funções no corpo humano, tanto a nível periférico, como hormona, como a nível central, como neuropeptídeo. A OXT desempenha um papel importante na cognição e comportamento social, o que justifica o interesse crescente que esta tem recebido. Este efeito na cognição social parece dever-se à ligação da OXT a áreas cerebrais específicas, no entanto, estas não foram ainda exploradas completamente. Esta revisão sistemática foi realizada usando estudos, controlados por placebo, que usaram a ressonância magnética funcional para investigar a influência da OXT intranasal no cérebro humano durante provas de cognição social. Foram identificados 16 estudos que respeitavam os nossos critérios de inclusão. Os resultados mostraram que a OXT influencia a atividade de várias áreas cerebrais: a amígdala, envolvida maioritariamente no processamento de expressões faciais, situações sociais e aprendizagem associativa; a insula, recrutada em tarefas que envolvem empatia e altruísmo; o córtex cingulado, ativado pela antecipação de uma "recompensa" ou um "castigo social"; o núcleo caudado e o putamen, ambos envolvidos em tarefas de cooperação; os lobos frontal e temporal, e as suas várias sub-regiões, recrutados, de uma maneira ou de outra, em todo o tipo de tarefas sociais; e o hipocampo. Os resultados também revelaram que o género e o tipo de tarefa influenciam grandemente o efeito da oxitocina nas diferente regiões.

Palavras-chave: oxitocina; cognição social; comportamento social; RMf; neuroimagem; circuitos neuronais.

Introduction

Social cognition refers to the abilities involved in the processing of socially relevant information, such as facial expressions, body language and eye-gaze direction, that allow us to infer others mental states and therefore, allow us to communicate with each other and to learn about the world (1)(2). Memory, decision-making, attention, motivation and emotion, are part of the social cognition mechanisms used when we are presented with socially relevant information (3). We can learn a lot just by looking at the people that surround us, for example, if we see someone with a disgust or painful face, we know that they are experiencing something unpleasant and that we should avoid that situation, or if someone has a fearful expression, we know that we should probably keep way from whatever is troubling them. In the same way, if we see someone with a happy or joyful face, we know that they are looking at something pleasant that maybe will make us happy too and that it is safe to approach it (1)(4). This comes to show, just how important visual cues are in our understanding of the world around us and how much of our learning depends on it. Moreover, some psychiatric disorders, like schizophrenia and autism, are characterized by deficits in social cognition, which leads to impairments in the recognition of facial emotions, integrating contextual information and inferring others mental states and, because of that, interacting with other people and society becomes even more challenging (5-7).

Evidence derived from functional imaging studies consistently shows that physiological processes underlying social cognition depend upon the activation of several brain areas (4). These include: the amygdala, implicated in the processing of facial expressions and assigning emotional value to environmental information, it also seems to moderate fear and anxiety, inducing hypoalgesia during aversive situations and it takes part in the prediction and anticipation of potential danger (4,8-10); the prefrontal cortex, which is responsible for social manners, sympathy, reasoning, decision making and emotional hunches

(9) and mentalizing or interpreting the mental states and actions of the others (4)(11); the anterior cingulate cortex, responsible for encoding choice predictions, reward-based learning and decision making (12); the temporoparietal junction which is associated with perspective taking and judging others beliefs (4)(13) and the insula, an important piece in the recognition of facial expressions, especially disgust and pain (9).

On the other hand, several studies have demonstrated that oxytocin (OXT) plays a key-role in enhancing social behavior and cognition, modulating social stress, emotion recognition and memory formation (1)(2). In fact, OXT is known to decrease anxiety and stress in social interactions (14-16) and increases trust (17), cooperation, generosity, altruism and empathy toward others (2). It also seems to help in the inferring of mental states in others and increasing the sensitivity to social cues (18). Although the effect of OXT in social cognition is likely to be due to its binding to structures implicated in those processes, as referred above, (19) the specific targets of OXT in the brain still remain to be determined. Understanding the sites of action of the OXT and how it affects the human brain and the human behavior might help the creation of an OXT-based treatment for psychiatric conditions.

In this systematic review we aim to determine how OXT influences the activity of different brain areas, by reviewing studies that used functional magnetic resonance imaging (fMRI) to investigate the action of intranasal OXT in the brain of healthy subjects during social cognitive tasks. We focused on the main areas involved in these tasks, how different tasks lead to the activation of different brain areas and the influence of gender in the effect of OXT.

Methods

Search strategies

To identify relevant studies for inclusion in this systematic review, we used a systematic search strategy following the PRISMA guidelines for systematic reviews (20). For this systematic review, we started by searching PubMed, to find relevant studies on the matter. Studies had to be an original study, using oxytocin as a manipulator of the brain activity, in humans, published between 2010 and 2017. No language restriction was applied, but all the studies found were written in English. Search terms were "oxytocin", "social cognition", "social behavior", "brain activity", "brain imaging", "neural circuits" and "fMRI". Search terms were kept broad to identify as many relevant publications as possible. A manual search of additional studies was conducted in the bibliographic references of the studies retrieved by the initial search. The authors reviewed the title of papers and identified abstracts for further inspection.

Selection criteria

Eligibility criteria were: 1) primary research studies using intranasal oxytocin in humans and measuring brain activity with fMRI during social-cognitive tasks based on visual-stimuli; 2) double-blind, placebo-controlled design; 3) studies with healthy participants with no history of neurological, psychiatric or endocrine disease, no intake of medication that could interfere with the experiment and no drug or alcohol abuse.

Studies were excluded if the subjects were animals, if no brain imaging was obtained or if the technique used was not fMRI, if the fMRI was acquired on resting-state, if the focus was only endogenous oxytocin or vasopressin and studies in which the social-cognitive task involved non-visual stimuli.

Data processing

The following variables were collected from each study: sample size, gender, race/ethnicity, mean age, study design, dose of oxytocin used, time between oxytocin administration and the fMRI scan, total scan duration, tasks and contrasts used and brain areas which responded to the administration of OXT.

