frontiers | Research Topics

The four streams of the prefrontal cortex

Edited by
Dorit Ben Shalom and Yoram S. Bonneh

Published in
Frontiers in Neuroanatomy
Frontiers in Human Neuroscience

ISSN 1664-8714
ISBN 978-2-8325-5791-4
DOI 10.3389/978-2-8325-5791-4

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

The four streams of the prefrontal cortex

Topic editors

Dorit Ben Shalom — Ben-Gurion University of the Negev, Israel

Yoram S. Bonneh — Bar-Ilan University, Israel

Citation

Ben Shalom, D., Bonneh, Y. S., eds. (2024). *The four streams of the prefrontal cortex*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5791-4

Table of contents

frontiers | Frontiers in Neuroanatomy

TYPE Editorial
PUBLISHED 16 October 2024
DOI 10.3389/fnana.2024.1487947

OPEN ACCESS

EDITED AND REVIEWED BY
Javier DeFelipe,
Universidad Politécnica de Madrid, Spain

*CORRESPONDENCE
Dorit Ben Shalom
✉ doritb@bgu.ac.il

RECEIVED 29 August 2024
ACCEPTED 02 October 2024
PUBLISHED 16 October 2024

CITATION
Ben Shalom D (2024) Editorial: The four streams of the prefrontal cortex.
Front. Neuroanat. 18:1487947.
doi: 10.3389/fnana.2024.1487947

Editorial: The four streams of the prefrontal cortex

Dorit Ben Shalom*

School of Brain Sciences and Cognition, Ben-Gurion University of the Negev, Be'er Sheva, Israel

KEYWORDS

prefrontal, motor, emotion, memory, sensory

Editorial on the Research Topic
The four streams of the prefrontal cortex

This volume was meant to explore the narrow prefrontal model in Ben Shalom and Bonneh (2019), who proposed a model of the narrow prefrontal cortex (BA 8, BA 9, BA 10, BA 11), in terms of the four streams of information: motor (BA 8), emotion (BA 9), memory (BA 10), and sensory (BA 11).

More specifically, starting with autism spectrum disorder (ASD), Ben Shalom (2009) conceptualized some core deficits in ASD in terms of four types of integration: medial BA 8—motor intergration; medial BA 9—emotion integration; medial BA 10—memory integration; medial BA 11—sensory integration. Ronel (2018) conducted a similar analysis for ADHD, in terms of four types of selection/inhibition: lateral BA 8—motor selection/inhibition; lateral BA 9—emotion selection/inhibition; lateral BA 10—memory selection/inhibition; lateral BA 11—sensory selection/inhibition (Figure 1).

The BA 8 (typical = human or animal with no known neurological disorder) study was authored by Dadario et al., and it concerns the motor stream, one of the four streams in the model.

Using data from the Human Connectome Project, the dorsolateral prefrontal cortex contains four subdivisions of BA8 (8BL, 8Ad, 8Av, and 8C) and two transitional areas between areas 6 and 8 (s6-8 and i6-8), while area 8BM is located in the medial prefrontal cortex (Glasser et al., 2016).

A visual inspection of the figures suggested that the two relevant subareas for the model are 8BM (medial) and 8BL (lateral). Indeed, in a study of the anatomical inputs to the sulcal portions of area 8Bm in the macaque monkey, dense labeling of cells was found in the pre-motor areas (F6 and F7) in the case with injection into the sulcal portion of area 8Bm (Eradath et al., 2015). 8BL, on the other hand, showed a high degree of functional connectivity throughout the frontal lobe, especially with other BA8 subdivisions in the dorsolateral prefrontal cortex.

The BA 9 (typical) 'by Ben Shalom and concerns the emotion stream, one of the four streams in the model.

Smith and Lane (2015) proposed a model of emotion processing with at least three stations: areas like the amygdala that process discrete body features areas like the anterior insula that process whole-body patterns and areas like the medial prefrontal cortex that process emotion concepts. Ben Shalom and Bonneh (2019) have proposed a model of the prefrontal cortex, in which the medial BA 9 integrates emotional states, and the lateral BA 9 performs selection/inhibition on these states. Taken together, the current article suggests a pathway for emotion processing with at least four stations: areas like the amygdala that process discrete body features, areas like the anterior insula that process whole-body patterns, medial BA 9 that integrates emotion concepts, and lateral BA 9,

that performs selection/inhibition on these concepts. Following the existing literature, it was then suggested that there is a significant involvement of the amygdala in psychopathy (Blair, 2008), the anterior insula in alexithymia (Bird et al., 2010), the medial BA 9 in deficits in somatosensory discrimination (Ben Shalom, 2009), and the lateral BA 9 in emotional impulsivity (Ronel, 2018).

The BA 10 (typical) article was authored by Faran. It concerns the memory stream of the four streams of the model. The study examined the involvement of BA10 in episodic memory, specifically, the predictions made by Ben Shalom and Bonneh (2019; i.e., that BA10 is involved in the integration of memory episodes) and by Ben Shalom (2009; i.e., that medial BA10 is involved in the representation of memory episodes themselves).

Based mainly on Bonasia et al. (2018), the author concluded that the association between BA10 and episodic memory indicates that incoming memory episodes are not represented in medial BA10. Instead, what is represented in medial BA10 is prior knowledge that, when activated, helps the integration of incoming episodes into prior knowledge. Thus, while there is indeed a connection between BA10 and episodic memory, as in the Ben Shalom and Bonneh (2019) model, it is not as straightforward as that of incoming memory episodes represented in medial BA10.

Leisman and Melillo provided evidence for a possible link between lateral BA 8 and motor selection/inhibition in ADHD. In their view, motor dysfunction in ADHD is a special case of an immature balance between 3 structural loops that connect the frontal cortex with the basal ganglia: the direct, indirect, and hyperdirect loops. Specifically, a relative weakness of the indirect and hyperdirect loops would result in a relative lack of the relevant functional inhibition, and in the case of motor inhibition, hyperactivity symptoms.

In terms of the four-stream model, both the direct and indirect pathways involve the promotor cortex, and thus potentially, also the pre-promotor cortex (lateral BA 8).

Sugimoto et al. provided evidence of a link between lateral BA 10 and memory selection/inhibition in ADHD.

Using a go/no-go task with a high percentage of go trials (which can arguably involve the inhibition of the relevant memory episodes), they used NIRS to measure lateral BA 10 activation in ADHD subjects during the no-go trials. Moreover, a positive correlation was observed between the right BA 10 activity and scores on Conners' Adult ADHD Rating Scales, suggesting a link between inefficiency in lateral BA 10 activation and selection/inhibition deficits in subjects with ADHD.

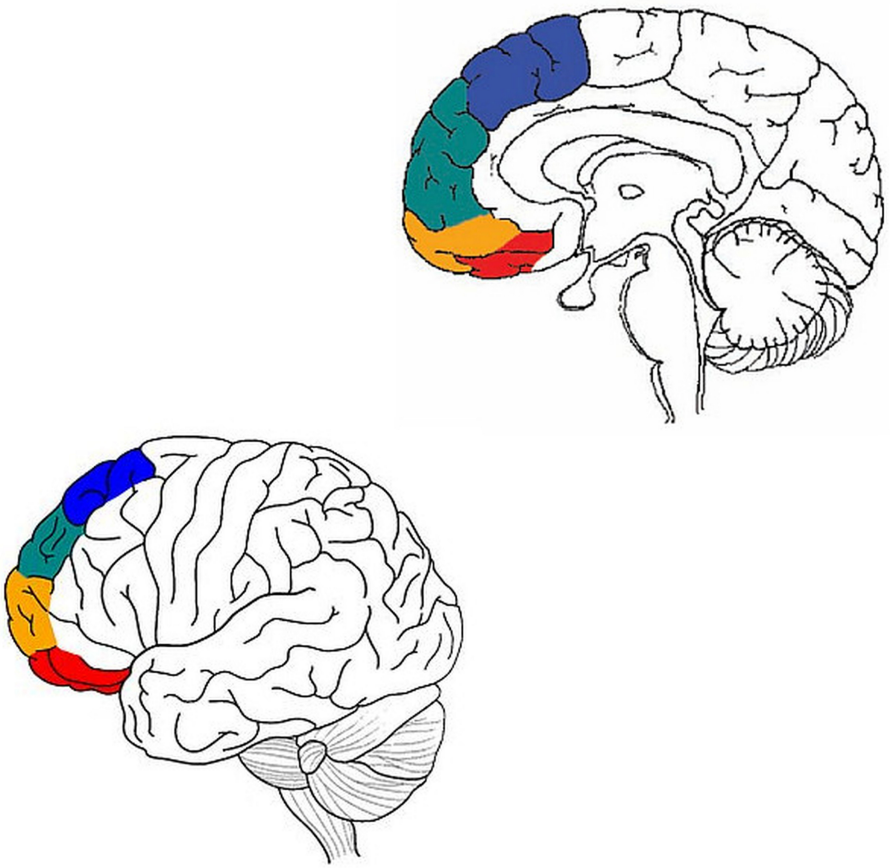


FIGURE 1
Adapted from Ben Shalom (2009) and Ronel (2018). Motor processing in blue, emotion in green, memory in orange, and sensory in red.

Segal and Elkana provided evidence of an indirect relationship between lateral BA 11, and emotionally-related sensory selection/inhibition in ADHD. Summarizing the evidence on BA 47 (which is adjacent to lateral BA 11, as opposed to BA 46, which is adjacent to lateral BA 10), they argued that the area is involved in perceptual selection that takes place through the active updating of information values linked to goal-oriented actions. In other words, while BA 46 is classically assumed to be involved in working memory for _events_, it can be argued that BA 47 is involved in working memory for emotionally relevant perceptual _objects_, thus supporting its role in the processing of emotionally relevant sensory objects.

Mohapatra and Wagner demonstrated an ambiguous and indirect connection between medial BA 9 and emotional integration in ASD. The authors described the role of two medical areas in the rodent frontal cortex, the paralimbic and infralimbic areas, in terms of socioemotional processing, including the integration of emotional states. However, they did not distinguish between the roles of the paralimbic area (arguably the rodent analog of the medial BA 9), and the infralimbic area (arguably the rodent analog of the medial BA 10; for proposed analogs of the four streams of the prefrontal cortex in the rodent brain, please see Ben Shalom and Skandalakis, 2024).

Minor et al. reviewed the evidence of a connection between the prefrontal cortex (arguably, notably medial BA 10), and memory integration in ASD. Specifically, they argued for differences in the integrity of relational memory representations and/or in the relationships between subcomponents of memory in autism.

Finally, and unexpectedly at the time, Skandalakis et al. performed population-based high-definition tractography using an averaged template generated from data from 1,065 healthy human subjects obtained from the Human Connectome Project to further elucidate the structural organization of the four streams. They reported on the structural connectivity of BA 8 with BA 6, BA 9 with the insula, BA 10 with the hippocampus, BA 11 with the temporal pole, and BA 11 with the amygdala. The four streams of the prefrontal cortex were shown to be subserved by a structural neural network that includes fibers from the anterior part of the superior longitudinal fasciculus-I and II, the corona radiata, the cingulum, the frontal aslant tract, and the uncinate fasciculus.

The full four-stream model, including both structural and functional connectivity has now been published as Ben Shalom and Skandalakis (2024).

In conclusion, this Research Topic presented functional and structural evidence for a model of the narrow prefrontal cortex (BA 8, 9, 10, and 11) in terms of four streams of information (motor, emotion, memory, and sensory, respectively). In terms of typical brain function, it is a functional neuroanatomy of the prefrontal cortex in humans, and perhaps, analogously, in mammals in general. In terms of pathological brain function, it may contribute to a better understanding of the neural circuits underlying behavioral changes in conditions such as ASD or ADHD. Future work is likely to build on this new understanding of differential information flow within the narrow prefrontal cortex.

Author contributions

DB: Writing – original draft, Writing – review & editing.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

References

Ben Shalom, D. (2009). The medial prefrontal cortex and integration in autism. *Neuroscientist* 15, 589–598. doi: 10.1177/1073858409336371

Ben Shalom, D., and Bonneh, Y. S. (2019). Editorial: The medial prefrontal cortex and integration in ASD and typical cognition. *Front. Hum. Neurosci.* 13:74. doi: 10.3389/fnhum.2019.00074

Ben Shalom, D., and Skandalakis, G. P. (2024). Four streams within the prefrontal cortex: integrating structural and functional connectivity. *Neuroscientist* 2024:10738584241245304. doi: 10.1177/10738584241245304

Bird, G., Silani, G., Brindley, R., White, S., Frith, U., and Singer, T. (2010). Empathic brain responses in insula are modulated by levels of alexithymia but not autism. *Brain* 133, 1515–1525. doi: 10.1093/brain/awq060

Blair, R. J. (2008). The amygdala and ventromedial prefrontal cortex: functional contributions and dysfunction in psychopathy. *Philos. Trans. Royal Soc. Lond. Ser. B Biol. Sci.* 363, 2557–2565. doi: 10.1098/rstb.2008.0027

Bonasia, K., Sekeres, M. J., Gilboa, A., Grady, C. L., Winocur, G., and Moscovitch, M. (2018). Prior knowledge modulates the neural substrates of encoding and retrieving naturalistic events at short and long delays. *Neurobiol. Learn. Mem.* 153, 26–39. doi: 10.1016/j.nlm.2018.02.017

Eradath, M. K., Abe, H., Matsumoto, M., Matsumoto, K., Tanaka, K., and Ichinohe, N. (2015). Anatomical inputs to sulcal portions of areas 9m and 8Bm in the macaque monkey. *Front. Neuroanat.* 9:30. doi: 10.3389/fnana.2015.00030

Glasser, M., Coalson, T., Robinson, E., Hacker, C., Harwell, J., Yacoub, E., et al. (2016). A multi-modal parcellation of human cerebral cortex. *Nature* 536, 171–178. doi: 10.1038/nature18933

Ronel, Z. (2018). The lateral prefrontal cortex and selection/inhibition in ADHD. *Front. Hum. Neurosci.* 12:65. doi: 10.3389/fnhum.2018.00065

Smith, R., and Lane, R. D. (2015). The neural basis of one's own conscious and unconscious emotional states. *Neurosci. Biobehav. Rev.* 57, 1–29. doi: 10.1016/j.neubiorev.2015.08.003

frontiers in Human Neuroscience

BRIEF RESEARCH REPORT
published: 26 November 2021
doi: 10.3389/fnhum.2021.755025

Influence of Atomoxetine on Relationship Between ADHD Symptoms and Prefrontal Cortex Activity During Task Execution in Adult Patients

Atsunori Sugimoto[1,2], Yutaro Suzuki[3,4], Kiyohiro Yoshinaga[2,5], Naoki Orime[3], Taketsugu Hayashi[2,5], Jun Egawa[5], Shin Ono[1,2], Takuro Sugai[6] and Toshiyuki Someya[5]*

[1]Department of Community Psychiatric Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]Department of Psychiatry, Niigata Psychiatric Center, Nagaoka, Japan, [3]Department of Psychiatry, Niigata University Medical and Dental Hospital, Niigata, Japan, [4]Department of Psychiatry, Suehirobashi Hospital Keiaikai, Niigata, Japan, [5]Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [6]Comprehensive Medical Education Center, Niigata University School of Medicine, Niigata, Japan

OPEN ACCESS

Edited by:
Dorit Ben Shalom,
Ben-Gurion University of the Negev, Israel

Reviewed by:
Kazuhiko Nakamura,
Hirosaki University, Japan
Mor Nahum,
Hebrew University of Jerusalem, Israel

***Correspondence:**
Atsunori Sugimoto
sugimoto.pedpsy@gmail.com

Specialty section:
This article was submitted to Brain Health and Clinical Neuroscience, a section of the journal Frontiers in Human Neuroscience

Received: 07 August 2021
Accepted: 01 November 2021
Published: 26 November 2021

Citation:
Sugimoto A, Suzuki Y, Yoshinaga K, Orime N, Hayashi T, Egawa J, Ono S, Sugai T and Someya T (2021) Influence of Atomoxetine on Relationship Between ADHD Symptoms and Prefrontal Cortex Activity During Task Execution in Adult Patients. Front. Hum. Neurosci. 15:755025. doi: 10.3389/fnhum.2021.755025

Objective: We conducted this non-randomized prospective interventional study to clarify the relationship between improved attention-deficit hyperactivity disorder (ADHD) symptoms and regional brain activity.

Methods: Thirty-one adult patients underwent near-infrared spectroscopy examinations during a go/no-go task, both before and 8 weeks after atomoxetine administration.

Results: Clinical symptoms, neuropsychological results of the go/no-go task, and bilateral lateral prefrontal activity significantly changed. A positive correlation was observed between right dorsolateral prefrontal cortex activity and Conners' Adult ADHD Rating Scales scores. Before atomoxetine administration, no correlations between prefrontal cortex activity and clinical symptoms were observed in all cases. When participants were divided into atomoxetine-responder and non-responder groups, a positive correlation was observed between prefrontal cortex activity and clinical symptoms in the non-responder group before treatment but not in the responder group, suggesting that non-responders can activate the prefrontal cortex without atomoxetine.

Conclusions: Individuals with increased ADHD symptoms appear to recruit the right dorsolateral prefrontal cortex more strongly to perform the same task than those with fewer symptoms. In clinical settings, individuals with severe symptoms are often observed to perform more difficultly when performing the tasks which individuals with mild symptoms can perform easily. The atomoxetine-responder group was unable to properly activate the right dorsolateral prefrontal cortex when necessary, and the oral administration of atomoxetine enabled these patients to activate this region. In brain imaging studies of heterogeneous syndromes such as ADHD, the analytical strategy used in this study, involving drug-responsivity grouping, may effectively increase the signal-to-noise ratio.

Keywords: atomoxetine, attention-deficit/hyperactivity disorder, Conners' adult ADHD rating scales, go/no-go task, near-infrared spectroscopy, responder group, response inhibition task

INTRODUCTION

Atomoxetine (ATX) is a representative drug used to treat attention-deficit hyperactivity disorder (ADHD) and is ranked as a first-line, non-stimulant treatment in national guidelines [Saito et al., 2016; Attention deficit hyperactivity disorder guideline committee of National Institute for Health and Care Excellence (NICE), 2018; Wolraich et al., 2019; Canadian ADHD Resource Alliance (CADDRA), 2020]. The use of stimulants should be carefully considered if the patient's pre-existing condition includes a history of substance abuse or tic disorders [Canadian ADHD Resource Alliance (CADDRA), 2020], in which case treatment with non-stimulants such as atomoxetine should be considered. In addition, if stimulants cause serious cardiovascular problems or growth retardation, they must be discontinued. In such cases, atomoxetine is an important option.

Abnormalities in the prefrontal cortex (PFC), striatum, and default mode network have been identified as the neural basis of ADHD (Posner et al., 2020), and reaction suppression and other executive functions that are considered to be abnormal in ADHD individuals are mainly related to the right PFC (Fernández-Jaén et al., 2015). Because of the high density of norepinephrine transporter (NET) and low density of dopamine transporter (DAT) in the PFC, reuptake of dopamine is mainly performed *via* NET (Madras et al., 2005) and ATX is a selective norepinephrine transporter inhibitor. Animal studies have revealed that ATX increases dopamine (DA) levels in the synaptic cleft by inhibiting NET activity in PFC (Bymaster et al., 2002; Ding et al., 2014), which is considered to be the primary mechanism through which ATX improves ADHD symptoms. Although previous human studies have demonstrated reduced lateral PFC activity in ADHD patients compared with typically developing (TD) individuals (Cortese et al., 2012; Albajara Sáenz et al., 2019) and ATX administration has been shown to increase lateral PFC activity (Ota et al., 2015; Nakanishi et al., 2017; Grazioli et al., 2019), no studies have revealed an association between changes in lateral PFC activity with ATX administration and improvement in ADHD symptoms. We conducted a non-randomized prospective interventional study using near-infrared spectroscopy (NIRS) measurement in ADHD patients before and after ATX administration to clarify the relationship between improved symptoms and lateral PFC activity.

Because NIRS does not use radiation or strong magnetic fields, it has the advantage of being less invasive for some patients. In addition, whereas blood oxygen level dependent functional magnetic resonance imaging (fMRI) can only measure deoxy-Hb, NIRS has the advantage of being able to measure both oxy-Hb and deoxy-Hb. NIRS does not require the strict movement restrictions that are needed for MRI, and higher time resolution is also a benefit of NIRS measurement (Aslin and Mehler, 2005; Lloyd-Fox et al., 2010). Difficulties in measuring NIRS can occur because of spurious signals caused by slippage of the probe on the scalp, or variations in the intensity of near-infrared light at the point of contact with the scalp. However, these problems can be suppressed by improving measurement methods and analysis techniques (Aslin and Mehler, 2005). On the basis of these considerations, we decided to use NIRS in the current study.

ADHD is assumed to represent a syndrome in which multiple etiologies are superimposed (Ball et al., 2019). Therefore, diagnoses based on biomarkers and the prediction of drug reactivity are not widespread. Several previous studies have attempted to group ADHD patients according to comorbidities, resulting in new insights. A meta-analysis conducted by Cortese et al. (2012) revealed that the default mode network was included in the hypoactive region when analyzed only in ADHD patients without comorbidities. However, to the best of our knowledge, no previous functional neuroimaging studies have grouped patients by responsiveness to ADHD drug treatments to examine the pathophysiology of ADHD. Therefore, in the current study, we investigated the pathophysiology of ADHD by grouping and analyzing participants based on ATX responsivity.

MATERIALS AND METHODS

Participants, Treatment Procedures, and Assessment of Symptoms

The participants in this study were 31 adult patients (19 male) who were diagnosed with ADHD according to The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition [DSM-5; American Psychiatric Association (APA), 2013]. Participants' ages ranged from 19 to 49 years, with a mean ± standard deviation (SD) of 31.2 ± 8.6 years. Regarding comorbid psychiatric disorders (with duplication), 10 participants had autism spectrum disorder, five had a mild intellectual disability, three had adjustment disorder, two had unspecified depressive disorder, one had a history of substance use disorder, and one had a history of child physical abuse and child neglect. All participants were confirmed to be right-handed using the Edinburgh Handedness Inventory (Oldfield, 1971). ATX treatment was started at a dose of 40 mg then increased by 40 mg every 2 weeks, with an upper limit of 120 mg, unless side-effects were detected. We used the self-reported Conners' Adult ADHD Rating Scales (CAARS^{TM}; Conners et al., 2012) to assess the clinical symptoms of all patients, both at baseline and 8 weeks after ATX treatment onset.

Go/No-go Task

NIRS measurements were taken during a 10-minute computerized, visual-response, inhibition task, called "ADHD test program" (Norupro Light Systems Inc, 2000). In this go/no-go task, the non-target stimulus A and a target stimulus B, which closely resembled A, were randomly presented. The participant was asked to press the space key using their index finger as quickly as possible when A was presented (response) and to refrain from pressing the space key when B was presented (response inhibition). Using the preset "Adult Standard 2" setting. The division area was set to five, the screen was divided into 5 × 5 = 25 squares, and targets appeared randomly at any position. The target appearance time was 200 ms, the interval wait time was 1,300 ms and the interval time randomization rate was 50%. With an interval wait time of 1,300 ms and

an interval time randomization rate of 50%, the time to the presentation of the next stimulus varied between 650 and 1, 950 ms. Therefore, the number of trials fluctuated slightly each time. However, because the target appearance time was 200 ms and the standard sensory standby time was 1,300 ms, the number of trials for 10 min converged at approximately 400 times. The target presentation rate was 50%, and the probability that stimulus B was presented was 50%. In most cases, go/no-go tasks have a target presentation rate of approximately 20%, but this high target presentation rate characterized our task. The screen used for stimulus presentation was 17 inches in size (33.7 cm × 27.0 cm), and the positions of the participant and the screen were adjusted to maintain a distance of 50 cm between the screen and the participants' eyes. To measure the Δ[Oxy-Hb] values purely associated with executing the reaction inhibition task, and to remove background elements, such as motion planning or motion starting, 10 s of pre- and post-task periods were provided. During the pre- and post-task periods, participants were asked to tap the desk iteratively with their index finger, using a motion that was equivalent to pressing the space key.

NIRS Data Acquisition

NIRS examinations were performed using a wearable 16 Ch-NIRS WOT-100 system (HITACHI, Tokyo, Japan) before and 8 weeks after the onset of ATX administration. All participants underwent two NIRS measurements. In pretreatment measurements, participants had never taken ATX before. In the post-treatment measurement, NIRS measurement was performed 12 h or more after the last ATX administration. NIRS measures changes in oxygenated hemoglobin levels (Δ[Oxy-Hb]) in the PFC, using near-infrared rays, and can evaluate activity during task execution. The location of each channel was estimated using the probabilistic estimation method (Singh et al., 2005; Atsumori et al., 2010) in the Montreal Neurological Institute (MNI) standard brain space, as shown in **Figure 1**. The sampling rate was set to 5 Hz, and baseline correction was performed using linear fitting based on two points of the pre- and post-task period. The pre-task baseline used for the baseline correction was the last point of the 10-s pre-task period, and the post-task baseline was the last point of the post-task period. As the activation value, we used the average time series data with baseline correction for the entire measurement period during task execution. Microsoft Excel was used for baseline correction and calculation of activation values.

Statistical Analysis

IBM SPSS Statistics 24 (IBM Japan, Tokyo, Japan) was used for all statistical analyses. A 10-min average of changes in Δ[Oxy-Hb] for each channel during the task was calculated, and prefrontal cortex activity was examined to detect changes after ATX administration. Then, for channels in which activity changed after ATX administration, the relationship between activity at that site and clinical symptoms evaluated by CAARS was examined. Paired Student's t-tests were used to test the difference, Pearson's correlation coefficient test was used to test the correlation, and the significance level was set to 5%.

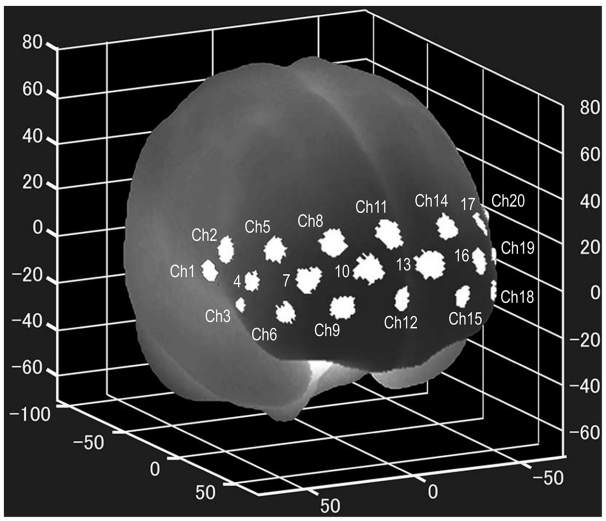


FIGURE 1 | Locations of the NIRS channels. The mean estimated locations of the studied channels of the wearable 16 Ch-NIRS WOT-100 system (HITACHI, Tokyo, Japan), represented in the MNI standard brain space, using the probabilistic estimation method for 10 volunteers (Atsumori et al., 2010). Ch 20, 21, and 22 are on the left side of the brain and are difficult to see in the figure. Ch 1, 2, 3, 20, 21, and 22 are optional channels, which our institution does not have access to. NIRS, near-infrared spectroscopy; MNI, Montreal Neurological Institute.

The Bonferroni correction was used to correct for multiple testing. However, in consideration of the criticism that the broad application of the Bonferroni correction is overly strict, the correction was separately adapted into four categories: each item of CAARS, task performance, changes in Δ[Oxy-Hb], and correlation between PFC activity and CAARS items. The change was calculated as "post–pre," and if the value decreased after treatment, the change was negative.

RESULTS

The final ATX doses ranged from 25 to 120 mg, with a mean ± SD of 95.3 ± 34.5 mg. The CAARS scores before and after administration are shown in **Table 1**, and all scores other than those for item D (Problems with self-concept) significantly improved after ATX administration. Results of the ADHD test program are also shown in **Table 1**. All indices except mean reaction time significantly improved after ATX administration. The Δ[Oxy-Hb] values before and after ATX administration are shown in **Table 2**, and activity changed in bilateral lateral PFC (Ch 5, 6, 17, 18).

Among the four channels, only Δ[Oxy-Hb] in the right dorsolateral PFC (Ch 5) showed positive correlations with the CAARS items D, F, G, and H of CAARS after ATX administration (r = 0.464, 0.430, 0.473, and 0.694, respectively; p = 0.020, 0.032, 0.017, and <0.001, respectively), and significant correlations were not observed for the other channels. Because the CAARS item H showed the strongest correlation with Ch5, item H was used to distinguish responders. The mean change in H-score after ATX administration was −4.19, the

TABLE 1 | Scores of Conners' Adult ADHD Rating Scales and ADHD test program.

	Baseline	8 week	*p* value
Conners' Adult ADHD Rating Scales (CAARS™)			
A: Inattention/Memory Problems	79.0 ± 9.0	72.2 ± 10.0	0.000075*
B: Hyperactivity/Restlessness	68.6 ± 11.8	65.1 ± 11.6	0.025*
C: Impulsivity/Emotional Lability	70.2 ± 12.9	64.6 ± 12.0	0.013*
D: Problems with Self-Concept	67.1 ± 8.2	66.3 ± 9.2	0.548
E: DSM-IV Inattentive Symptoms	81.9 ± 9.3	73.8 ± 10.4	0.000054*
F: DSM-IV Hyperactive-Impulsive	74.4 ± 12.6	66.1 ± 13.0	0.001*
G: DSM-IV ADHD Symptoms Total	81.4 ± 8.4	72.5 ± 10.2	0.000096*
H: ADHD Index	76.0 ± 7.8	71.2 ± 8.9	0.005*
ADHD test program (NoruPro Light Systems Inc.)			
Correct answer rate (%)	92.7 ± 6.2	95.3 ± 5.3	0.000179*
SD of correct answer rate	3.72 ± 1.74	2.96 ± 1.85	0.007*
Mean reaction time (ms)	494.0 ± 53.7	495.2 ± 50.9	0.877
SD of reaction time	76.3 ± 19.4	66.9 ± 15.6	0.001*
Omission error (%)	0.15 ± 0.03	0.13 ± 0.03	0.000019*
Commission error (%)	3.75 ± 5.54	2.35 ± 4.06	0.008*

*Each score is expressed as mean ± SD; *... <0.05. ADHD, attention-deficit hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders.*

TABLE 2 | Prefrontal activity as Δ[Oxy-Hb] measured by near-infrared spectroscopy.

	Baseline	8 week	*p*		Baseline	8 week	*p*
Ch4	−0.05 ± 0.20	−0.03 ± 0.30	0.621	Ch12	0.01 ± 0.20	−0.02 ± 0.22	0.549
Ch5	0.28 ± 0.15	0.83 ± 0.13	0.016*	Ch13	0.03 ± 0.17	0.01 ± 0.27	0.737
Ch6	−0.02 ± 0.16	0.05 ± 0.15	0.039*	Ch14	0.03 ± 0.14	0.05 ± 0.12	0.405
Ch7	−0.05 ± 0.32	0.05 ± 0.22	0.137	Ch15	−0.03 ± 0.18	0.03 ± 0.17	0.112
Ch8	0.02 ± 0.13	0.06 ± 0.19	0.374	Ch16	0.01 ± 0.14	0.09 ± 0.21	0.070
Ch9	−0.002 ± 0.18	0.02 ± 0.17	0.590	Ch17	0.01 ± 0.19	0.08 ± 0.12	0.031*
Ch10	−0.12 ± 0.51	0.06 ± 0.27	0.138	Ch18	−0.0004 ± 0.11	0.08 ± 0.16	0.015*
Ch11	0.04 ± 0.13	0.01 ± 0.20	0.567	Ch19	0.03 ± 0.14	0.06 ± 0.24	0.588

*Each score is expressed as mean ± SD; *... <0.05.*

SD was 8.22, and the median was −2. The distribution of changes in item H exhibited a clear bimodality between participants exhibiting an improvement of 6 points or more and those exhibiting an improvement of 2 or less (including no change and deterioration). No participants exhibited H-score changes of −3, −4, or −5. On the basis of these findings, we defined participants with an H-score improvement of 4 or more after ATX administration as the responder group, and those with an improvement of 3 or less (unchanged or worse) as the non-responder group. As shown in **Figure 2**, no correlation was found between Δ[Oxy-Hb] values and H-score before ATX administration in the responder group, whereas in the non-responder group, a positive correlation was observed.

Regarding the correlation between dose and changes in symptoms and PFC activity, in all participants, there were no correlations between the dose, change in item H, and change in Ch5 (r = 0.252, 0.246; p = 0.214, 0.182). When only responders were analyzed, there were no correlations between the dose, the change in item H, and the change in Ch5 (r = 0.443, 0.334; p = 0.149, 0.273).

Regarding the correction for multiple tests, even after Bonferroni correction, significant differences were found in CAARS items A, E, F, G, and H for symptom improvement ($p < 0.00625$), and in the correct answer rate, SD of the correct answer rate, SD of reaction time, omission errors, and commission errors in task performance ($p < 0.00833$). Although the increase in Δ[Oxy-Hb] in the lateral PFC after ATX administration could not be maintained after correction ($p < 0.0125$), a significant correlation between Ch 5 and item H was maintained for the correlations between Ch 5, 6, 17, 18 and CAARS items A, B, C, E, F, G, H ($p < 0.00179$).

DISCUSSION

Relationship Between ADHD Symptoms and Prefrontal Cortex Activity

The results of this study suggested that ATX administration increased lateral PFC activity, indicating that right dorsolateral PFC (DLPFC) activity may be related to clinical ADHD symptoms. Although previous studies have demonstrated reduced lateral PFC activity in ADHD patients compared with TD individuals (Cortese et al., 2012; Albajara Sáenz et al., 2019) and ATX administration has been shown to increase lateral PFC activity (Ota et al., 2015; Nakanishi et al., 2017; Grazioli et al., 2019), the current study clarified the relationship between ATX-induced change in right DLPFC activity and clinical ADHD symptoms. The positive correlation observed between right DLPFC activity and each CAARS item did not allow conclusions about causality. However, pathologically, given that brain activity is always unidirectional in causing symptoms, it is likely that ADHD symptoms were more severe in individuals with more intense PFC activity when performing the same task. In clinical practice, it is often observed that people with severe

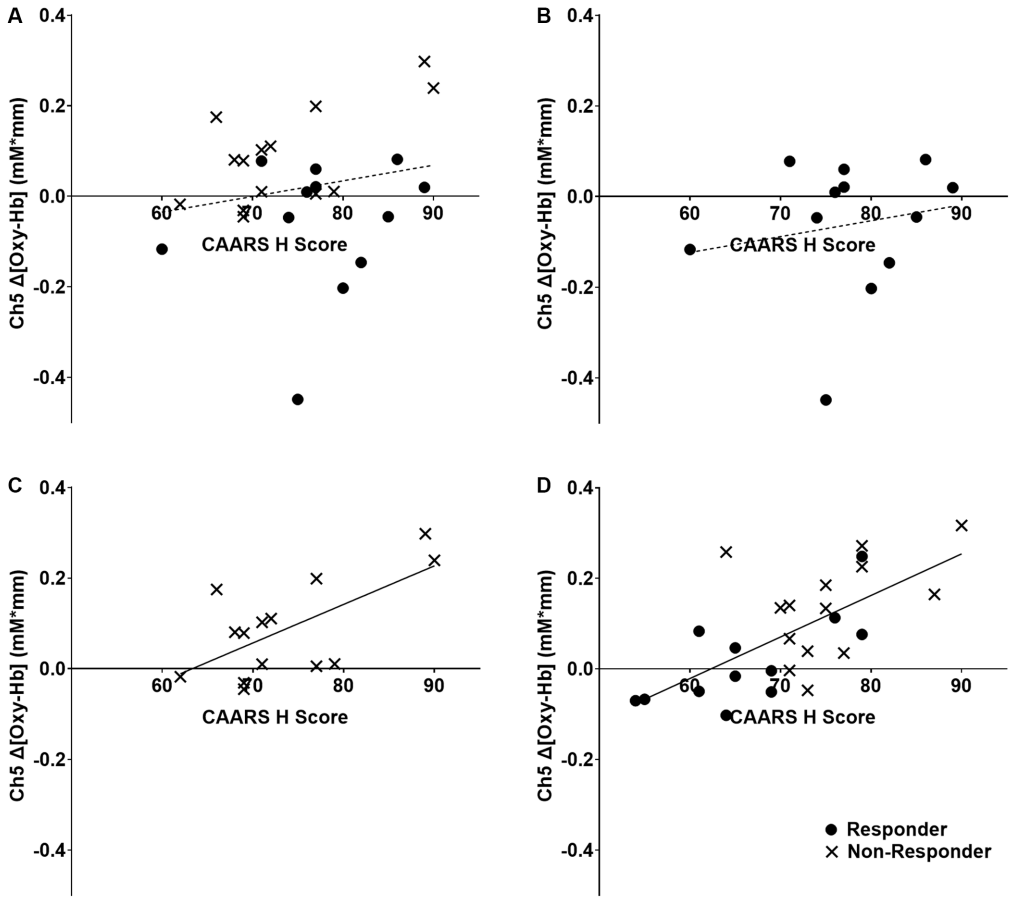


FIGURE 2 | Relationship between right dorsolateral prefrontal cortex activity and clinical ADHD symptoms. The dashed line indicates that there is no significant correlation, and the solid line indicates that there is a significant correlation. The regression lines refer to all individuals in the panel, including both responder and non-responder groups. **(A)** All participants at baseline, $r = 0.129$, $p = 0.522$. **(B)** ATX-responder group at baseline, $r = 0.179$, $p = 0.579$. **(C)** ATX non-responder group at baseline, $r = 0.646$, $p = 0.013$. **(D)** All participants at 8 weeks, $r = 0.694$, $p < 0.001$. ADHD, attention-deficit hyperactivity disorder; ATX, Atomoxetine.

symptoms need to mobilize more concentration to perform tasks that people with mild symptoms can easily perform. This positive correlation suggests that all participants in both groups exhibited the right DLPFC activity that was correlated with symptoms during task performance after ATX administration. However, before ATX administration, a correlation was observed between right DLPFC activity and ADHD symptoms in the non-responder group, whereas no similar correlation was observed in the responder group. These findings suggest that the non-responder group showed right DLPFC activity that was correlated with symptoms during task performance even before ATX administration, whereas individuals in the responder group did not show similar activity before treatment, and the same site showed symptom-correlated activity only after treatment. These mechanisms can explain the improvement of ADHD symptoms by ATX administration and have important implications for understanding brain local drug reactions that bridge the molecular-level mechanisms (Bymaster et al., 2002; Ding et al., 2014) and symptom-level findings of previous studies.

It is necessary to consider the mechanisms underlying the strong correlation between ADHD symptoms and right DLPFC activity, and the lack of a correlation between ATX dose and changes in symptoms or changes in right DLPFC activity. The level of symptoms exhibited by the responders who received ATX and the non-responders who did not receive ATX, and the extent of right DLPFC activation during task performance (both of which were correlated) appeared to be defined by some other factor. This factor may be related to features such as the striatum, cerebellum, and the broader default mode network. In other words, although ATX may provide a way of releasing suppression or mask, the degree of symptoms of responders after releasing suppression or mask appears to be defined by some other factor. Thus, the effect of releasing suppression or mask on an individual's symptoms (i.e., how much the symptoms apparently change because of treatment) is not correlated with the dose of ATX.

Although Schulz et al. (2012) reported that increased right inferior frontal gyrus activity was significantly associated with improved ADHD symptoms following ATX treatment, no study

has reported a similar correlation for right DLPFC activity. Both the inferior frontal gyrus and the DLPFC, especially in the right hemisphere, are involved in response inhibition functions (Garavan et al., 2006). However, the DLPFC is associated with "selecting" the inhibitory response, whereas the inferior frontal gyrus is associated with "inhibiting" the response. We used a task involving a high rate of target stimuli and a low commission error rate (Norupro Light Systems Inc, 2000), whereas Schulz et al. (2012) used a task with a low rate of target stimuli and a high commission error rate (Durston et al., 2002). When the appearance rate of target stimuli is low, the factor that "inhibits" the response is strengthened, and when the appearance rate of target stimuli is high, the factor that "selects" response inhibition is strengthened. Therefore, these differences in tasks may explain the differences in results between the two studies. Given the above points, the importance of task selection should be examined in more depth in future functional brain imaging studies, including fMRI and fNIRS studies.

In the current results, CAARS items A, B, C, E, F, G, and H were significantly improved, but item D was not significantly changed. For items A, B, C, E, F, G, and H, which are the core symptoms of ADHD, ATX administration has a direct effect, and it is possible that the symptoms improved relatively early. Although the observation period for this study was 8 weeks, if there is any improvement in item D (which indicates problems with self-concept), it may appear later.

Grouping by Drug Responsivity

Whereas previous studies did not separately examine drug-responder and non-responder groups, the adoption of this grouping method in the current study may have successfully clarified the mechanisms of symptom improvement induced by ATX. Although Cortese et al. (2012) divided ADHD individuals into several groups based on comorbidities in their meta-analysis of fMRI studies, which provided new insight associated with functional imaging of ADHD patient brains, grouping by drug reactivity should also be considered. In functional brain imaging studies and genetic studies, if patients are a heterogeneous population with multiple pathologies, the signal-to-noise ratio cannot be effectively increased simply by increasing the size of samples, such as by performing meta-analyses. Rather, the signal-to-noise ratio must be increased by extracting and analyzing specific and uniform groups of patients. The division of ADHD patients into drug-responder and non-responder groups represents a reasonable approach that should be applied in future functional brain imaging and genetic studies. However, although the analyses of this study were successfully performed following the classification based on the CAARS score for convenience, the actual patient population remains a spectral aggregate. Future researchers should consider this point, even when stratifying patients into two or more categories.

Limitations

An important limitation is that this study was not a randomized controlled trial. Furthermore, because CAARS was self-assessed, expectancy effects cannot be ruled out, particularly for CAARS changes after ATX administration. However, we believe that the changes in task performance and the statistical robustness of the correlation between right DLPFC activity and symptoms enabled the current study to overcome some of the limitations of previous studies.

In this study, we did not include a TD group as a control group. Assuming that the ATX non-responder group exhibits ADHD symptoms because of a condition other than the impairment of PFC function, a TD group would be expected to exhibit similar distribution on the y-axis and left side distribution on the x-axis than the non-responder group in the graph shown in **Figure 2**. If this prediction is correct, the whole ADHD group, including both the ATX-responder and non-responder groups, would be expected to have lower y-axis values than the TD group, which would be consistent with the observations in previous studies showing reduced PFC activity in ADHD patients compared with that in the TD group (Albajara Sáenz et al., 2019). Further research should examine differences in regional brain function between an ATX-responder group, a non-responder group, and a TD group.

The problem of multiple testing is considered to be an important limitation of this study. Although most of the main results of this study were maintained after correction for multiple testing, the increase in Δ[Oxy-Hb] after ATX administration was not maintained after Bonferroni correction. We carefully considered this point before interpreting and considering the results, and readers should take this issue into account when interpreting the current findings.

Because of the wide age range in the sample (19–49 years) in the current study, there may have been age-related variability in task performance and PFC activity. Although the lack of a method for controlling for the effect of age on task performance and PFC activity is a limitation of this study, it should be noted that there was no significant correlation between age and task performance or PFC activity.

In the current study, we found no associations between clinical symptoms and task performance. The lack of a correlation between neuropsychological task performance and the self-reported symptom scale has been previously reported for ADHD patients (Toplak et al., 2013). Leontyev et al. (2018) performed a dynamic assessment and argued that inattention or hyperactivity in ADHD patients appears during the process of deciding the optimized final choice (movement of the mouse cursor up to that point) and during unpurposive behavior in which the participant self-decided their conduct, which cannot be measured when only considering the optimized final selection in a time-limited environment. The go/no-go task used in this study only measured the optimized final selection, potentially explaining why no correlation was observed between task performance and clinical symptoms. Leontyev et al. (2018) proposed a go/no-go task that traces the movement of the mouse cursor until the final selection is made, as a countermeasure. Such an approach may be necessary to detect associations between clinical symptoms and task performance. However, a previous study (Yasuhara, 2006) clarified the differences between the ADHD group and the control group, and, in this study as well, the parameters changed significantly after ATX administration, confirming a

robust correlation between brain activity and symptoms during task execution. On the basis of these factors, we believe that this task was appropriate for addressing our research questions.

Previous studies (Ishii-Takahashi et al., 2015; Kim et al., 2015; Schulz et al., 2017) have attempted to predict responses to drug treatments before administration, based on functional brain imaging findings. However, as shown in **Figure 2**, the distribution of responders and non-responders before ATX administration overlapped, and the clinical application of predicted effectiveness appears to be relatively difficult. However, approaches that use machine learning are promising for predicting drug responses (Kim et al., 2015). Further considerations of multiple etiologies, such as those described above, by performing comprehensive examinations of differential activities in multiple regions of interest, may be necessary to predict drug responsiveness using brain functional imaging findings.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the datasets generated and/or analyzed during the current study are not publicly available due to lack of ethics committee permission and not having been part of the consent process. The reasonable request will be raised with Niigata University Genetic Ethics Review Committee. Requests to access the datasets should be directed to ethics@adm.niigata-u.ac.jp.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Genetic Ethics Review Committee of Niigata University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS: conceptualization, methodology, validation, investigation, data curation, formal analysis, writing—original draft, writing—review and editing, project administration, and funding acquisition. YS: conceptualization, methodology, validation, formal analysis, writing—review and editing, and project administration. KY, NO, and TH: investigation and resources. JE: methodology, validation, and writing—review and editing. SO and TSu: writing—review and editing, funding acquisition. TSo: methodology, validation, formal analysis, writing—review and editing, supervision, and project administration.

FUNDING

This work was supported by the following research funding: contract research funds [156195-J15F0001] from the Hospitals Bureau Niigata Prefecture Government received by AS and SO, and KAKENHI Basic Research C [26461763] from the Japan Society for the Promotion of Science received by TSu. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGMENTS

We would like to thank the doctors, nurses, psychologists, clerks, secretaries, and other staff at Niigata University Graduate School of Medical and Dental Science and Niigata University Medical and Dental Hospital for their cooperation in the promotion of this study. We thank Lisa Giles, PhD, and Benjamin Knight, MSc from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

REFERENCES

Albajara Sáenz, A., Villemonteix, T., and Massat, I. (2019). Structural and functional neuroimaging in attention-deficit/hyperactivity disorder. *Dev. Med. Child Neurol.* 61, 399–405. doi: 10.1111/dmcn.14050

American Psychiatric Association (APA). (2013). *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5).* Japanese Edition. Tokyo, Japan: Igaku-Syoin.

Aslin, R. N., and Mehler, J. (2005). Near-infrared spectroscopy for functional studies of brain activity in human infants: promise, prospects and challenges. *J. Biomed. Opt.* 10:11009. doi: 10.1117/1.1854672

Atsumori, H., Kiguchi, M., Katura, T., Funane, T., Obata, A., Sato, H., et al. (2010). Noninvasive imaging of prefrontal activation during attention-demanding tasks performed while walking using a wearable optical topography system. *J. Biomed. Opt.* 15:046002. doi: 10.1117/1.3462996

Attention deficit hyperactivity disorder guideline committee of National Institute for Health and Care Excellence (NICE). (2018). Attention deficit hyperactivity disorder: diagnosis and management. *NICE Guideline*. Available online at: https://www.nice.org.uk/guidance/ng87. Accessed March 10, 2021.

Ball, G., Malpas, C. B., Genc, S., Efron, D., Sciberras, E., Anderson, V., et al. (2019). Multimodal structural neuroimaging markers of brain development and ADHD symptoms. *Am. J. Psychiatry* 176, 57–66. doi: 10.1176/appi.ajp.2018.18010034

Bymaster, F. P., Katner, J. S., Nelson, D. L., Hemrick-Luecke, S. K., Threlkeld, P. G., Heiligenstein, J. H., et al. (2002). Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 27, 699–711. doi: 10.1016/S0893-133X(02)00346-9

Canadian ADHD Resource Alliance (CADDRA). (2020). Canadian ADHD practice guidelines 4.1 edition. Available online at: http://www.caddra.ca/download-guidelines/. Accessed March 10, 2021.

Conners, C. K., Erhardt, D., Sparrow, E., Nakamura, K., Someki, F., and Onishi, M. (2012). Conners' adult ADHD rating scales (CAARS™). *Japanese Edition* Available online at: http://www.kanekoshobo.co.jp/book/b183695.html. Accessed March 10, 2021.

Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P., et al. (2012). Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *Am. J. Psychiatry* 169, 1038–1055. doi: 10.1176/appi.ajp.2012.11101521

Ding, Y. S., Naganawa, M., Gallezot, J. D., Nabulsi, N., Lin, S. F., Ropchan, J., et al. (2014). Clinical doses of atomoxetine significantly occupy both norepinephrine and serotonin transports: implications on treatment of depression and ADHD. *Neuroimage* 86, 164–171. doi: 10.1016/j.neuroimage.2013.08.001

Durston, S., Thomas, K. M., Worden, M. S., Yang, Y., and Casey, B. J. (2002). The effect of preceding context on inhibition: an event-related fMRI study. *Neuroimage* 16, 449–453. doi: 10.1006/nimg.2002.1074

Fernández-Jaén, A., López-Martín, S., Albert, J., Fernández-Mayoralas, D. M., Fernández-Perrone, A. L., de La Peña, M. J., et al. (2015). Cortical thickness differences in the prefrontal cortex in children and adolescents with ADHD in relation to dopamine transporter (DAT1) genotype. *Psychiatry Res.* 233, 409–417. doi: 10.1016/j.pscychresns.2015.07.005

Garavan, H., Hester, R., Murphy, K., Fassbender, C., and Kelly, C. (2006). Individual differences in the functional neuroanatomy of inhibitory control. *Brain Res.* 1105, 130–142. doi: 10.1016/j.brainres.2006.03.029

Grazioli, S., Mauri, M., Crippa, A., Maggioni, E., Molteni, M., Brambilla, P., et al. (2019). Light up ADHD: II. Neuropharmacological effects measured by near infrared spectroscopy: is there a biomarker? *J. Affect Disord.* 244, 100–106. doi: 10.1016/j.jad.2018.10.100

Ishii-Takahashi, A., Takizawa, R., Nishimura, Y., Kawakubo, Y., Hamada, K., Okuhata, S., et al. (2015). Neuroimaging-aided prediction of the effect of methylphenidate in children with attention-deficit hyperactivity disorder: a randomized controlled trial. *Neuropsychopharmacology* 40, 2676–2685. doi: 10.1038/npp.2015.128

Kim, J.-W., Sharma, V., and Ryan, N. D. (2015). Predicting methylphenidate response in ADHD using machine learning approaches. *Int. J. Neuropsychopharmacol.* 18:pyv052. doi: 10.1093/ijnp/pyv052

Leontyev, A., Sun, S., Wolfe, M., and Yamauchi, T. (2018). Augmented Go/No-Go task: mouse cursor motion measures improve ADHD symptom assessment in healthy college students. *Front. Psychol.* 9:496. doi: 10.3389/fpsyg.2018.00496

Lloyd-Fox, S., Blasi, A., and Elwell, C. E. (2010). Illuminating the developing brain: the past, present and future of functional near infrared spectroscopy. *Neurosci. Biobehav. Rev.* 34, 269–284. doi: 10.1016/j.neubiorev.2009.07.008

Madras, B. K., Miller, G. M., and Fischman, A. J. (2005). The dopamine transporter and attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 57, 1397–1409. doi: 10.1016/j.biopsych.2004.10.011

Nakanishi, Y., Ota, T., Iida, J., Yamamuro, K., Kishimoto, N., Okazaki, K., et al. (2017). Differential therapeutic effects of atomoxetine and methylphenidate in childhood attention deficit/hyperactivity disorder as measured by near-infrared spectroscopy. *Child Adolesc. Psychiatry Ment. Health* 11:26. doi: 10.1186/s13034-017-0163-6

Norupro Light Systems Inc. (2000). Psychological test softwares. Available online at: http://www.norupro.ne.jp/heart/index.htm. Accessed March 10, 2021

Oldfield, R. C. (1971). The assessment and analysis of handedness: the edinburgh inventory. *Neuropsychologia* 9, 97–113. doi: 10.1016/0028-3932(71)90067-4

Ota, T., Iida, J., Nakanishi, Y., Sawada, S., Matsuura, H., Yamamuro, K., et al. (2015). Increased prefrontal hemodynamic change after atomoxetine administration in pediatric attention-deficit/hyperactivity disorder as measured by near-infrared spectroscopy. *Psychiatry Clin. Neurosci.* 69, 161–170. doi: 10.1111/pcn.12251

Posner, J., Polanczyk, G. V., and Sonuga-Barke, E. (2020). Attention-deficit hyperactivity disorder. *Lancet* 395, 450–462. doi: 10.1016/S0140-6736(19)33004-1

Saito, K., Iida, J., Miyajima, Y., Ota, T., Tanaka, Y., Nakata, Y., et al. (2016). *Attention Deficit / Hyperactivity Disorder -ADHD- Guidelines of Diagnosis and Treatment Fourth Edition.* Tokyo: Jiho.

Schulz, K. P., Bédard, A.-C. V., Fan, J., Hildebrandt, T. B., Stein, M. A., Ivanov, I., et al. (2017). Striatal activation predicts differential therapeutic responses to methylphenidate and atomoxetine. *J. Am. Acad. Child Adolesc. Psychiatry* 56, 602–609.e2. doi: 10.1016/j.jaac.2017.04.005

Schulz, K. P., Fan, J., Bédard, A.-C. V., Clerkin, S. M., Ivanov, I., Tang, C. Y., et al. (2012). Common and unique therapeutic mechanisms of stimulant and nonstimulant treatments for attention-deficit/hyperactivity disorder. *Arch. Gen. Psychiatry* 69, 952–961. doi: 10.1001/archgenpsychiatry.2011.2053

Singh, A. K., Okamoto, M., Dan, H., Jurcak, V., and Dan, I. (2005). Spatial registration of multichannel multi-subject fNIRS data to MNI space without MRI. *Neuroimage* 27, 842–851. doi: 10.1016/j.neuroimage.2005.05.019

Toplak, M. E., West, R. F., and Stanovich, K. E. (2013). Practitioner review: do performance-based measures and ratings of executive function assess the same construct? *J. Child Psychol. Psychiatry* 54, 131–143. doi: 10.1111/jcpp.12001

Wolraich, M. L., Hagan, J. F., Jr., Allan, C., Chan, E., Davison, D., Earls, M., et al. (2019). Clinical practice guideline for the diagnosis, evaluation and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 144:e20192528. doi: 10.1542/peds.2019-2528

Yasuhara, A. (2006). Continuous Performance Test (CPT) using personal computer in children with Attention Deficit/Hyperactivity Disorders (ADHD). *Jpn. J. Clin. Neurophysiol.* 34, 152–159.

Conflict of Interest: The authors declare no conflicts of interest with respect to this study, except for the following financing issues. AS and SO have received contract research funds from the Hospitals Bureau Niigata Prefecture Government. YS has received research support or honoraria from Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co. Ltd., and Otsuka Pharmaceutical Co. Ltd. SO and TSu have received Grant-in-Aid for Scientific Research (KAKENHI) from Japan Society for the Promotion of Science. TSo has received research support or honoraria from Asahi Kasei Pharma Corp., Astellas Pharma Inc., Daiichi Sankyo Co. Ltd., Dainippon Sumitomo Pharma Co. Ltd., Eisai Co. Ltd., Eli Lilly Japan K.K., GlaxoSmithKline K.K., Janssen Pharmaceutical K.K., Meiji Seika Pharma Co. Ltd., Mitsubishi Tanabe Pharma Co. Ltd., Mochida Pharmaceutical Co. Ltd., MSD K.K., Otsuka Pharmaceutical Co. Ltd., Pfizer Japan Inc., Shionogi & Co. Ltd., Tsumura & Co., and Yoshitomi Pharmaceutical Industries. The other authors have received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors for this research. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Neuroanatomy

TYPE Hypothesis and Theory
PUBLISHED 23 August 2022
DOI 10.3389/fnana.2022.936025

OPEN ACCESS

EDITED BY
Dorit Ben Shalom,
Ben-Gurion University of the Negev, Israel

REVIEWED BY
Rosa Angela Fabio,
University of Messina, Italy
Adam Winter,
Cleveland Chiropractic College, United States

*CORRESPONDENCE
Gerry Leisman
g.leisman@alumni.manchester.ac.uk

RECEIVED 04 May 2022
ACCEPTED 29 July 2022
PUBLISHED 23 August 2022

CITATION
Leisman G and Melillo R (2022) Front and center: Maturational dysregulation of frontal lobe functional neuroanatomic connections in attention deficit hyperactivity disorder.
Front. Neuroanat. 16:936025.
doi: 10.3389/fnana.2022.936025

Front and center: Maturational dysregulation of frontal lobe functional neuroanatomic connections in attention deficit hyperactivity disorder

Gerry Leisman[1,2]* and Robert Melillo[1]

[1]Movement and Cognition Laboratory, Department of Physical Therapy, University of Haifa, Haifa, Israel, [2]Department of Neurology, University of Medical Sciences of Havana, Havana, Cuba

Frontal lobe function may not universally explain all forms of attention deficit hyperactivity disorder (ADHD) but the frontal lobe hypothesis described supports an internally consistent model for integrating the numerous behaviors associated with ADHD. The paper examines the developmental trajectories of frontal and prefrontal lobe development, framing ADHD as maturational dysregulation concluding that the cognitive, motor, and behavioral abilities of the presumptive majority of ADHD children may not primarily be disordered or dysfunctional but reflect maturational dysregulation that is inconsistent with the psychomotor and cognitive expectations for the child's chronological and mental age. ADHD children demonstrate decreased activation of the right and middle prefrontal cortex. Prefrontal and frontal lobe regions have an exuberant network of shared pathways with the diencephalic region, also having a regulatory function in arousal as well as with the ascending reticular formation which has a capacity for response suppression to task-irrelevant stimuli. Prefrontal lesions oftentimes are associated with the regulatory breakdown of goal-directed activity and impulsivity. In conclusion, a presumptive majority of childhood ADHD may result from maturational dysregulation of the frontal lobes with effects on the direct, indirect and/or, hyperdirect pathways.

KEYWORDS

ADHD, frontal lobe, prefrontal cortex, indirect pathway, direct pathway, hyperdirect pathway

Introduction

We think that attention deficit hyperactivity disorder (ADHD) results from differences, when compared with the normally developing child, in the trajectory of cortical maturation and well as from deviations in the trajectory of asymmetric brain development (Rubia, 2007; Janssen T. W. P. et al., 2017; Bouziane et al., 2018; Ha et al., 2020). These developmental differences in the development of hemispheric asymmetries significantly relate to the expression of the characteristics of ADHD and can explain many of the symptoms that are

evidenced (Ha et al., 2020; Chen et al., 2021; Postema et al., 2021). The condition speaks to the relationship between the functions of the hemispheres. Overactivity of the left hemisphere can lead to hyperactivity of movement and hyperkinetic behavior (Wasserstein and Stefanatos, 2016; Helfer et al., 2020). The right hemisphere is mainly responsible for attention especially sustained attention which is the main attentional deficit in ADHD (Longo et al., 2015; Bartolomeo and Malkinson, 2019). Therefore, underdevelopment of the right hemisphere is related to the attentional deficit (Zou and Yang, 2021). This hyperreactivity of one cerebral hemisphere combined with underdevelopment of contralateral hemisphere speaks to the nature of many neurobehavioral disorders (Melillo and Leisman, 2009; Douglas et al., 2018).

The beginning of the brain's developmental interregional communication differences in ADHD as compared with neurotypical children has been thought to commence *in utero* or early in post-partum development (Hanć et al., 2018; Vizzini et al., 2019; Xi and Wu, 2021). The right hemisphere develops first in the womb and for the first 3 years (Uda et al., 2015; Caccappolo and Honig, 2016). Early childhood functional brain asymmetry has been confirmed by cerebral blood flow changes measured at rest between 1 and 3 years of age, blood flow studies demonstrate the predominance of the right hemispheric, largely associated with the activity in the posterior associative area (Paniukov et al., 2020). Asymmetry modulates to the left after approximately 3 years of age (Tzourio-Mazoyer et al., 2017). After 3 years of age, the time course of changes appears to follow the emergence of functions localized initially on the right, but later on the left hemisphere (i.e., visuospatial and later language abilities) (Spagna et al., 2016; Olulade et al., 2020). These findings support the hypothesis that, in human infancy and early childhood, the right hemisphere develops its functions earlier than the left (Chiron et al., 1997; Melillo and Leisman, 2010, 2015). The left hemisphere takes the lead in development for the next 3 years (Chiron et al., 1997; Melillo and Leisman, 2010, 2015).

This one-side-at-a-time developmental activity of the hemispheres is thought to be an important factor that is highly associated with the development and lateralization of the brain in infancy and early childhood (Melillo and Leisman, 2010). This asymmetry and lateralization impart great advantage to the brain as it leads to regional specialization which increases the efficiency of the brain (Duboc et al., 2015). The brain does not like redundancy as it renders its ability to communicate between regions less optimized and slows down the brain's responsivity to internal and external stimulation and adversity (Hiratani and Fukai, 2018).

In order to speed-up brain responsivity to external or internal voluntary action control, fronto-basal ganglia pathways must play a significant role in the control of voluntary action and in motor response inhibition. Response inhibition can be facilitated by a fast hyperdirect pathway that would connect the right inferior frontal gyrus and the pre-supplementary motor area with the subthalamic nucleus or, through the indirect pathway between the cortex and caudate. These considerations are explored further below.

Top-down and bottom-up communication in ADHD

The brain develops from the bottom up starting in the lower brainstem and with the brainstem nuclei acting as precursors to higher levels of brain development and with the ultimate development of Brodmann areas that have both structural and functional differences (Zelazo, 2015; Onofrj et al., 2022). Once there is bottom-up completion of development there then can be completion of top-down development which allows the brain and neocortex to ultimately control all functions of the body (Emberson et al., 2015). As part of this top-down development, the brain and especially the prefrontal cortex develops feedback pathways with the basal ganglia and thalamus that ultimately control and regulate much of human behavior (Petrovic and Castellanos, 2016; Emberson, 2017; Choi et al., 2018). There are at least five loops with connections from the prefrontal cortex to the basal ganglia and entering the direct or indirect pathways. The direct pathway is facilitatory and the indirect pathway, inhibitory.

Direct, indirect, and hyperdirect pathways in ADHD

The original model by Alexander et al. (1986) described five feedback loops that included the promotor area [Broca's Area (BA) 6] to control motor function, the dorsolateral prefrontal cortex (BA 9, 46) for executive function (EF), the frontal eye field (BA 8) for control of volitional saccadic eye movement, the orbitofrontal cortex (OFC) (BA 11, 12) for control of social behavior and the anterior cingulate (AC) (BA 24, 25, 32, 33) for control of motivation. Middleton and Strick (2000), however, created a revised version of this that expanded the number of feedback loops to seven motor subcircuits, three oculomotor circuits, four dorsolateral prefrontal circuits (DLPFC), five OFC circuits, and two cingulate circuits.

All of these circuits project from a specific area of the cortex to the basal ganglia and from there to the thalamus then returning to the cortex (Zikopoulos and Barbas, 2007; Sherman, 2011). Each one of these circuits projects either to the indirect or direct pathways and will either activate or inhibit a specific behavior or function in the direct pathway or in the indirect pathway, respectively. Motor behavior is in large measure dependent on a dynamic balance between these two pathways where neither pathway gains dominance over the other (Cui et al., 2013; Macpherson et al., 2014;

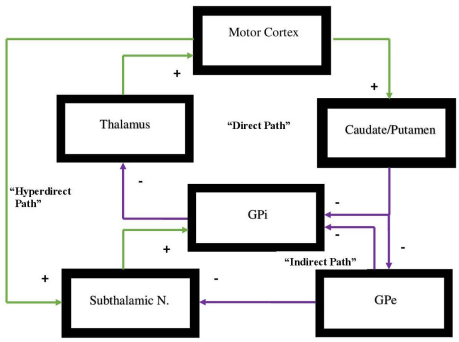


FIGURE 1
Representation of the direct vs. indirect pathways of the basal ganglia indicating facilitatory vs. inhibitory components of motor activity. In the direct pathway, Input from the cerebral cortex to the striatum is associated with triggering of inhibitory neurons in the striatum. This subsequently is associated with increased inhibitory output projecting to the globus pallidus-internal [GPi]. Subsequently, decreased inhibitory output from GPi to the ventral anterior [VA] and ventral lateral [VL] nuclei of the thalamus is evidenced that in turn projects through excitatory pathways to the premotor cortex. The direct pathway regulates motor and premotor cortical excitation that is involved in planning and movement initiation. The indirect pathway, when appropriately functioning, should inhibit movement when cortically generated excitatory activity enables inhibitory neurons in globus pallidus external [GPe]. These subsequently inhibit tonic inhibitory output neurons associated with decreased tonic inhibition of the subthalamic nucleus [STN]. The result is increased excitatory output to GPi. Excitatory input to GPi adds inhibitory output from GPi to the thalamus which, in turn, decreases excitatory feedback to cerebral cortex. The result, under normal circumstances, should lead to the inhibition of motor activity. Dopamine supports the activity of the direct pathway suppressing activity of indirect pathway. The hyperdirect pathway is exceptional as it circumvents the striatum with a direct link from the cortex to the subthalamic nucleus, then directing excitatory projections to the GPi. The hyperdirect pathway is key for containing non-purposeful movement. When the system is impaired, individuals are less able to inhibit unplanned motor activity.

Hikosaka et al., 2019; Kwak and Jung, 2019). The pathways are represented in **Figure 1**.

There exists an additional pathway that plays a significant role in oscillating between direct and indirect pathways and is critical to this dynamic balance between these pathways and behavioral flexibility. This is termed the hyperdirect pathway and it originates from the right cerebral hemisphere alone (Koirala et al., 2018; Chen et al., 2020). There are two regions of the right hemisphere that are the points of origin of the hyperdirect pathway which specifically activates the indirect pathway at the caudate and putamen and specifically connects to the subthalamic nucleus of Luys, the main source of the indirect pathway's effect (Chen et al., 2020; Temiz et al., 2020). The hyperdirect pathway has one component arising from the premotor area (BA 6) in the right hemisphere. This pathway primarily inhibits motor activity (Chen et al., 2020).

The hyperdirect pathway suppresses unwanted movement and it will subsequently inhibit movement once an action has been completed (Nambu et al., 2002; Chen et al., 2020). If there exists a motor activity deficit or underdevelopment of this pathway and its connections, overactivity of the premotor loop on the left hemisphere will likely be evidenced (Singer et al., 2015; Dalley and Robbins, 2017; Guo et al., 2018; Temiz et al., 2020; Sival et al., 2022), which will, in turn, activate the direct pathway and increase motor activity that can be exemplified by motor tics (Leisman and Sheldon, 2022), or stereotypical movements not infrequently evidenced in hyperkinetic disorders such as ADHD, Tourette's syndrome, autism spectrum disorder (ASD), etc. (Melillo and Leisman, 2009; Temiz et al., 2020; Hannah and Aron, 2021). The other part of the hyperdirect pathway arises from the inferior frontal gyrus (BA 44, 45, 47) in the right hemisphere alone (Chen et al., 2020; Narayanan et al., 2020). This is thought to regulate the limbic, and associative loops, which includes the DLPFC, OFC, and the AC by specifically activating the indirect pathway to eliminate unwanted or inappropriate, emotions, social behavior, thoughts, etc. (Janssen M. L. et al., 2017; Temiz et al., 2020).

Therefore, in ADHD, we can see that many of the symptoms can be explained by overactivity of the left hemisphere's connections to the direct pathway related to the underdevelopment and underactivity of the right hemisphere and the indirect and hyperdirect pathways (Chen et al., 2016; Hauser et al., 2016; Ziegler et al., 2016) This can explain the hyperactive motor behavior seen in ADHD with overactivity of BA 6 in the left hemisphere associated with underdevelopment of BA 6 on the right. This also can explain the underdevelopment of sustained attention abilities which is related to the ventral attention network, lateralized more to the right hemisphere and subserving sustained attention (Vossel et al., 2014) and is reflected in **Figure 2**. This is also connected to the salience network represented in **Figure 3** which is predominately constituted by the insula cortex (IC) (BA 13) and the (AC) (BA 25,32) (Sridharan et al., 2008; Menon, 2011; Nekovarova et al., 2014). This developmental maturational imbalance between all of these loops can explain of the symptoms seen in ADHD.

Central executive and default mode networks in ADHD: In support of goal-directed behavior

Default mode network

Neuroimaging studies have led us to theorize that the fundamental differences between rest and agency can be based on an organized level of baseline activity that is diminished during goal-oriented cognition. It has also been thought that the

brain maintains a "default mode" in the absence of cognitive demands (Gusnard and Raichle, 2001; Gusnard et al., 2001; Raichle and Gusnard, 2005) so as to enable a readiness state that is capable of responding to changes in one's environment (Raichle et al., 2001). The Default Mode Network (DMN) is a network of coherent brain regions active during daydreaming or unfocused behavior. Some investigators have linked activity of the DMN to the processing of self-referential information as brain regions such as the posterior cingulate (PCC) and medial prefrontal cortex (mPFC) have been demonstrated to subserve self-reflection, introspective mental imagery, and self-awareness (Northoff et al., 2006; Buckner et al., 2008; Schneider et al., 2008).

A meta-analysis (Spreng et al., 2009) identified components of the DMN, such as the anterior cingulate cortex (ACC), the PCC, mPFC, and the middle temporal gyrus and. Central Executive Network (CEN) activation tasks have been reliably confirmed to stimulate decrease activation (deactivation) in the DMN. McKiernan et al. (2003) demonstrated that with increased task difficulty, task-related deactivation increased. Two studies by Fransson (Fransson, 2006; Fransson and Marrelec, 2008) examined DMN connectivity during challenging cognitive tasks and found significantly reduced functional connectivity within the DMN with excessive working memory load.

Different groups (Buckner et al., 2008; Spreng and Grady, 2010) have discussed the notion that the DMN might consist of numerous subsystems. Uddin et al. (2009, 2010) and Uddin (2021) showed significant differences by examining the anticorrelations of seed regions in the PCC and mPFC. This indicated that distinct nodes of the DMN may modulate activity in task-positive networks differently. Alterations in connectivity of the DMN have been discussed as possible biomarkers for psychiatric conditions such as autism (Calhoun et al., 2008). Specifically related to ADHD, Rubia et al. (2014), have noted that individuals with ADHD have greater gray matter volume in nodes within the DMN. When performing a task, the DMN activity infringes on the task-positive cognitive systems necessary for task completion (Rubia et al., 2014). We acknowledge that our personal DMN has been active when we suddenly return from having been "zoned-out" and realize it. When we engage in goal-oriented tasks that are attention-demanding, the DMN decreases its activity. Although in normal development, difficulties inhibiting or deactivating the DMN is likely, individuals with ADHD have significantly greater difficulty in inhibiting the DMN. In other words, individuals with ADHD have a stronger gravitational pull toward this cognitive resting state and, as a result, it requires significantly greater effort to gravitate away from it and attend to the task. Uddin et al. (2008) found reduced DMN nodal homogeneity in ADHD individuals when compared to age-matched controls, that was most evidenced between the precuneus and other DMN regions. This finding provides further support for the notion that altered precuneus connectivity is implicated in ADHD.

Central executive network

The CEN is usually related to the appropriate functioning of the PFC and related regions such as the cingulate cortex (Cohen, 2017). The CEN has often been considered synonymous with the earlier concept of EF. In both, behavioral regulatory activity can optimize goal-directed behavior and prevent automaticity in a way similar to the difference between automatic and controlled responding (Schneider and Shiffrin, 1977). This approximately aligns with the distinction between habit and goal-directed responsivity (Balleine and O'Doherty, 2010). One would expect the absence of the CEN to produce automatic behavior as controlled responses are flexible and goal-directed.

Miller and Cohen (2001) thought that the CEN "...stems from the active maintenance of patterns of activity in the PFC that represent goals and the means to achieve them. They provide bias signals to other brain structures whose net effect is to guide the flow of activity along neural pathways that establish the proper mappings between inputs, internal states, and outputs needed to perform a given task" (p. 167). This conception of the role of PFC in the CEN basically consists of the contextual biasing of attention (e.g., instructions) to exert attentional control and to resolve conflicts. In a modified Stroop task, Kerns et al. (2005) found that the theory was supported by an fMRI study demonstrating that ACC activation was supplemented by activity in the DLPFC associated with top-down adjustments of response control. Therefore, in Miller and Cohen's (2001) model, the ACC can identify conflict resolved by the top-down biasing of response options from the DLPFC. This theoretical scheme has provided support for a CEN process mediated by interactive PFC circuitry.

Both the CEN and DMN are lateralized (Sripada et al., 2014). The CEN tends to be more left (Silk et al., 2016) and more focused on the external environment (Antshel et al., 2014) which is overactive in ADHD (Bilevicius et al., 2018). The DMN tends to be more lateralized to the right (Sripada et al., 2014) and appears to be more internally focused (Lanier et al., 2021) the results of which are significant features of ADHD (Seli et al., 2015). Individuals with ADHD manifest a reduced connection to their bodies (Wiersema and Godefroid, 2018) as well as reduced sensory awareness of body parts (Sanz-Cervera et al., 2017).

Additionally, not only is there a reported decrease in pain perception (Wolff et al., 2016) as well as sensory perception to tactile (Puts et al., 2017) and proprioceptive stimulation (Tseng et al., 2018; Tarbanie, 2020), but individuals with ADHD also have reduced interoception (Kutscheidt et al., 2019) which is related to the functioning of the right insula and the salience network (Uddin, 2015; Zhang et al., 2019) which, in turn, is

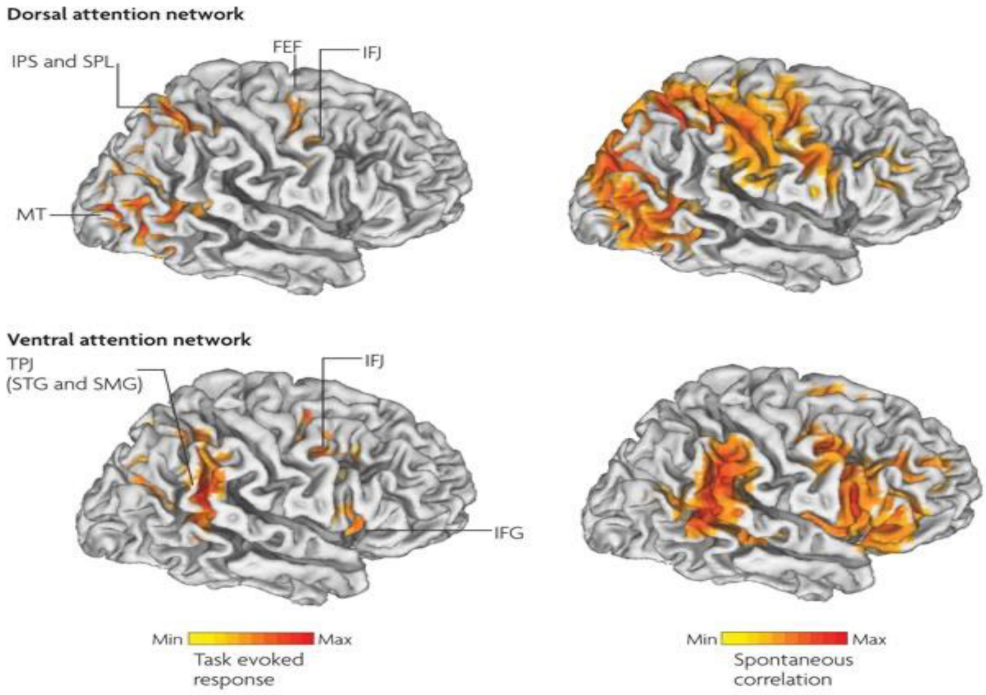


FIGURE 2
Interaction between the dorsal attention networks and ventral (salience) enables active control of attention in relation to bottom-up sensory stimulation and top-down goals. The top-down dorsal-frontoparietal system which includes the frontal eye fields (FEF) and the intraparietal sulcus that supports voluntary attention to particular aspect of the visual field locations or objects and the ventral-frontoparietal system is concerned with attention to unexpected features. The ventral attention network involves the ventral-frontal cortex and the temporoparietal junction (TPJ), and usually responds to behaviorally relevant but unexpected stimuli. The biasing of sensory areas toward particular stimuli derives from the frontoparietal cortex. There exists a connection between sensory cortical areas involving the intraparietal sulcus and the FEF. These two areas have top-down influences on the orienting of attention. These top-down effects are known to out-weigh bottom up effects from the visual cortex (after Vossel et al., 2014 with permission).

associated with the ventral attention network and sustained attentional function (Janssen et al., 2018). Salience also tends to be more lateralized to the right hemisphere (Uddin, 2015; Zhang et al., 2019). In addition, the left DLPFC supports setting goals (Vetter et al., 2018) and the left hemisphere is more active when sustaining goals OFC and goal intensity (Chiang et al., 2015), in turn, largely associated with the left hemisphere's BA 44 (Pagliaccio et al., 2017).

Developmental delay in neuroanatomic maturational dysfunction of the frontal lobes in ADHD

The frontal lobes exemplify a complex neurological system. The prefrontal cortex is integrated within the frontal lobes and is thought to combine intentional responses that require intended and synchronized action sequences (Laubach et al., 2015). Frontal lobe complexity is demonstrated by prefrontal cortex interconnectedness with the motor regions of the frontal lobes (Bernard et al., 2016), the posterior associative cortex (Barbas, 2015; Fuster, 2015), the limbic (motivational) (Barbas, 2015; Tucker and Luu, 2021), and ascending reticular activating system (arousal) (Jang and Kwon, 2015). These interconnections, in particular, with the dorso thalamic nucleus projections, describe the primary features of prefrontal cortical organization (Leisman and Melillo, 2012; Bubb et al., 2017; Kamali et al., 2020).

There are three classes of neuropsychological functioning associated with the prefrontal cortex: regulatory, social, and executive (Fuster, 2015). The prefrontal cortex supports the maintenance of set, in problem-solving tasks (Friedman and Robbins, 2022), and in implementing strategic and sequential planning (Desrochers et al., 2015; Schuck et al., 2015), performing mental representations of a task (Monk et al., 2021), planning and self-monitoring of performance (Joensson et al., 2015), abiding by social rules (Rozzi and Fogassi, 2017), and employing environmental cues (Fuster, 2015; Hall-McMaster et al., 2017). In adults with lesions of the frontal lobes, there exists evidence of impairment in action or response planning, anticipation of events, establishment of goals, self-monitoring ability, cognitive flexibility with comorbidities with

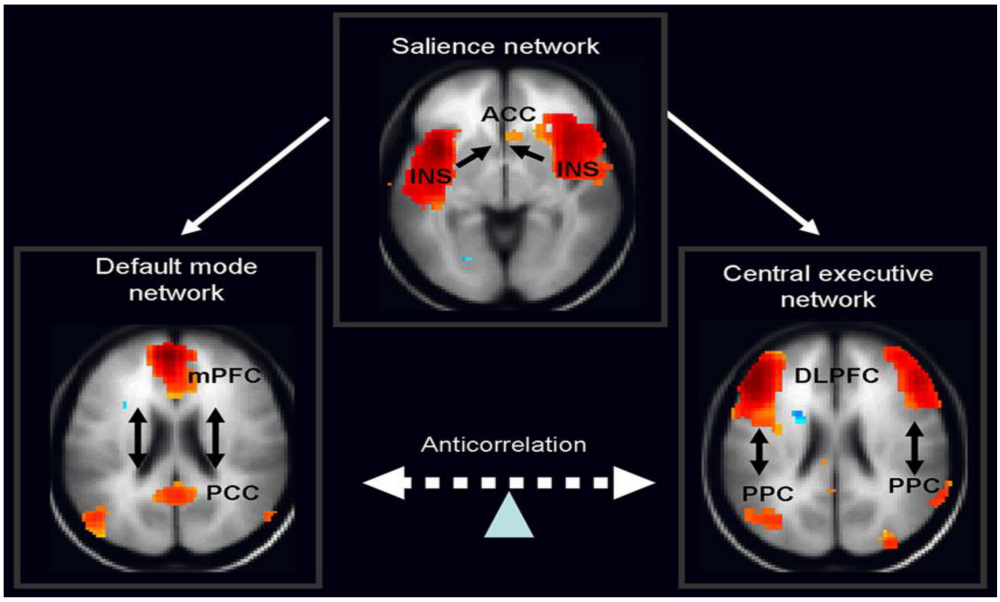


FIGURE 3
The salience network is theorized to mediate switching between the default mode network (DMN) and central executive network (CEN) (adapted from Vossel et al., 2014, with permission).

conditions such as ticking behavior (Leisman and Sheldon, 2022) and other neurobehavioral disorders such as ASD and OCD (Melillo and Leisman, 2009). Frontal lobe lesioned adults present with disinhibition, perseverative behavior, and difficulty in employing environmental cues to modulate behavior (Fuster, 2015; Serrien and Sovijärvi-Spapé, 2015).

Frontal lobe lesions in adults allows us to observe hyperactivity control mechanisms more readily (Clay et al., 2019; Hagiescu, 2021). Hyperactivity, both in childhood and in adulthood, can be viewed as a disturbance of higher levels of cortical inhibition manifested as an absence of orienting responses inhibition (Posner et al., 1998; Brown et al., 2021; Williams and Das, 2021), an inhibitory deficit of inappropriate responses (Posner et al., 1998) and/or a disinhibition of inhibitory cortical reflexes (Neely et al., 2017), or retained primitive reflexes (Melillo and Leisman, 2010; Melillo et al., 2020; Bob et al., 2021; Sigafoos et al., 2021). Given the apparent similarity in the behavioral manifestations of ADHD and adults with dysfunction of or damage to the frontal lobe, we can hypothesize a common origin for ADHD and frontal lobe dysfunction, even though it has long been argued (Fletcher and Taylor, 1984, p. 46; cf. Fletcher, 2021), that, "Similarity of behavior in the absence of independent assessment does not provide sufficient evidence of common origins" in adults and children.

ADHD as a manifestation of maturational dysregulation has been largely supported by MRI studies. Volumetric measurements of right and left hemispheres, of gray and white matter within each lobe, and cerebral and cerebellar volume have been reported to be approximately 4% smaller in ADHD individuals relative to controls (Castellanos et al., 2002). Significant differences have also been noted in cortical thickness (Shaw et al., 2007). While in ADHD and control g children, peak cortical thickness was developed earlier in the sensory regions as compared to association cortical regions. However, control children developed peak thickness between 7 and 8 years, of age relative to ADHD children who attained it later, between 10 and 11 years. This evidence supports a common course of regional brain development sequencing in both ADHD and control children but with cortical maturational dysregulation in ADHD.

More evidence in support of widespread volumetric reductions in ADHD subjects comes from cross-sectional studies comparing ADHD and control subjects in smaller samples than in the above studies (see reviews Seidman et al., 2005; Shaw and Rabin, 2009). While there are many mixed findings in this body of work, the majority indicated that volumes were reduced in ADHD subjects relative to age-matched controls. The loci of the reported reductions are in multimodal association cortices such as the frontal lobes and its subregions, premotor cortex, posterior cingulate, anterior and medial temporal lobes, cerebellar lobules, and basal ganglia structures (caudate, globus pallidus, putamen, and ventral striatum).

Cognitive and motor affect assessment in the context of the frontal lobe hypothesis of ADHD has been partly obstructed by argument about the developmental stage at which

functioning of the frontal lobes matures. Earlier, Luria (2012) had proposed that prefrontal regions are not capable of agency and preparedness for action until between of 4 to 7 years of age under normal circumstances. Golden, on the other hand (Bradley and Golden, 2001; Golden and Hines, 2010) noted that the frontal areas do not become functionally mature until much later, in adolescence. Since Luria and Golden, we have learned that frontal lobe behaviors develop rapidly from the age of approximately 6 years and almost reach adult levels of control between 10 and 12 years of age (Norbom et al., 2020; Wang et al., 2020).

Conclusion

The issue of developmental trajectories is singularly important as it frames the disorder of ADHD as a maturational dysfunction. The result, therefore, is that the cognitive and behavioral abilities of the ADHD child are not disordered or dysfunctional, but are rather developmentally inappropriate for the child's chronological and mental age.

Compared to neurotypical children, those with ADHD demonstrate decreased activation of the right and middle prefrontal cortex across all age groups (Yasumura et al., 2019). However, while frontal lobe function may not universally explain all forms of ADHD, the frontal lobe hypothesis described here does provide an internally consistent model for the elucidation of many of the findings associated with ADHD. Prefrontal regions of the frontal lobes have an exuberant network of shared pathways with the diencephalic region (Bubb et al., 2017), which has a regulatory function in arousal (Martella et al., 2020), as well as with the ascending reticular formation which, for reasons previously indicated, has a capacity for response suppression to task-irrelevant stimuli. Prefrontal lesions oftentimes are associated with regulatory breakdown of goal-directed activity and impulsivity. Individuals with frontal and prefrontal lesions have an impediment in subduing ongoing activities independent of environmental feedback and demonstrate amplified responsiveness to extraneous stimuli (impulsivity and distractibility), associated with deficient goal-directed behavior. Frontal lobe lesions in adult humans often leads to hyperactivity/hyperreactivity. In childhood, however, we are likely looking at ADHD as a problem of the trajectory of normal maturation of the frontal lobes with effects on the direct, indirect and/or hyperdirect pathways.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

Both authors shared equally in preparation of the manuscript, contributed to the article, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Alexander, G. E., DeLong, M. R., and Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* 9, 357–381. doi: 10.1146/annurev.ne.09.030186.002041

Antshel, K. M., Hier, B. O., and Barkley, R. A. (2014). "Executive functioning theory and ADHD," in *Handbook of executive functioning*, eds S. Goldstein and J. A. Naglieri (New York, NY: Springer), 107–120. doi: 10.1007/978-1-4614-8106-5_7

Balleine, B. W., and O'Doherty, J. P. (2010). Human and rodent homologies in action control: Corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology* 35, 48–69. doi: 10.1038/npp.2009.131

Barbas, H. (2015). General cortical and special prefrontal connections: Principles from structure to function. *Annu. Rev. Neurosci.* 38, 269–289. doi: 10.1146/annurev-neuro-071714-033936

Bartolomeo, P., and Malkinson, T. S. (2019). Hemispheric lateralization of attention processes in the human brain. *Curr. Opin. Psychol.* 29, 90–96. doi: 10.1016/j.copsyc.2018.12.023

Bernard, J. A., Orr, J. M., and Mittal, V. A. (2016). Differential motor and prefrontal cerebello-cortical network development: Evidence from multimodal neuroimaging. *Neuroimage* 124, 591–601. doi: 10.1016/j.neuroimage.2015.09.022

Bilevicius, E., Kolesar, T. A., Smith, S. D., Trapnell, P. D., and Kornelsen, J. (2018). Trait emotional empathy and resting state functional connectivity in default mode, salience, and central

executive networks. *Brain Sci.* 8:128. doi: 10.3390/brainsci8070128

Bob, P., Konicarova, J., and Raboch, J. (2021). Disinhibition of primitive reflexes in attention deficit and hyperactivity disorder: Insight into specific mechanisms in girls and boys. *Front. Psychiatry* 12:430685. doi: 10.3389/fpsyt.2021.430685

Bouziane, C., Caan, M. W., Tamminga, H. G., Schrantee, A., Bottelier, M. A., de Ruiter, M. B., et al. (2018). ADHD and maturation of brain white matter: A DTI study in medication naive children and adults. *Neuroimage Clin.* 17, 53–59. doi: 10.1016/j.nicl.2017.09.026

Bradley, J. D., and Golden, C. J. (2001). Biological contributions to the presentation and understanding of attention-deficit/hyperactivity disorder: A review. *Clin. Psychol. Rev.* 21, 907–929. doi: 10.1016/s0272-7358(00)00073-8

Brown, H. R., Hareli, M., Breaux, R., Lugo-Candelas, C. I., Gair, S. L., Harvey, E. A., et al. (2021). Behavioral and neural markers of emotion competence as predictors of later psychopathology in children with and without hyperactive/impulsive symptoms. *J. Atten. Disord.* 25, 1395–1406.

Buckner, R. L., Andrews-Hanna, J. R., and Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38. doi: 10.1196/annals.1440.011

Bubb, E. J., Kinnavane, L., and Aggleton, J. P. (2017). Hippocampal–diencephalic–cingulate networks for memory and emotion: An anatomical guide. *Brain neurosci. Adv.* 1:2398212817723443. doi: 10.1177/2398212817723443

Caccappolo, E., and Honig, L. S. (2016). 6 Development of the central nervous system. *Textb. Clin. Neuropsychol.* 83, 11–19.

Calhoun, V. D., Maciejewski, P. K., Pearlson, G. D., and Kiehl, K. A. (2008). Temporal lobe and "default" hemodynamic brain modes discriminate between schizophrenia and bipolar disorder. *Hum. Brain Mapp.* 29, 1265–1275. doi: 10.1002/hbm.20463

Castellanos, F. X., Lee, P. P., Sharp, W., Jeffries, N. O., Greenstein, D. K., Clasen, L. S., et al. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA* 288, 1740–1748. doi: 10.1001/jama.288.14.1740

Chiang, H. L., Chen, Y. J., Lo, Y. C., Tseng, W. Y. I., and Gau, S. S. F. (2015). Altered white matter tract property related to impaired focused attention, sustained attention, cognitive impulsivity and vigilance in attention-deficit/hyperactivity disorder. *J. Psychiatry Neurosci.* 40, 325–335. doi: 10.1503/jpn.140106

Chen, J. L., Voigt, F. F., Javadzadeh, M., Krueppel, R., and Helmchen, F. (2016). Long-range population dynamics of anatomically defined neocortical networks. *Elife* 5:e14679

Chen, W., de Hemptinne, C., Miller, A. M., Leibbrand, M., Little, S. J., Lim, D. A., et al. (2020). Prefrontal-subthalamic hyperdirect pathway modulates movement inhibition in humans. *Neuron* 106, 579–588. doi: 10.1016/j.neuron.2020.02.012

Chen, S., Guan, L., Tang, J., He, F., and Zheng, Y. (2021). Asymmetry in cortical and subcortical structures of the brain in children and adolescents with attention-deficit/hyperactivity disorder. *Neuropsychiatr. Dis. Treat.* 17:493. doi: 10.2147/NDT.S292444

Chiron, C., Jambaque, I., