LETTER TO THE EDITOR

Does imitation act as an oxytocin nebulizer in autism spectrum disorder?

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Sir,

There is a growing interest in using oxytocin to improve the social and emotional impairments of individuals with autistic spectrum disorder (ASD). In an elegant paper recently published in Brain, oxytocin was shown to enhance both the score of correct inferences and the low autistic brain activity in the right anterior insula when inferring the emotions and beliefs of others (Aoki et al., 2014). Using a revisited version of the Sally-Anne Task, Aoki and colleagues suggest that reduced activity of the right anterior insula is a potential neural marker of autistic deficit in social inferences. Oxytocin may target this abnormal insula activity.

Children and adults with ASD are described as lacking empathy, affiliative behaviour and social overture. Several studies have suggested that oxytocin has therapeutic effects on autistic deficits in social responses and the understanding of emotion in others (Andari et al., 2010; Striepens et al., 2012). More generally, literature on human and non-human primates presents converging evidence of oxytocin’s positive effects on prosocial behaviour (Guastela and MacLeod, 2012; Chang and Platt, 2014). Recently, 7- to 14-day-old macaques where found to increase their facial gesturing at a human caregiver after oxytocin nebulization (Simpson et al., 2014). Moreover, being imitated predicted oxytocin-associated increases in affiliative behaviours. Even without nebulization, newborn macaques are shown to display more affiliation toward humans who imitate them; they look longer at imitators, spend more time in their proximity and prefer exchanging tokens with them (Paukner et al., 2009). Such results promote the idea that an empathic connection results from behavioural matching. Indeed, our own research with low-functioning children with ASD similarly assessed the affiliative role of being imitated; children come in close proximity, smile, look at the unacquainted experimenter, touch or kiss the experimenter and decrease self-injuring gestures (Nadel et al., 2000; Field et al., 2001). An affiliative link has been created with children whose communicative skills are deeply impaired. In typical adults, being imitated has been described as an affiliative behaviour acting as social glue (Chartrand and Bargh, 1999). Put together, such findings strongly suggest an important link between oxytocin, imitation and affiliative behaviour.

We wish to build on the results from Aoki and colleagues and share our recent findings from work with adults who have ASD using imitation in the functional MRI.
environment. Our procedure was inspired by our previous study conducted with typical adults (Guionnet et al., 2012). The design of that study consisted of an innovative functional MRI set-up that enabled behavioural and brain recordings to be synchronized during social interaction. We replicated previous findings demonstrating the existence of an imitative neural network (Iacoboni et al., 1999), and most importantly revealed the involvement of the dorsolateral prefrontal cortex and other regions in social anticipation and adjustment when free reciprocal imitation is in play (Guionnet et al., 2012). Further, we showed that imitating and being imitated activate similar brain areas. Beyond the similarities, the ‘being imitated’ condition appeared to present a greater activation in dorsal anterior cingulate cortex and insula combined with an increased deactivation in the default mode network. We interpreted the insula activity in the ‘being imitated’ condition as reflecting increased salience of emotional and social signals emitted during the social exchange. The paper by Aoki and colleagues suggests a link between the activity of the insula and the level of oxytocin. Our purpose here was to investigate the link between being imitated and the insula in autism. Without inhaling oxytocin, can imitation activate insula activity in the same way?

To test this hypothesis, we used a within-subject design in which adults with ASD were scanned before and after exposure to imitation. Exposure to being imitated was delivered during functional MRI acquisition and between two functional MRI sessions.

Six high-functioning male adults with ASD (age 23 ± 4.9 years; years of education = 13.2 ± 1.7) participated in the study. All participants had normal to corrected normal vision. They were right-handed. All were volunteers and had given their informed written consent according to the Declaration of Helsinki. The institutional ethical review board for biomedical research of the hospital approved the experimental protocol. ASD was diagnosed by psychiatrists and neuropsychologists according to DSM-IV (4th edition, text revision) criteria (American Psychiatric Association, 2002) using the autism diagnosis observation schedule-generic (Lord et al., 2000) module 4 (social-communication score) and medical records. Exclusion criteria were current or past neurological comorbidity, traumatic brain injury with any known cognitive consequences, a history of electroconvulsive therapy and substance abuse or addiction, or a participation in another study during the experiment.

The functional MRI protocol was designed as a before-after procedure with the first image acquisition preceding a tapping episode where subjects were intensively imitated and the second acquisition following this episode. In the MRI environment, the imitation task was inspired by the one used in the study by Guionnet et al. (2012) and required simple hand gestures from participants. The task required a specific set-up composed of a double-video system allowing visual capture of the other’s hand movements. An MRI-compatible video camera captured the participant’s hand gestures that were simultaneously displayed on the experimenter’s screen. Likewise, a digital camera projected the experimenter’s hand gestures onto a screen visible to the participant lying in the scanner.

Two different activation conditions were recorded: (i) observation: the subjects watch the experimenter’s hand movements online without moving; and (ii) being imitated: subjects continuously move their hands while watching the experimenter’s hand movements who was instructed to imitate the participant.

