Serotonin manipulations and social behavior

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CHAPTER 3

STUDYING THE NEUROBIOLOGY OF HUMAN SOCIAL INTERACTION: MAKING THE CASE FOR ECOLOGICAL VALIDITY

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Abstract

With this commentary we wish to make the case for an increased focus on the ecological validity of the measures used to assess aspects of human social functioning. Impairments in social functioning are seen in many types of psychopathology, negatively affecting the lives of psychiatric patients and those around them. Yet the neurobiology underlying abnormal social interaction remains unclear. As an example of human social neuroscience research with relevance to biological psychiatry and clinical psychopharmacology, this commentary discusses published experimental studies involving manipulation of the human brain serotonin system that included assessments of social behavior. To date, these studies have mostly been laboratory-based and included computer tasks, observations by others, or single-administration self-report measures. Most laboratory measures used so far inform about the role of serotonin in aspects of social interaction, but the relevance for real-life interaction is often unclear. Few studies have used naturalistic assessments in real life. We suggest several laboratory methods with high ecological validity as well as ecological momentary assessment, which involves intensive repeated measures in naturalistic settings. In sum, this commentary intends to stimulate experimental research on the neurobiology of human social interaction as it occurs in real life.

3.1 Introduction

Interactions with others are important for mental wellbeing (House, Landis, & Umberson, 1988). Psychiatric patients often suffer from problems in the social domain (Hames et al., 2013; Thoma, Friedmann, & Suchan, 2013). For example, individuals with schizophrenia have difficulties in accurately inferring others' affective states (Lee, Zaki, Harvey, Ochsner, & Green, 2011) and the relationships of depressed individuals tend to be marked by rejection, dissatisfaction, and low intimacy (Gotlib & Lee, 1989). It is often thought that social impairments are concomitants of the disorder and simply subside with clinical improvement (e.g. Vittengl, Clark, & Jarrett, 2004). However, deficits in social functioning may be more trait-like and actively cause interpersonal stress, thereby contributing to the onset and maintenance of psychopathology (Evraire & Dozois, 2011; Segrin & Flora, 2000). Thus, understanding the neurobiology of human social interaction is imperative.

Serotonin is an evolutionarily ancient neurotransmitter. It is involved in many biological processes and has often been studied in relation to psychopathology (Lucki, 1998; Maron & Shlik, 2006). Two recent reviews provide an excellent overview of the current understanding of the role of serotonin in human social interaction. Kiser, Steemers, Branchi, and Homberg (2012) reviewed representative studies in both humans and other animals. They argued that serotonin regulates several aspects of social interaction throughout life and that the serotonin system is highly responsive to social influences. Young (2013c) described the association between human social behavior and mood and how the two may be regulated by serotonin. Notably, Young argued that while a substantial number of human social neuroscience studies have focused on social cognition and its neuroanatomical underpinnings, approaches to measure actual social behavior have been limited. This may be due to (a) limited availability of laboratory tasks for the assessment of human social behavior and (b) limited ecological validity of the measures used.

Ecological validity refers to whether a measurement procedure accurately represents the typical conditions under which a certain phenomenon occurs in the real world (Mehl & Conner, 2012a). As such, ecological validity differs from reliability, i.e. the extent to which repeated application of a measurement procedure produces the same outcome, and from construct validity, i.e. the degree to which a measurement procedure displays empirical patterns that are consistent with the theoretical construct of interest. Ecological validity of laboratory measures is important because laboratory measures may be used to predict real-world functioning (Adler, Bush, & Pantell, 2012; Yager & Ehmann, 2006). However, few studies have considered the predictive value of laboratory measures and fewer still find that laboratory measures have predictive value. For exam-

ple, Janssens et al. (2012) measured facial expression recognition with a computer task in the laboratory and assessed social functioning in real life by repeatedly asking participants about the context and appraisal of their social situation for 6 days. Participants were psychotic patients and controls. In both groups there was no significant association between the laboratory measure of facial expression recognition and real-life social functioning. Though the real-life measure may not have fully captured social functioning it is difficult to imagine how the presence of others and appraisal of the social situation would not reflect real-life social functioning to a degree. It is more likely that the laboratory task was not representative of real-life social functioning.