After screening all the studies, we found which brain areas were more responsive to the oxytocin administration and focused on those that were mentioned repeatedly across studies - the amygdala, the insula, the cingulate cortex, the hippocampus, the caudate nucleus, the putamen, the temporal lobe and the frontal lobe.

Assessing the Risk of Bias

To assess the methodological quality of the included studies, two researchers independently rated each study, using the "Cochrane Collaboration's tool" (21), that contemplates the "selection bias" (how were the subjects randomized and how was the allocation concealment done), the "performance bias" (the blinding of the participants and the researchers), the "detection bias" (blinding of the outcome assessment), the "attrition bias" (amount, nature, or handling of incomplete outcome data) and the "reporting bias" (selective outcome reporting).

Results

About the studies

The results from the literature search are illustrated in the PRISMA diagram (in the Supplementary Information section). Sixteen studies met our inclusion criteria (Table 1).

A total of 696 subjects were included, 226 being females (note that Feng et al. (22) includes the sample in Rilling et al. (23) and Rilling et al. (24), and therefore the samples from the Rilling's studies were not considered individually). Sample sizes ranged from 14 to 196, with a mean size of 49.7 subjects. Sample ages ranged from 19.8 to 39.3 years, with a mean age across studies of 23.9 years. Nine studies used only male subjects (23,25-32), five studies used only female subjects (24,33-36) and two used both male and female subjects (22,37).

All studies used a double-blind, placebo-controlled design. Six used a within-subject design (25,28,32,33,36) and eleven used a between-subject design (22-24,26,27,29-31,34,37) (one of the studies (35) used both, within-subject and between subject, designs). Four studies used a paradigm measuring explicit processing of facial emotions or social situations (26,30,33,36), another four used a paradigm measuring implicit processing of facial emotions or social situations (29,31,32,37) and three used a cooperation game/interaction (the "Prisoner's Dilemma Task") (22-24). The other five used different tasks: one involving empathy for pain (25) and another involving altruistic interactions (28), a social incentive delay task (34), exposure to animations of moving shapes depicting either random movement or social interaction (35) and a reinforcement association learning task (27). All the tasks were based on visual cues.

Table 1: Overview of the included studies									
Study	Sample Size*	Gender	Mean age (years)	Race	Study design	OXT dose, IU	Min between OXT admin. and fMRI scan	Total scan duration (min)	Task used
Bos et al. (25)	24	M	23.1	Caucasian	Double-blind, placebo-controlled, within-subject, counter balanced crossover design	24	55	-	Empathy for pain - exposure to movie clips showing male hands being subjected to a "pain condition" or a "control condition"
Domes et al. (33)	16	F	24.2±2.5	-	Double-blind, placebo-controlled, within-subject crossover design	24	45-60	40	Explicit facial emotion processing - exposure to pictures of fearful, angry, happy and neutral faces and rating of the "emotional arousal"
Feng et al. (22) [1]	196 (101PBO, 95 OXT)	98F 98M	20.5F 20.7M	-	Double-blind, placebo-controlled, between-subject design	24	-	12	Cooperation game/interaction: Prisoner's Dilemma task
Gamer et al. (26)	46 (23PBO, 23OXT)	M	25.0±3.7	-	Double-blind, placebo-controlled, between-subject design	24	45	45	Explicit facial emotion processing - exposure to pictures of fearful and happy faces and classification of the depicted emotional expression
Groppe et al. (34)	28 (14PBO, 14OXT)	F	26.64±5.55	-	Double-blind, randomized, placebo-controlled, between-subject, parallel-group design	26	30	20	Social incentive delay task: visualization of a cued target symbol, followed by social reward or punishment (through male faces with different expressions), depending in the actions of the subject
Hecht et al. (35)	28 (Scan1: 28PBO; Scan2: 14PBO, 14OXT)	F	OXT: 22.08±0.71 PBO: 24.08±0.75	6 Caucasian, 8Asian, 13 African-American, 1 Other.	Double-blind, placebo-controlled, both between and within-subject design	24	40	20	Exposure to animations of moving shapes, depicting either random movement or social interaction: the Dynamic Interactive Shape Clips
Hu et al. (27)	54 (27PBO, 27OXT)	M	19.8±1.49	Han Chinese	Double-blind, placebo-controlled, between-subject design	24	45	45	Reinforcement association learning task
Hu et al. (28)	22	M	25.10 ± 3.88	Caucasian	Double-blind, placebo-controlled, within-subject design	24	45	30	Altruistic interaction: third-party help/punishment paradigm

Kanat et al. (29)	43 (21PBO, 22OXT)	M	PBO: 23.9± 2.74; OXT: 24.32± 3.43	-	Double-blind, placebo-controlled, between-subject design	24	55	14	Implicit facial processing – identification of the gender of masked fearful or happy eyes
Lischke et al. (36)	14	F	23.79±2.32	-	Double-blind, placebo-controlled and counter-balanced within-subject design	24	45	-	Explicit processing – exposure to positive, negative and neutral scenes and rating of the "emotional arousal"
Luo et al. (37)	84 (41PBO, 43OXT)	42M 42F	22.42 ± 2.072	Han Chinese	Double-blind, placebo-controlled, between-subject design	24	45	-	Implicit facial processing - identification of the gender of happy, angry, fearful, sad and disgust faces
Radke et al. (30)	52 (28PBO, 24OXT)	M	22.4±3	-	Double-blind, randomized, placebo-controlled, between-subjects design	24	45	-	Explicit facial processing - fMRI- compatible social approach-avoidance task, by exposure to happy and angry facial expressions
Rilling et al. (23)	59 (33PBO, 26OXT)	M	20.2	-	Double-blind, placebo-controlled, between-subject design	24	40	12	Cooperation game/interaction: Prisoner's Dilemma task
Rilling et al. (24)[2]	55 (28PBO, 27OXT)	F	20.4	-	Double-blind, placebo-controlled, between-subject design	24	40	12	Cooperation game/interaction: Prisoner's Dilemma task
Striepens et al. (31)	70 (35PBO, 35OXT)	M	26 ± 4	-	Double-blind, randomized, placebo-controlled, between-subject design	24	45	28	Implicit processing of social scenes- exposure to negative and neutral pictures paired with nouns, followed by a memory task
Wittfoth-Schardt et al. (32)	19	M	39.3±6.2	-	Double-blind, placebo-controlled, within-subject design	24	30	-	Implicit facial processing - exposure to pictures of familiar and unfamiliar faces

F= female; fMRI= functional magnetic resonance; IU= international units; M= male; Min= minutes; OXT= oxytocin; PBO= placebo

*Sample size includes only de participants in the OXT and PBO groups. Some studies have other branches, in which other participants were included, but were no relevant to our study.