The functional MRI sessions were composed of three runs, each comprising two 30-s blocks of each of the activation conditions randomly ordered. Five 20-s blocks of a resting condition were distributed once in every couple of activation blocks for baseline estimation. The duration of one run was 5 min 40 s, and one session lasted ~16 min. All MRI data were acquired on a 3 T scanner. High-resolution 3D T1-weighted images were acquired through the whole-brain for anatomical localization. Functional MRI scans were performed using a T2* gradient-echoplanar sequence (repetition time: 2170 ms, echo time: 28 ms). The slices covered the whole brain and were acquired parallel to the anterior-posterior commissure plane. Each run lasted 460 s resulting in 158 volumes. The first three volumes of each functional run were automatically discarded in order to allow longitudinal magnetization to approach equilibrium. The general procedure of the experiment is described in Fig. 1.

Functional MRI data were processed using SPM8 software. Standard preprocessing of data was performed (slice
timing, movement correction, and spatial normalization and smoothing with a kernel of 8 mm). An individual statistical parametric map was computed for each subject using a general linear model. Each condition was modelled using a block approach and convolved with the canonical haemodynamic response function to create regressors of interest [being imitated (Bl) and observation (O)]. A high-pass filter (cut-off of 128 s) was applied and motion realignment parameters included as regressors of non-interest. The following first-level individual t-contrast images were obtained for the haemodynamic response function estimates: ‘being imitated versus observation’ and ‘observation versus being imitated’.

We focused the second-level analysis on the insula and the default mode network with an a priori region of interest approach (Guionnet et al., 2012; Aoki et al., 2014). A paired t-test analysis was performed to assess the difference in activation of the insula and default mode network between both MRI scans. The mean signals were extracted from the regions of interest at Scan 1 and Scan 2 using MarsBar software (http://marsbar.sourceforge.net).

After exposure to being imitated (MRI Scan 2 versus Scan 1), the individuals with ASD displayed an increased activation in the right insula \( t(5) = 1.65, P = 0.04 \) one-tailed and an increased deactivation in the precuneus \( t(5) = 1.76, P = 0.035 \) one-tailed and the bilateral inferior parietal lobule [right: \( t(5) = 2.4, P = 0.015 \); left: \( t(5) = 1.64, P = 0.04 \) one-tailed] within the default mode network during the condition ‘being imitated’ compared to ‘observation’ (Fig. 2).

Several studies have repeatedly observed abnormal reactivity of insula in subjects with ASD in response to social and emotional signals (Uddin and Menon, 2009). Likewise, impaired deactivation and abnormal connectivity of the default mode network has been described in adults with ASD (Kennedy et al., 2006). We were able to demonstrate that male adults with ASD showed a modulation of these regions using a simple hand gesture task.

After exposure to imitation, adults with ASD enhanced their insula activity when being imitated. The insula is a component of the salience network including among others regions the amygdala and the dorsal anterior cingulated cortex. The insula is a central node in this network that detects and integrates behaviourally relevant stimuli. Due to its connection with other neural networks, the right anterior insula is also involved in coordinating neural resources and network dynamics (Uddin, 2015). Here we found that beyond the modulation of insula activity, being imitated in adults with ASD is also associated with a bigger

**Figure 2** Difference in activation of the insula and default mode network between MRI scans. (A) Mean blood oxygenation level-dependent signal from the right insula, the precuneus and the bilateral inferior parietal lobules for Scans 1 and 2 in individuals with ASD (\( n = 6 \)). The bar graphs plot the contrast estimates between being imitated and observation (± standard error of mean). Paired t-test analysis, \( P < 0.05 \) one-tailed. (B) Difference in activation (being imitated > observation contrast) of the right insula and deactivation (observation > being imitated contrast) of the precuneus and bilateral inferior parietal lobules between Scans 1 and 2 (voxel-wise paired t-test region of interest analysis, \( P < 0.05 \) uncorrected). For the insula, the region of interest was anatomically defined using the included automated anatomical labelling atlas in Wake Forest University Pickatlas tool (Lancaster et al., 2000; Maldjian et al., 2003). For the default mode network, the peak coordinates from the findings of Guionnet and colleagues (2012) were used as centres of 10 mm radius spheres (Montreal Neurological Institute coordinates: ventral medial prefrontal cortex, 2 60 −4; precuneus, 2 −58 32; bilateral inferior parietal lobules, 52 −62 38/−54 −58 30). IPL = inferior parietal lobule.
deactivation of the default mode network after exposure to imitation.

Consistent with previous behavioural studies (Nadel, 2014), our results suggest that being imitated may increase the salience of social signals through modulation of strategic brain regions involved in self and other processing.

It is striking that both oxytocin (Aoki et al., 2014) and being imitated target the same brain region, namely the right insula. As suggested by studies in monkeys and humans at the behavioural level, both oxytocin and being imitated promote affiliative behaviours. Our results add new findings to this literature by showing similar effects of oxytocin and being imitated at the neural level. In other words, being imitated acts as a nebulization of oxytocin for affiliative behaviour in persons with ASD. A systematic use of being imitated is suggested here to have therapeutic effects similar to those offered by oxytocin in adults with ASD.

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