The purpose of this commentary is not to give an exhaustive overview of the role of serotonin in social interaction. Rather, its purpose is to focus on the ecological validity of the measures used in previous experimental studies that involved a manipulation of the brain serotonin system and subsequently assessed aspects of social functioning in humans. These studies are used as an example of past research on the neurobiology of human social interaction and to make a case for the importance of considering ecological validity when studying the neurobiology of human social interaction. Experimental studies are preferable, because they go beyond merely revealing associations and contribute to the disentanglement of cause and effect. Yet experimental studies are often confined to the laboratory (Young, 2013c) and thus at risk for low ecological validity. Therefore it is important to consider to what extent the findings of experimental studies relate to real-life social interaction. To this end we surveyed published serotonin manipulation studies that measured social or interpersonal behavior, and evaluated the ecological validity of the measures used.

3.2 Social behavior assessment in serotonin manipulation studies

To evaluate studies that manipulated serotonin and subsequently involved a social or interpersonal measure, we searched the online PsycInfo and Medline databases for relevant experimental studies using the following string of search terms: ("seroton*" AND "social" OR "interpersonal"). Studies were selected if social behavior was clinician-rated, self-reported, observed, or recorded in response to social stimuli.

Table 1 (Supplementary Material, see page 43) shows the 46 papers that were ultimately evaluated for the measures used (final search date: June 20, 2014). Specific attention was paid to their ecological validity. Further, we were interested in the extent to which authors discussed ideas about the implications of the data obtained for social interaction in everyday life.

About one third of the surveyed studies involved a decrease in serotonin, the rest involved an increase in serotonin. Most studies were conducted in individuals without a psychiatric diagnosis. A variety of social behavior measures was used, ranging from more indirect (e.g., computer tasks to assess appraisal of relationships, cooperation, or moral judgement) to more direct (e.g., observations of aggression, eye contact, and dyadic interaction). The majority were laboratory studies. By and large, acute decreases as well as longer-term decreases in serotonin had a negative impact on social interaction (Figure 1), while both acute and long-term increases in serotonin had the opposite effect (Figure 2).

3.3 Computer tasks used to date have limited ecological validity

One-fourth of the evaluated studies included facial expression recognition tasks. These tasks required participants to indicate the type of emotion expressed in faces briefly presented on a computer screen (Attenburrow et al., 2003; Harmer et al., 2003; Kerestes et al., 2009). Adaptations were used by others (Beacher et al., 2011; Bilderbeck et al., 2013; Di Simplicio et al., 2013; Passamonti et al., 2012; Simonsen et al., 2014). For example, Beacher et al. (2011) asked participants to rate faces in terms of attractiveness. The authors of only a few of the surveyed studies explained how their measures were related to the flow of social interactions in everyday life, i.e. enhanced perception (Harmer et al., 2003) and attractiveness ratings (Beacher et al., 2011) of happy faces were suggested to facilitate interpersonal approach behavior.

Facial expression recognition tasks are helpful for studying how serotonin influences the way people may see others, as well as for studying how serotonin influences the (explicit or implicit) processing of socially relevant signals. The data obtained from facial expression recognition tasks have thus often been taken to inform about social cognition as an intrapersonal process. Further, they have been employed in an imaging environment, thereby allowing for investigating the underlying neural correlates of social cognition (Di Simplicio et al., 2013; Kerestes et al., 2009; Passamonti et al., 2012).

However, the implications of facial expression recognition alterations for interpersonal behavior remained unclear. For example, manipulation of serotonin has been shown to affect the perception of fearful faces (Figures 1 and 2). Fearful faces may indicate the presence of a threat (Harmer et al., 2003) and might therefore elicit avoidance behavior from the perceiver. Yet fearful faces may also signal distress and a request for help (Parkinson, 1996), thus resulting in a different interpersonal response by the perceiver when interpreted accordingly.