[1]This study includes and expands upon the samples in Rilling's studies (23,24);

[2]The results from this study were then compared with the results obtained by a previous study by Rilling et al. (23).

Assessing the Risk of Bias with the Cochrane Collaboration's Tool

After evaluating the studies, according to the Cochrane Collaboration's Tool's parameters we got the results described in the following table (Table 2).

Table 2: The Cochrane Collaboration's tool for assessing risk of bias

Study	Selection Bias: Sequence generation	Performance bias: Blinding of participants and personnel	Detection bias: Blinding of outcome assessments	Attrition bias: incomplete outcome data	Reporting bias: Selective outcome report
Bos et al. (25)	Unclear	Low	Low	Low	Low
Domes et al. (33)	Unclear	Low	Low	Low	Low
Feng t al. (22)	Unclear	Low	Low	High	Low
Gamer et al. (26)	Unclear	Low	Low	Low	Low
Groppe et al. (34)	Low	Low	Low	Low	Low
Hecht et al. (35)	Unclear	High	High	Low	Low
Hu et al. (27)	Unclear	Low	Low	Low	High
Hu et al. (28)	Unclear	Low	Low	High	Low
Kanat et al. (29)	Unclear	Low	Low	High	Low
Lischke et al. (36)	Unclear	Low	Low	Low	Low
Luo et al. (37)	Unclear	Low	Low	Low	Low
Radke et al. (30)	Unclear	Low	Low	High	High
Rilling et al. (23)	Unclear	Low	Low	High	Low
Rilling et al. (24)	Unclear	Low	Low	High	Low
Striepens et al. (31)	Unclear	Low	Low	Low	Low
Wittfoth-Schardt et al. (32)	Unclear	Low	Low	Low	Low

None of the studies (except one) explained how the sequence generation and allocation concealment were made, and therefore it is "Unclear" if the Allocation to the different interventions was biased or not. Only Groppe (34), explained that a randomization code generated by the assigned drug provider was used for the subjects allocation, which puts this study at "Low risk" for Selection Bias.

About the Performance Bias and the Detection Bias, all of the studies used a double-blind design (except one), which means that the blinding of participants, personnel and outcome assessments was achieved, and therefore all of these studies are at a "Low risk" for Performance and Detection bias. In Hecht's study (35) the Performance and Detection Bias were inevitable, since the experimenters knew that in the first scan all of the participants were

taking the placebo, which puts this study at “High risk” in this section.

Ten studies (25-27,31-37) had no exclusions of participants or incomplete outcome data, which puts them at “Low risk” of bias. The rest of the studies (22-24,28-30) excluded some participants and didn’t mention how these exclusions were overcome or treated in terms of the outcome data, and therefore the risk of bias here is “High”.

Regarding the Reporting Bias, two studies (27,30) didn’t report the outcomes of every variable they have aimed to study in the beginning: Hu (27) only reported the results from the “feedback phase” to correct responses “due to their much higher frequency” compared with the frequency of incorrect answers, and Radke (30) only gives detailed information of the results acquired in the “approach of angry faces” contrast and neglects the other three contrasts (“avoidance of angry faces”, “approach of happy faces” and “avoidance of happy faces”), and therefore this two studies are at a “High risk” of bias in this parameter. All the other studies were classified as “Low risk” of bias.

Brain areas affected by Oxytocin

For an easier consultation, the results were summarized in Supporting Table 1, in the Supplementary Information section.

Amygdala

Nine studies reported a significant effect of OXT in the activation of amygdala during social tasks (23,24,26,27,29-31,33,36).

Oxytocin induced a higher increase in the activity of the amygdala, bilaterally, during exposure to negative social scenes, since in the placebo condition, the amygdala was also activated by negative social scenes, but not in the same extent (36). A decrease in the activity

of the amygdala, in both hemispheres, was noticed when subjects chose to approach an angry face (30).

Exposure to OXT led to the activation of the right amygdala during the anticipation of a smiling/angry face (a positive/negative reinforcement), in a reinforcement association learning task (27), and during exposure to positive social scenes (36). Conversely, OXT induced a reduction in the function of the right amygdala when participants were exposed to fearful faces (29) and negative/neutral social scenes (31).

In females exposed to fearful expressions and experiencing "reciprocated cooperation", OXT led to the activation (33) and inhibition (24) of the left amygdala, respectively, while males manifested the opposite pattern (23,24,26).

Insula

The insula activity was shown to be altered by OXT in seven studies (23–25,28,31,33,37).

The right insula was numbed when subjects made the altruistic decision of helping a third-party (28).

The left insula's activity was amplified by OXT when subjects were exposed to both fearful (33,37) and happy faces (33), when subjects witnessed a computer make an altruistic decision toward a third-party (28) and when subjects remembered a negative stimuli they've been exposed to previously (31). The left insula was negatively modulated by OXT only when subjects witnessed pain being inflicted in a stranger (25).

The insula was activated bilaterally when male subjects experienced "reciprocated cooperation" (23,24).

Cingulate Cortex

The cingulate cortex was reported to be affected by OXT in six studies (23–25,27,29,37).

The left portion of the anterior cingulate cortex (ACC) was numbed during exposure to fearful, rather than happy faces, in males (29), but in females, the exposure to fearful faces led to an increase of its activity (37). The ACC was bilaterally depressed during the exposure to fearful faces in males (37) and when subjects experienced a "cooperation defection" from a "human partner", rather than a "computer partner" (23).

The mid cingulate cortex activity was bilaterally decreased when subjects witnessed pain being inflicted in a stranger (25).

The right posterior cingulate cortex (PCC) was activated when subjects received cooperation from a human, rather than a computer (23). The left PCC was activated during the anticipation of a positive/negative reinforcement (in the form of a "social female") (27) and numbed when females experienced "reciprocated cooperation" (24). Conversely, when males experienced "reciprocated cooperation", it led to a bilateral increase of the PCC activity (24).

The right cingulate cortex (no region was specified) was activated while subjects anticipated a positive/negative reinforcement (in the form of a "non-social light") (27).

Hippocampus

The Hippocampus had its activity modulated by OXT in four studies (24,27,32,33).

The right hippocampus was activated when subjects were exposed to happy faces (33) and when expecting a positive/negative reinforcement (in the form of a "social female") (27).

The left hippocampus was depressed when fathers viewed pictures of unfamiliar child, compared with familiar child (32).

The hippocampus was bilaterally activated when males experienced “reciprocated cooperation” (24).

Caudate Nucleus

The caudate is mentioned in four studies (22-24,32).

The left caudate nucleus was activated when male subjects experienced “reciprocated cooperation” (23,24) and when fathers viewed pictures of their own child, rather than an unfamiliar child (32).

In another study, males experiencing “reciprocated cooperation” led to a bilateral increase of the caudate nuclei activity, while in females, it resulted in a bilateral decrease in its activity (22).

Putamen

The putamen appeared to be modulated by OXT in four studies (22-24,27).

One study reported that the right putamen was more active in males experiencing “reciprocated cooperation” than in females (24), but another one reported that this difference was noticed bilaterally (bilateral activation of the putamen by OXT in males, and bilateral deactivation in females) (22). Yet, another study, using only male subjects, showed a bilateral increase of the putamen’s activity in males experiencing “reciprocated cooperation” (23).

The left putamen was activated by OXT during the anticipation of a positive/negative reinforcement (in the form of a “social female”), in a reinforcement association learning task (27).

Temporal Lobe

The temporal lobe appears to be the brain area that responded the most to OXT administration, being mentioned in ten out of the sixteen studies (22,23,27-29,32-36). The temporal lobes can be divided into different areas, so the results will be reported according to this division.

The right superior temporal gyrus (STG) activity was amplified by OXT, since it was already active in the placebo group, during the anticipation of a positive/negative reinforcement (in the form of a "social emoticon") (27). Activation of the left STG was noticed when subjects viewed pictures of fearful and happy faces (33) and negative social scenes (36), when asked to explicitly process social emotional faces/scenes, but also when subjects witnessed a computer make the decision to help a third-party (28). On the contrary, the left STG was depressed when the subjects themselves made the decision to help the third-party (28) and when fathers viewed pictures of unfamiliar child, compared with familiar child (32). The Planum Polare (PP), part of the STG, received special attention in two study's, being bilaterally activated when subjects experienced cooperation from a "human partner", instead of a "computer partner" (23), and the left PP being activated by OXT during "reciprocated cooperation" in males, and deactivated in females (22).

The left middle temporal gyrus (MTG) was significantly more activated by OXT in several occasions: when anticipating social reward (34), when subjects viewed pictures of negative scenes (36) and also when experiencing cooperation from a "human partner" instead of a "computer partner" (23). Administration of OXT diminished the activation of the left MTG when subjects were told to focus on the "social relationship" of an animation clip of moving shapes instead of the "physical relationship" (35), when subjects made the altruistic decision to help a third-party (28) and while viewing pictures of fearful eyes, compared to

happy eyes (29). Finally, the MTG was diminished, in greater extent, bilaterally, when fathers viewed pictures of unfamiliar child compared to pictures of familiar child (32).

The inferior temporal gyrus (ITG) was mentioned three times: the left ITG's activity was amplified when subjects viewed pictures depicting negative social scenes (36); when subjects were exposed to masked fearful eyes, versus happy eyes, OXT led to an activation of the right ITG, which didn't occur in the placebo group (29); and the ITG was bilaterally more activated by the cooperation from a "human partner", compared with a "computer partner" (23).

The fusiform gyrus (FG) also appeared to be a highly responsive area to OXT: in all of the studies that mentioned the FG, OXT had an augmenting effect in its activity. The left FG was activated during exposure to happy faces (33) and when subjects were anticipating a positive/negative reinforcement (in the form of a "social emoticon"), its activity, already high in the placebo group, was even higher after OXT administration (27). The FG was activated bilaterally when subjects viewed pictures of fearful faces (33). When anticipating a positive/negative reinforcement (in the form of a "non-social light" or a "social female") and after receiving a positive reinforcement, the FG activity was bilaterally amplified, in comparison to the placebo group (27).

The left medial temporal lobe was activated during the viewing of both fearful and happy faces (33).

The left temporoparietal junction was activated when subjects witnessed a computer make an altruistic decision toward a third-party and deactivated when the subjects themselves made the altruistic decision to help the third-party (28).

Frontal Lobe

Eight studies reported modulatory effects of OXT in the frontal lobe (22,23,27,28,32–34,37). Once again, the results will be described according to the different areas in the frontal lobe.

Starting with the prefrontal cortex (PFC), the right dorsolateral PFC (dlPFC) was numbed by both fearful and happy faces, but angry faces led to its activation (33); The right inferior PFC was also activated by angry faces (33). The ventrolateral PFC (vlPFC) was bilaterally activated by angry faces (33) and the left vlPFC was activated by unreciprocated cooperation, as well as the ventromedial PFC (23).

The right orbitofrontal cortex was more active when a "human partner", instead of a "computer partner" cooperated with the subject (23). The right frontal pole, during "reciprocated cooperation", was more active, after OXT administration, in males, but less active in females (22).

The left precentral gyrus (PCG) activity rose when subjects witnessed a computer make an altruistic decision towards a third-party (28) and when a "human partner" cooperated with the subject, instead of a "computer partner" (23). The left PCG had the opposite reaction (decreased function) when fathers viewed pictures of unfamiliar child, compared with familiar child (32). The PCG was bilaterally deactivated by the anticipation of social punishment (34) and when subjects made the altruistic decision of helping a third-party (28).

The right medial frontal gyrus was activated during the anticipation of a positive/negative reinforcement (in the form of a "social emoticon") and when subjects received a positive reinforcement (in the form of a smiling emoticon or female) (27). Bilaterally, the medial frontal gyrus was more activate in males, after OXT administration, but less active in females, after experiencing "reciprocated cooperation" (22).

The inferior frontal gyrus (IFG) was bilaterally numbed in males exposed to fearful, angry and sad faces (37) but in females it was bilaterally activated by fearful and sad faces, and angry faces caused an increase only in the right IFG (37). The left IFG was activated when a "human partner" cooperated with the subject, instead of a "computer partner" (23) and when the subject witness an altruistic decision toward a third-party being made by a computer (28).

The middle frontal gyrus (MFG) was activated in the left side of the brain when subjects were anticipating a positive/negative reinforcement (in the form of a "non-social light") (27) and the right MFG was more activated when a "human partner" cooperated with the subject, instead of a "computer partner" (23).

Discussion

With the present review, we examined studies investigating the effect of OXT in the activity of the human brain during social cognition tasks. We found that the effect of OXT varied with the type of task and with the gender of the subjects, but overall, OXT had an influence in every single study reviewed.

Oxytocin is known to be implicated in the processing of facial expressions (16). We found that, after OXT administration, happy and fearful faces were processed in very similar ways, leading to an activation of the left insula (33,37), fusiform gyrus (FG) (33), left medial temporal lobe (33) and a deactivation of the right dorsolateral prefrontal cortex (dlPFC) (33). Angry faces had a different effect, leading to a bilateral deactivation of the amygdala (when subjects chose to approach angry faces) (30), an activation of the right dlPFC (contrary to the happy and fearful faces), right prefrontal cortex (PFC) and bilateral ventrolateral PFC (33). The amygdala was modulated by OXT in four of the five studies (26,29,30,33) that focused on the processing of facial emotion, three using fearful faces (26,29,33), and one angry faces (30), and even though it was not possible to set a pattern of its activity, this findings corroborate with other reviews (38,39); it is also worth noticing that the amygdala was not implicated in the processing of happy faces. The main difference found here, was between men and women: while in women, fearful faces led to an activation of the left amygdala (33), left anterior cingulate cortex (ACC) (37), temporal lobe (33) and inferior frontal gyrus (IFG) (37), happy faces led to the activation of the temporal lobe (33) and sad and angry faces to the activation of the IFG (37), in men, when exposed to the same facial expressions, all of this structures were deactivated by OXT (26,29,37). Besides this, it must be taken into consideration that the number of studies from which we drew this conclusion is very limited, and therefore this information should be considered carefully. Yet, the differences between

gender in the processing of facial expressions, and how OXT interacts with gender, had already been described (8,40,41). The influence that gender has over the effect of OXT in animals has been attributed to the to the interaction between estrogens and OXT (16). In humans, there is still no suitable explanation for this difference, and more work is needed to clarify this question.

In the processing of social scenes, we also noticed that gender influenced the effects of OXT. When females were exposed to negative social scenes, there was a bilateral activation of the amygdala (36), but in males there was a deactivation of the right amygdala instead (31). This could also be explained by the fact that the task used in the females involved explicit processing of the social scenes, and in males, the task used was based on implicit processing. Even though no evidence was found supporting that implicit and explicit processing of facial emotions occurs differently (40), we can't extrapolate those results to the processing of social scenes. But, again, it should be taken into consideration that there were only two studies on this matter, within our inclusion criteria, and therefore this information should be considered carefully, and more studies should be carried out to explain these results. In females, exposure to negative social scenes after OXT administration also activated the left middle temporal gyrus (MTG), left inferior temporal gyrus (ITG) and left superior temporal gyrus (STG) (36). Curiously, positive social scenes had the same effect on the amygdala as negative social scenes, in females: a bilateral increase of its activity (36).

In macaques, brain areas like the amygdala, ITG, the superior temporal sulcus and the medial temporal lobe are activated by featural and expressive aspects of faces and bodies, including facial identity, facial actions, eye gaze and lip movement (41). In humans, as described above, these same areas appear to be involved in facial emotion recognition and social scenes processing, suggesting a similarity in social cognition processes between humans and other primates.

Three studies used the Prisoner's Dilemma Task to study the effect of OXT on the subjects cooperation (22-24). The second study by Rilling (24) used only female subjects and compared the results with the ones obtained in the previous study also by Rilling (23), that used only male subjects. Feng (22) used the combined sample from the other two studies and added more subjects from both genders. In males, reciprocated cooperation led to the activation the left amygdala, left medial frontal cortex, right frontal pole, bilateral caudate nuclei, putamen, insula and PCC (22,23). Reciprocated cooperation when playing with a human partner, but not a computer partner, in males, led to the activation of the right posterior cingulate cortex (PCC), right orbitofrontal cortex and right middle frontal gyrus (MFG), a bilateral activation of the ITG and the planum polare and the activation of the left MTG, left precentral gyrus (PCG) and left inferior frontal gyrus (IFG) (23). In females, there was a deactivation of the left amygdala and PCC (24), bilateral caudate nuclei and putamen, right frontal pole and left medial frontal cortex (22). The caudate nucleus and the putamen were persistently activated by reciprocated cooperation, in males. The putamen, appears to facilitate cognitive functions more limited to stimulus-response, or habit, learning (42). The caudate nucleus is involved in goal-oriented action, that is, the selection of behavior based on the changing values of goals and a knowledge of which actions lead to what outcomes (42). In the Prisoner's Dilemma Task, one person has to decide to cooperate or to defect, and another person has to decide to reciprocate the cooperation or to defect. Higher payoffs, for both players, are obtained by reciprocated cooperation. However, if the first person decides to cooperate, the second person receives a higher payoff if they decide to defect. But, betraying the first person can lead to their defection in the next round, meaning a lower payoff to the second person. So, in the long-run, reciprocated cooperation leads to higher payoffs for both players. With this in mind, it makes sense that the caudate nucleus is activated in this task: there is a goal – to obtain the largest amount of money – and there is way to achieve it –

reciprocated cooperation – and OXT seems to facilitate this process. The fact that this only happened in males, could mean that they face this task as a competition and OXT could be increasing their natural competitiveness and their ability to strategize, since it has been reported that OXT increases men's perception of competition and aggressive-behaviors toward competing out-groups (43), while women appear to shy away from competition (44). In animals, the caudate nucleus appears to have a similar function, being critical for aspects of response switching, including cognitively driven strategy switching, which is, adapting the behavior according to the changing values of goals and knowing which actions lead to what outcomes (42). Also, this kind of task usually associates with the reward system (45), and our findings are consistent with that idea, since reciprocated cooperation resulted in the activation of the amygdala, insula, putamen and orbitofrontal cortex, all reward-related areas (45).

Fathers viewing pictures of their own child, compared to pictures of familiar and unfamiliar child, resulted in the deactivation of the left globus pallidus (not reported in the results) and activation of the left caudate nucleus, respectively (32). Both of these areas are part of the striatum, which is known as part of the reward-system (45). The fact that OXT stimulates the reward-system by increasing the activity of the caudate nucleus more when fathers are shown pictures of their own child, rather than an unfamiliar child, shows that OXT promotes the father-child bond, which is another important known role that OXT plays (46).

We also noticed that the left insula was activated when subjects witnessed an altruistic attitude toward a third-party (28) and deactivated when subjects witnessed a third-party being hurt (25). This could mean that the insula has a role in differentiating good from bad attitudes, or that OXT induces such ability. It has already been established that the insula has an important role in pain perception and empathy for pain (47,48). The insula (more specifically, its anterior sectors) receives visual input and integrates it with inputs from the frontal lobe, from all sensory modalities and from the limbic structures, being responsible for processing

the affective-motivational dimension of the nociceptive input (47,49). In other words, the insula mediates convergence between bodily states and emotional experience and so OXT may directly affect emotional experience when interacting with the insula. It has been shown that the insula is activated both when the self experiences pain and while witnessing other's pain (48). But the administration of OXT here resulted in the deactivation of the insula (25), which is not to say that OXT reduces empathy for pain, but rather, it could mean that it decreases the perception of pain, with a protective purpose, which has already been described, both in animals and humans (49,50). The left temporoparietal junction (TPJ) was activated when the subjects witnessed an altruistic decision being made toward a third-party by a computer, but when the subjects made that decision themselves, the left TPJ was deactivated by OXT, as well as the right insula, left STG, left MTG and bilateral PCG (28). The TPJ is involved in perspective taking, modulating, together with the insula, the altruistic behavior (51). It has been proved that OXT increases altruism and empathy and that it increases the TPJ activity (52), which happened here (28) when subjects witnessed the altruistic attitude, but not when they made that altruistic decision. We could not find supporting evidence to explain this, which means that more studies should be conducted on the effect of OXT in the brain areas associated with altruism and empathy. Curiously, the amygdala, which appears to have a central role in modulating empathy-driven altruism (52), was not implicated in this study (28).

Two studies focused on the brain response to OXT during social reward/punishment anticipation, but the results were very distinct. In a Reinforcement association learning task (27), during the response phase, OXT activated the right amygdala, left PCC, right cingulate cortex, right hippocampus, left putamen, right STG, bilateral FG, right medial frontal gyrus and left MFG. Receiving a positive feedback resulted in the activation of the right medial frontal gyrus and bilateral FG (27). The amygdala and the putamen are associated with the

reward-system and associative learning, both in humans and other animals (45,53). The cingulate cortex is also a reward-related area (45), and all three of these areas are reactive during the anticipation of positive social feedback (54). Oxytocin has already been shown to modulate these processes (41). In a Social incentive delay task (34), OXT activated the left MTG, when expecting social reward, and deactivated the bilateral PCG when expecting social punishment. Due to the similarity between these two tasks, it would be expected that the same brain areas would be summoned, but that was not the case.

To conclude, it is becoming clearer which brain areas are in charge of social cognition. Some of them are involved in multiple tasks, like the amygdala, the insula, the temporal and frontal lobes, and others appear to be task-specific. But given the importance of social cognition in the life and survival of every single animal on this planet, its characterization is very important, and finding mechanisms to help improve it, is essential. So, more studies should be conducted. Different tasks and areas of social cognition should be explored, since different tasks integrate different areas or the same area in a different way. Future studies should also focus on the gender differences: what differences are there, and why is it different. Also, more studies on the effect of OXT (and other substances, like vasopressin) on social cognition and its brain circuits are necessary, because from the research already available their potential is immense, but not yet fully understood.

Acknowledgements

To my supervisor, Professor Joaquim Cerejeira, for his guidance throughout the whole process, for the suggestions that enriched this paper and for always being available to answer all my questions.

To my family, and specially, to my mother, for all the support and constant concern and encouragement.

To Alexandre, for the patience, support and encouragement.

To my friends, for always being there, ready to help and support me.

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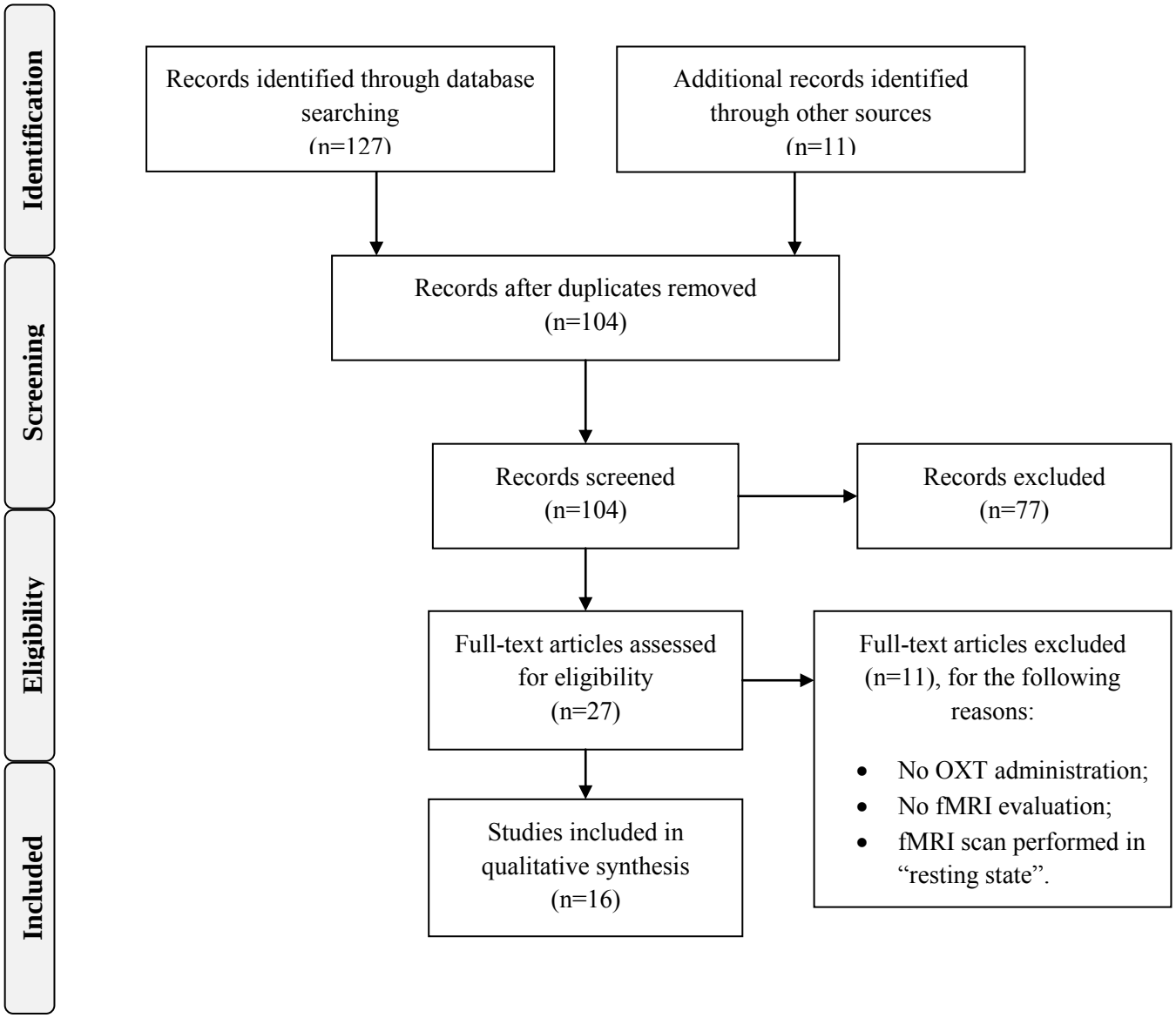
Supplementary Information

PRISMA 2009 Flow Diagram



Supporting Table 1: Main brain areas affected by Oxytocin					
Part of the brain Study	Task	Contrast	Effect		Specific area
			Left	Right	
Amygdala					
Domes et al. (33)	Explicit facial emotion processing	Fearful>Neural	↑	↔	
Gamer et al. (26)	Explicit facial emotion processing	Fearful>Neural	↓	↔	
		Gaze shifting toward the eye region	↔	↑	
Hu et al. (27)	Reinforcement association learning task	Response phase with Social Female	↔	↑	
Kanat et al. (29)	Implicit facial processing	Fearful>Neutral	↔	↓	
Lischke et al. (36)	Explicit processing of social scenes	Negative>Neutral	↑	↑	
		Positive>Neutral	↔	↑	
Radke et al. (30)	Explicit facial processing	Incongruent response: Approaching angry faces	↓	↓	
Rilling et at. (23)	Cooperation game/interaction	Reciprocated cooperation	↑	↔	
Rilling et al. (24)	Cooperation game/interaction	Reciprocated cooperation (females)	↓	↔	
		Reciprocated cooperation (males>females)	↑	↔	
Striepens et al. (31)	Implicit processing of social scenes	Negative+Neutral>Baseline	↔	↓	
		Negative>baseline	↔	↓	
		Neutral>Baseline	↔	↓	
Insula					
Bos et al. (25)	Empathy for pain	Exposure to the pain condition	↓	↔	
		Pain condition>Control condition	↓	↔	
Domes et al. (33)	Explicit facial emotion processing	Fearful>Neutral	↑	↔	
		Happy>Neutral	↑	↔	
Hu et al. (28)	Altruistic interaction	Help>Punish (computer decision)	↑	↔	
		Help>Punish (self-decision)	↔	↓	
Luo et al. (37)	Implicit facial processing	Females: FN>NN	↑	↔	
Rilling et al. (23)	Cooperation game/interaction	Reciprocated cooperation	↑	↑	
Rilling et al. (24)	Cooperation game/interaction	Reciprocated cooperation (males>females)	↑	↑	
Striepens et al. (31)	Implicit processing of social scenes	Later remembered negative>later forgotten negative	↑	↔	

Cingulate cortex					
Bos et al. (25)	Empathy for pain	Pain condition>Control condition	↓	↓	Mid cingulate cortex
Hu et al. (27)	Reinforcement association learning task	Response phase to Non-social light Response phase to Social Female	↔ ↑	↑ ↔	 PCC
Kanat et al. (29)	Implicit facial processing	Fearful>Happy	↓	↔	ACC
Luo et al. (37)	Implicit facial processing	Males: FN>NN Females: FN>NN	↓ ↑	↓ ↔	ACC ACC
Rilling et al. (23)	Cooperation game/interaction	HP cooperation>CP cooperation HP defection>CP defection	↔ ↓	↑ ↓	PCC Subgenual ACC
Rilling et al. (24)	Cooperation game/interaction	Reciprocated cooperation (females) Reciprocated cooperation (males>females)	↓ ↑	↔ ↑	PCC PCC
Hippocampus					
Domes et al. (33)	Explicit facial emotion processing	Happy>Neutral	↔	↑	
Hu et al. (27)	Reinforcement association learning task	Response phase to Social Female	↔	↑	
Rilling et al. (24)	Cooperation game/interaction	Reciprocated cooperation (males>females)	↑	↑	
Wittfoth-Schardt et al. (32)	Implicit facial processing	Unfamiliar child>Familiar child	↓	↔	
Caudate Nucleus					
Feng et al. (22)	Cooperation game/interaction	Reciprocated cooperation (males>females)	↑	↑	
Rilling et al. (23)	Cooperation game/interaction	Reciprocated cooperation	↑	↔	
Rilling et al. (24)	Cooperation game/interaction	Reciprocated cooperation (males>females)	↑	↔	
Wittfoth-Schardt et al. (32)	Implicit facial processing	Own child>Unfamiliar child	↑	↔	
Putamen					
Feng et al. (22)	Cooperation game/interaction	Reciprocated cooperation (males>females)	↑	↑	
Hu et al. (27)	Reinforcement association learning task	Response phase to Social Female	↑	↔	
Rilling et al. (23)	Cooperation game/interaction	Reciprocated cooperation	↑	↑	
Rilling et al. (24)	Cooperation game/interaction	Reciprocated cooperation (males>females)	↔	↑	

Temporal Lobe					
Domes et al. (33)	Explicit facial emotion processing	Fearful>Neutral	↑ ↑ ↑	↔ ↔ ↑	MTL STG FG
		Happy>Neutral	↑ ↑ ↑	↔ ↔ ↔	MTL STG FG
Feng et al. (22)	Cooperation game/interaction	Reciprocated cooperation (males>females)	↑	↔	Planum polare
Groppe et al. (34)	Social incentive delay task	Social reward anticipation	↑	↔	MTG
Hecht et al. (35)	Exposure to animations of moving shapes	Social relationships>Physical relationship	↓	↔	MTG
Hu et al. (27)	Reinforcement association learning task	Response phase OXT>PBO	↑	↑	FG
		Response phase to Non-social light	↑	↑	FG
		Response phase to Social Emoticon	↔ ↑	↑ ↔	STG FG
		Response phase to Social Female	↑	↑	FG
		Feedback phase (correct answers) OXT>PBO	↑	↑	FG
Hu et al. (28)	Altruistic interaction	Help>Punish (computer decision)	↑ ↑	↔ ↔	STG TPJ
		Help>Punish (self-decision)	↓	↔	STG/MTG/TPJ
Kanat et al. (29)	Implicit facial processing	Fearful>Happy	↓	↔	MTG
		Fearful>Happy (Eyes)	↔	↑	ITG
Lischke et al. (36)	Explicit processing of social scenes	Negative>Neutral	↑ ↑ ↑	↔ ↔ ↔	STG MTG ITG
Rilling et al. (23)	Cooperation game/interaction	HP cooperation>CP cooperation	↑ ↑ ↑	↑ ↑ ↔	ITG Planum polare MTG
Wittfoth-Schardt et al. (32)	Implicit facial processing	Unfamiliar child>Familiar child	↓ ↓	↓ ↔	MTG STG

Frontal lobe					
Domes et al. (33)	Explicit facial emotion processing	Fearful>Neutral	↔	↓	dlPFC
		Angry>Neutral	↔	↑	inferior PFC
			↑	↑	vlPFC
			↔	↑	dlPFC
		Happy>Neutral	↔	↓	dlPFC
Feng et al. (22)	Cooperation game/interaction	Reciprocated cooperation (males>females)	↑	↑	Medial frontal gyrus
			↔	↑	Frontal pole
Groppe et al. (34)	Social incentive delay task	Social punishment anticipation	↓	↓	PCG
Hu et al. (27)	Reinforcement association learning task	Response phase to Non-social light	↑	↔	MFG
		Response phase to Social Emoticon	↔	↑	Medial Frontal Gyrus
		Feedback phase(correct answers): Social Emoticon	↔	↑	
		Feedback phase (correct answers): Social Female	↔	↑	
Hu et al. (28)	Altruistic interaction	Help>Punish (computer decision)	↑	↔	PCG/IFG
		Help>Punish (self-decision)	↓	↓	PCG
Luo et al. (37)	Implicit facial processing	Males: FN>NN	↓	↓	IFG
		AN>NN	↓	↓	IFG
		SN>NN	↓	↓	IFG
		Females: FN>NN	↑	↑	IFG
		AN>NN	↔	↑	IFG
		SN>NN	↑	↑	IFG
Rilling et al. (23)	Cooperation game/interaction	Unreciprocated cooperation	↑	↔	vlPFC
			↑	↔	vmPFC
		HP cooperation>CP cooperation	↔	↑	Orbitofrontal cortex
			↔	↑	MFG
			↑	↔	PCG
			↑	↔	IFG
Wittfoth-Schardt et al. (32)	Implicit facial processing	Unfamiliar child>Familiar child	↓	↔	PCG

ACC: Anterior Cingulate Cortex; dlPFC: dorso-lateral Prefrontal Cortex; FG: Fusiform Gyrus; IFG: Inferior Frontal Gyrus; ITG: Inferior Temporal Gyrus; MFC: Medial Frontal Cortex; MTL: Medial Temporal Lobe; MFG: Middle Frontal Gyrus; MTG: Middle Temporal Gyrus; PCG: Precentral Gyrus; PCC: Posterior Cingulate Cortex; STG: Superior Temporal Gyrus; TPJ: Temporoparietal Junction; vlPFC: Ventrolateral Prefrontal Cortex; vmPFC: Ventromedial Prefrontal Cortex; AN, FN, NN, SN: masked emotions, angry, fearful, neutral and sad, respectively; ↓: decreased activity; ↑: increased activity; ↔: no alterations in the activity.