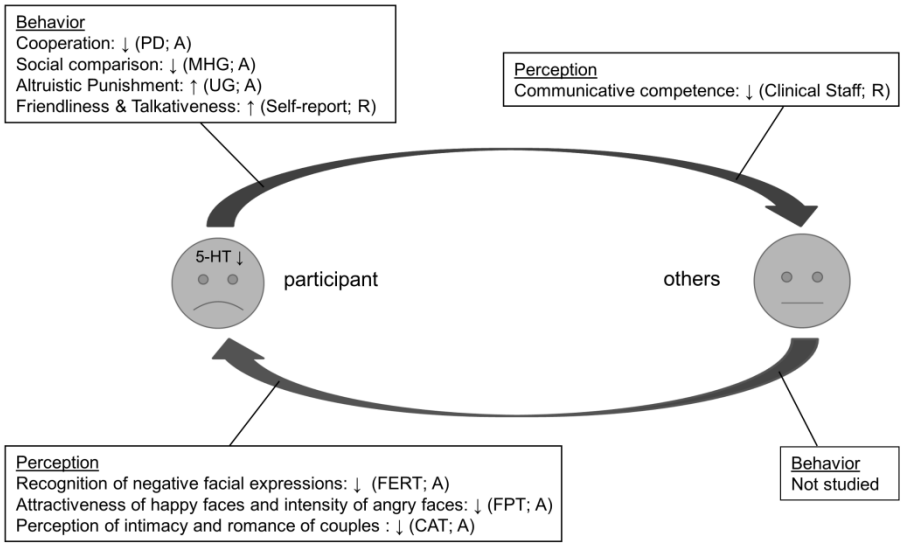

Figure 1. Cycle of social interaction: effects of acute (A) and repeated (R) serotonin decreases. The separate papers can be found in the text and table 1. 5-HT: serotonin; PD: prisoners dilemma; MHG: Multiplayer Harvesting Game; UG: ultimatum game; FERT: facial expression recognition task; FPT: face processing task; CAT: couples appraisal task.

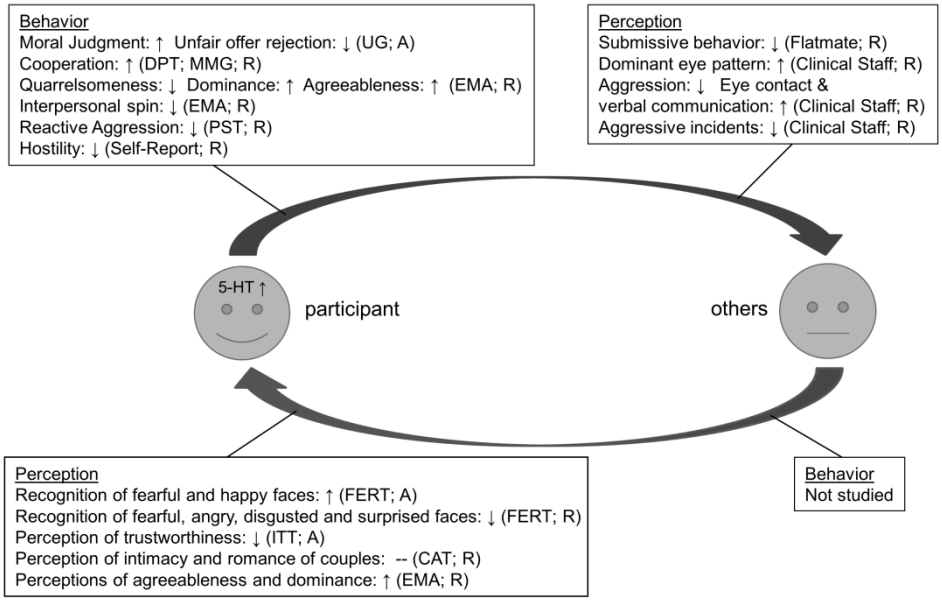

Figure 2. Cycle of social interaction: effects of acute (A) and repeated (R) serotonin increases. The separate papers can be found in the text and table 1. 5-HT: serotonin; UG: ultimatum game; DPT: dyadic puzzle task; MMG: mixed-motive game; EMA: ecological momentary assessment; PST: point subtraction task; FERT: facial expression recognition task; ITT: interpersonal trust task; CAT: couples appraisal task.

aan het Rot, Hogenelst, and Gesing (2013) asked participants how quarrelsome vs. agreeable and how dominant vs. submissive they would behave in response to facial expressions. Participants responded in a quarrelsome-submissive way towards highly fearful faces, thus indicating a wish to avoid the faces. However, towards mildly fearful faces, participants responded in an agreeable-dominant way, which is consistent with providing help. Therefore, while the evaluated studies showed that serotonin influenced the recognition of facial expressions, they did not inform about how serotonin influenced behavioral responses to facial expressions and thus largely ignored the fact that facial expressions provide an important means of interpersonal communication (Parkinson, 1996; Parkinson, 2005).

In the evaluated facial expression recognition studies, the face stimuli were static pictures of strangers. In reality however, facial expressions constitute highly dynamic social signals. Further, most interactions are with known others rather than with strangers (Tice et al., 1995). As mentioned above, a recent study in patients with a psychotic disorder and controls assessed facial expression recognition in the laboratory and social functioning in real life (Janssens et al., 2012). The ability to recognize facial expressions was unrelated to real-life social functioning. The authors pointed out that the laboratory task may not have been a good indicator of real-life social functioning, as the latter involves the complex interplay of several cognitive and behavioral components, of which facial expression recognition is just one.

Computers have also been used to assess the role of serotonin in regulating aggression (Krämer et al., 2011) and performance on a prisoner's dilemma game (Wood et al., 2006), an ultimatum game (Crockett et al., 2008), or a multiplayer harvesting game (Bilderbeck et al., 2014). Accepting fair offers and cooperating in the prisoner's dilemma were both suggested to indicate motivation to engage in positive social interaction (Crockett et al., 2013; Wood et al., 2006). It has been suggested that these laboratory assessments may indicate how people respond to unfairness, or work together for a reward (Crockett et al., 2010; Tse & Bond, 2002b). However, behavioral variation is significantly compromised as research participants are forced to choose among a limited array of responses. Several researchers have questioned the degree to which the prosocial behaviors exhibited under laboratory conditions reflect behavioral patterns outside the lab (Guala, 2012; Levitt & List, 2007). Thus, serotonin manipulation may have effects on laboratory aggression and cooperation, but the implications for social functioning in real life remain unclear.

In summary, computer tasks used so far to assess the role of serotonin in regulating social behavior are easy to administer but their low ecological validity limits their potential to inform about the role of serotonin in real-life social interaction.

3.4 Observer ratings of social behavior: often in artificial settings

One-third of the surveyed studies employed observation as an assessment tool. Serotonin-induced changes in social behaviors such as aggression (de Koning et al., 1994; McDougle et al., 1996), eye contact, or verbal responsiveness (Brodkin et al., 1997; McDougle et al., 1992) were often assessed by clinical staff. One study collected audio recordings of standardized conversations and analyzed them for communicative competence (e.g., turn-taking in speaking) (Soper et al., 1990). In another study, observations of hand fiddling and eye-contact during dyadic interactions were made by research staff and participants' flatmates were asked to retrospectively report on participants' social behavior over the past 14 days (Tse & Bond, 2002a). In yet another study, cooperation in a dyadic puzzle task was assessed by independent coders (Knutson et al., 1998).

An advantage of observation studies is that by training them to obtain high inter-rater reliability, observers can provide an accurate assessment of the behavior displayed. Unfortunately, a number of observational studies involved either a global assessment of functioning, or were limited to an interaction with a stranger (Tse & Bond, 2002a; Tse & Bond, 2002b). Neither approach is very informative with respect to how someone interacts with known others, which may at least partly explain why none of the studies made predictions about the extent to which the observed role of serotonin in regulating behavior may generalize to real life. There are important differences between interactions with a stranger, friend, or romantic partner (Barker & Lemle, 1987; Rook, Pietromonaco, & Lewis, 1994; Tice et al., 1995). This is particularly relevant when studying psychiatric patients. For example, depressed individuals have been found to be more likely to experience interpersonal difficulties with romantic partners than with others (Joiner, 2002). Instead of observing behavior in a single setting, a better approach would be to observe behavior in multiple settings with multiple (known) others.

3.5 Self-report questionnaires: risk of recall bias

A number of the surveyed studies assessed hostility by self-report (Harmer et al., 2004; Kamarck et al., 2009; Knutson et al., 1998). The Buss-Durkee Hostility Inventory, a trait measure, was administered to assess hostility before and after 7 days of selective serotonin reuptake inhibitor (SSRI) treatment (Harmer et al., 2004). An adapted version assessed hostility over the past week, and was administered before and after 1 and 4 weeks of SSRI treatment (Knutson et al., 1998). In another study, participants resided in a laboratory for 13 days while receiving fenfluramine daily aimed to increase serotonin release

(Foltin et al., 1996). Participants reported how friendly, talkative, and irritable they felt ten times a day.

Single-administration self-report measures can provide a good fit to assess the construct of interest (Moskowitz & Young, 2006). However, trait measures such as the BDHI are not designed to assess a change of state in the context of treatment. Further, participants who are retrospectively asked about a past time period may be subject to recall bias. People tend to be inaccurate about daily feelings when asked to recall their feelings over longer periods of time (Mokros, 1993). To assess the role of serotonin in actual day-to-day feelings and behaviors, retrospective self-reports may not be the method of choice. These limitations may explain why none of the surveyed studies discussed the extent to which their findings had implications for the role of serotonin in real life social interaction.

3.6 Ecological momentary assessment (EMA)

EMA is a structured technique to frequently and repeatedly assess individuals in their daily living environment. Three of the surveyed studies investigated the effects of increased serotonin on social interactions in everyday life, using a form of EMA designed to sample everyday interactions over a period of about two weeks (aan het Rot et al., 2006; Moskowitz et al., 2001; Moskowitz et al., 2011). With this method, levels of agreeable, quarrelsome, dominant, and submissive behaviors can be estimated across interactions (Moskowitz & Sadikaj, 2012). Further, participants can report on their perceptions of others (Moskowitz &Zuroff, 2005). Furthermore, in addition to analyzing mean levels of behavior one can consider variability in behavior (Moskowitz et al., 2011). High variability may imply inadequate control of social behavior and has been shown to negatively influence interpersonal relationships (Cote, Moskowitz, & Zuroff, 2012).

An advantage of EMA over more traditional self-report measures is that the variables of interest are sampled repeatedly. This allows for aggregation across multiple data points to decrease the error variance in the measure (Brown & Moskowitz, 1998; Epstein, 1979; Moskowitz & Schwarz, 1982). As a result, the measure is more sensitive to change, which is particularly relevant in the context of pharmacological interventions such as those aimed at increasing serotonin levels. Another advantage of EMA is that variables of interest are sampled close in time to occurrence, thereby minimizing recall bias (Moskowitz & Young, 2006; Shiffman, Stone, & Hufford, 2008). Furthermore, unlike laboratory studies, which are often limited in the types of interactions that may be assessed, EMA allows for sampling interactions with various others in multiple real-life social

contexts and therefore has high ecological validity to investigate the role of serotonin in social interaction.

Like other methods, EMA has its drawbacks. For both research participants and researchers, procedures can be more demanding than completing a computer task or meeting with a clinician on a limited number of occasions. Further, most EMA methods depend on self-report, thus relying on the ability of participants to accurately report on their behaviors and feelings. However, we are not always aware of our social performance and subjective experience may not capture more indirect processes (e.g., implicit recognition or neural processing of social signals) that are relevant to social behavior. Self-reporting also depends on the motivation of participants which may limit the validity of EMA. Yet in one study in which participants were asked to record their own behavior, there was a high correlation with how their behavior was rated by independent observers (Moskowitz, 1990). This indicates that accurate self-report of behavior is possible.

3.7 Future directions in studying the neuroscience of social interaction

As an example of studying the neurobiology of social interaction, we provided an overview of studies that manipulated serotonin and subsequently used computer tasks, observations, single administration self-reports, and EMA to assess social behavior. Advantages and disadvantages of these methods used to elucidate the role of serotonin in regulating social interaction were discussed. Below we provide several suggestions for improvement.

Within laboratory settings, the ecological validity of facial expression recognition tasks might be improved in several ways. Research could include an outcome variable that is more closely related to actual behavior. For example, studies may investigate the role of serotonin -and other neurochemicals- in regulating approach and avoidance of different facial expressions (Heuer, Rinck, & Becker, 2007; Marsh, Ambady, & Kleck, 2005; Seidel et al., 2010). Another possibility is to add a social simulation approach to studies that assess facial expression recognition (e.g., Meyer & Kurtz, 2009). This allows researchers to determine the extent to which a specific pattern of facial expression recognition may predict social behavior during an actual social interaction with a confederate. Further, researchers could enhance ecologically validity by using dynamic rather than static facial expressions (Ambadar et al., 2005; 2006) or combinations of face stimuli and speech content. For example, Zaki et al. (2008) developed a computer task that requires participants to watch video clips of others (targets) and to continuously rate how targets felt while narrating autobiographical emotional events; this task has previously been

shown to be sensitive to oxytocin manipulation (Bartz et al., 2010). Furthermore, the recent emergence of virtual-reality paradigms involving real-world social situations (Kim et al., 2009) as well as live face-to face interaction during fMRI (Redcay et al., 2010) opens new opportunities for investigating the neurobiology of social interaction. Virtual-reality and fMRI paradigms can both be combined with pharmacological interventions.

For ethical reasons, interventions aimed at decreasing serotonin in humans can only be conducted in laboratory settings. In contrast, interventions aimed at increasing serotonin have also been employed outside of the laboratory. Yet only three studies to date included real-life measures of social interaction. These studies used EMA to explore the effects of tryptophan administration on everyday social behaviors and perceptions (aan het Rot et al., 2006; Moskowitz et al., 2001; Moskowitz et al., 2011). These studies involved healthy working individuals, but EMA studies involving a pharmacological intervention in psychiatric patients are also possible (Moskowitz & Young, 2006). For example, it could be tested if serotonin-induced improvements in social interaction contribute to the clinical effects of antidepressants (Young et al., 2014).

Figures 1 and 2 show that serotonin manipulation may alter behavior towards others and perceptions of others' behavior. The latter suggests that others' behavior may also change following serotonin manipulation; however no studies thus far have examined this. Such studies are certainly relevant for biological psychiatry and clinical psychopharmacology, for example positive changes in relatives' behavior towards patients who are taking antidepressant medication may help improve their relationship and thus potentially contribute to the depressed patients' recovery. An EMA study in which both partners in a couple rated their own and the other's feelings in daily life (Gadassi et al., 2011) is a good example of how the behavior of dyads could be assessed. Future studies could examine the extent to which antidepressants affect not only patients' behavior but also how their romantic partners or other significant others respond to them.

Overall, laboratory tests and EMA approaches are probably best seen as complementary when studying the neurobiology of social interaction. Whereas laboratory studies can provide important insights into the psychological mechanisms that underlie social behaviors, EMA can be used to explore how those mechanisms are ultimately relevant for the flow of interactions in daily life. Both approaches have merits as well as drawbacks for the study of the neurobiology of social interaction; hence one suggestion is to combine them whenever possible. For example, studies may assess the extent to which the effect of increasing serotonin on the perception of happy faces in the laboratory (Harmer et al., 2003) is related to the effect of increasing serotonin on perceptions of agreeableness in daily life, measured with EMA (aan het Rot et al., 2006).

In addition to serotonin, the role of other neurochemicals in regulating social interaction may also be studied. Manipulation of dopamine and noradrenaline levels can be achieved in several ways, e.g. by depleting levels of their amino acid precursors phenylalanine and tyrosine (Booij et al., 2003) or by administering selective noradrenaline reuptake inhibitors (Harmer et al., 2004; Tse & Bond, 2002a). Further, hormones such as oxytocin and testosterone can be administered intranasally (Veening & Olivier, 2013) and orally (Bos, Terburg, & van Honk, 2010), respectively. In humans, a limited number of experimental studies have investigated the impact of these neurochemicals on performance on a social or interpersonal measure (Bartz et al., 2010; Davis et al., 2013; Eisenegger, Naef, Snozzi, Heinrichs, & Fehr, 2010; Harmer et al., 2004; e.g.,Tse & Bond, 2002a). By and large, these studies used measures similar to the measures used in the serotonin manipulation studies evaluated here. The ecological validity of the studies' findings has thus been limited. In short, this commentary is relevant to research aimed at elucidating the role of serotonin and that of other neurochemicals, in regulating social interaction.

3.8 Summary and conclusion

This commentary focused on studies assessing social behavior following serotonin manipulation as an example of studying the neurobiology of human social interaction. The role of serotonin in regulating social behavior has been studied using computer tasks, observations, single-administration self-report measures, and EMA. Laboratory measures can be used to study the role of serotonin and other neurochemicals in the psychological processes that presumably underlie human social functioning, but it is not always clear how the data obtained relate to actual social interaction. Laboratory measures with better ecological validity are available, but these have yet to be applied to experimental studies on the neurobiology of social interaction. An exception is a study of the effects of oxytocin on a realistic empathic accuracy task (Bartz et al., 2010). As a real-life measure, EMA provides high ecological validity, but it can be more demanding than other types of assessment. Overall, we feel that laboratory and EMA strategies are best seen as complementary. They can both informative to examine the neurobiology of human social interaction, but at different levels of analysis.

Many psychiatric diagnoses involve abnormal social functioning. The use of laboratory measures with improved ecological validity, but also measures of social behavior in real life, holds great promise for studying the neurobiology of social interaction experimentally.

SUPPLEMENTARY MATERIAL

Supplementary table 1. Overview of papers included in the commentary.

	Participants		Intervention		Assessment	
Serotonin manipulation	N (% ♀)	Diagnosis	Treatment (length[1])	Placebo[2]	Social behavior	Format
Acute decrease						
aan het Rot et al., 2010	30 (100)	None	ATD	Yes (w)	Facial emotion recognition	Computer task
Harmer et al., 2003	38 (47)	None	ATD	Yes (b)	Facial emotion recognition	Computer task
Passamonti et al., 2012	19 (47)	None	ATD	Yes (w)	Gender recognition of emotion faces	Computer task
Williams et al., 2007	10 (0)	None	ATD	Yes (w)	Facial emotion recognition	Computer task
Beacher et al., 2011	15 (100)	None	ATD	Yes (w)	Appraisal of facial emotions	Computer task
Bilderbeck et al., 2010	39 (49)	None	ATD	Yes (b)	Appraisal of couple pictures	Computer task
Bilderbeck et al., 2014	32 (50)	None	ATD	Yes (b)	Social comparison in resource management	Computer task
Wood et al., 2006	24 (50)	None	ATD	Yes (w)	Cooperation	Computer task
Crocket et al., 2008	20 (70)	None	ATD	Yes (w)	Moral judgment	Computer task
Crocket et al., 2013	30 (57)	None	ATD	Yes (w)	Moral judgment	Computer task
Krämer et al., 2011	30 (0)	None	ATD	Yes (b)	Reactive aggression	Computer task
Salomon et al., 1994	14 (7)	IED	ATD	Yes (w)	Aggression	Observation
McDougle et al., 1996	17 (12)	ASD	ATD	Yes (w)	Eye contact, verbal responsiveness	Observation
Longer term decrease						
Foltin et al., 1996	9 (44)	None	Fenfluramine (13 d)	Yes (w)	Friendliness, talkativeness	Self-report
Soper et al., 1990	8 (13)	SZ	Fenfluramine (12 wk)	Yes (w)	Communicative competence	Audio analysis
Duker et al., 1991	11 (36)	ASD	Fenfluramine (12 wk)	Yes (w)	Communicative behaviors	Observation
August, et al., 1987	10 (10)	ASD	Fenfluramine (16 wk)	Yes (w)	Social/emotional functioning	Observation
Groden, et al., 1987	4 (25)	ASD	Fenfluramine (18 wk)	Yes (w)	Social/emotional behavior	Observation
Acute increase						
Tse and Bond, 2002	40 (?)	None	SSRI	Yes (b)	Social interaction in dyads, verbal behavior	Observation, speech analysis
Crocket et al., 2010	30 (57)	None	SSRI	Yes (w)	Moral judgment	Computer task
Harmer et al., 2003	24 (100)	None	SSRI	Yes (b)	Facial emotion recognition	Computer task
Kerestes et al., 2009	12 (0)	None	SSRI	Yes (w)	Facial emotion recognition	Computer task
Labuschagne et al., 2010	14 (0)	None	SSRI	Yes (w)	Facial emotion recognition	Computer task
Simonsen et al., 2014	40 (100)	None	SSRI	Yes (b)	Trustworthiness of facial emotions	Computer task
Attenburrow et al., 2003	24 (100)	None	Tryptophan	Yes (b)	Facial emotion recognition	Computer task
Longer term increase						
Knutson et al., 1998	48 (42)	None	SSRI (4 wk)	Yes (b)	Cooperation, hostility	Observation, self-report
Tse and Bond, 2002	10 (40)	None	SSRI (2 wk)	Yes (w)	Affiliation, cooperation, verbal behavior	Computer task, observation
Di Simplicio et al., 2013	34 (53)	None	SSRI (7 d)	Yes (b)	Gender recognition of emotion faces	Computer task
Bilderbeck et al., 2013	44 (50)	None	SSRI (8 d)	Yes (b)	Appraisal of couple pictures	Computer task
Harmer et al., 2004	28 (50)	None	SSRI (7 d)	Yes (b)	Facial emotion recognition, Hostility	Computer task, self-report

Supplementary table 1 (continued).

	Participants		Intervention		Assessment	
Serotonin manipulation	(% ♀)	Diagnosis	Treatment (length[1])	Placebo[2]	Social behavior	Format
Kamarck et al., 2009	159 (50)	None	SSRI (9 wk)	Yes (b)	Hostility	Self-report
Moskowitz et al., 2001	98 (49)	None	Tryptophan (12 d)	Yes (w)	Quarrelsomeness, agreeableness, dominance, submissiveness	EMA
aan het Rot et al., 2006	39 (49)	None	Tryptophan (15 d)	Yes (w)	Quarrelsomeness, agreeableness, dominance, submissiveness	EMA
Moskowitz et al., 2011	137 (49)	None	Tryptophan (9 d)	Yes (w)	Interpersonal spin	EMA
Gowin et al., 2010	11 (36)	None	Zolmitriptan (4 wk)	Yes (w)	Reactive aggression	Computer task
Brodkin et al., 1997	33 (27)	ASD	TCA (12 wk)	No	Aggression, eye contact, verbal responsiveness	Observation
McDougle et al., 1992	5 (40)	ASD	TCA (12 wk)	No	Aggression, eye contact, verbal responsiveness	Observation
McDougle et al., 1996	30 (10)	ASD	SSRI (12 wk)	Yes (b)	Aggression, eye contact, verbal responsiveness	Observation
McDougle et al., 1998	42 (36)	ASD	SSRI (12 wk)	No	Aggression, eye contact, verbal responsiveness	Observation
Phan et al., 2013	21 (62)	SAD	SSRI (12 wk)	No	Facial emotion recognition (implicit)	Computer task
De Koning et al., 1994	160 (38)	MR	Eltoprazine (8 wk)	Yes (b)	Aggression	Observation
Victor et al., 2010	10 (?)	MDD	SSRI (8 wk)	No	Facial emotion recognition (implicit)	Computer task
Fu et al., 2004; 2007	19 (68)	MDD	SSRI (9 wk)	No	Facial emotion recognition (implicit)	Computer task
Kasckow et al., 2010	198 (22)	SZ	SSRI (12 wk)	Yes (b)	Social skills in role plays	Observation
Vartiainen et al., 1995	19 (32)	SZ	SSRI (24 wk)	Yes (w)	Aggression	Observation

[1]Fenfluramine dose was 1.5 mg/kg or 60-120 mg (20-40 mg in healthy participants); Eltoprazine: 10-30 mg; SSRIs: Citalopram 10-60 mg; Fluoxetine 20 mg; Fluvoxamine 50-300 mg; Paroxetine 20 mg; Sertraline 50-200 mg; Tryptophan: 1.8 g acute or 3 g/d; TCA: Clomipramine 75-250 mg; Zolmitriptan: 5 mg, [2] w: within subjects; b: between subjects, ATD: Acute Tryptophan Depletion; IED: Intermittent Explosive Disorder; ASD: Autism Spectrum Disorder; SZ: Schizophrenia; SAD: Social Anxiety Disorder; MR: Mental Retardation; MDD: Major Depressive Disorder; EMA: Ecological Momentary Assessment.

Note: while all of the surveyed studies were experimental in nature, several (6 of 46) did not include a control condition. This limits the interpretation of the effects of the intervention with respect to causality.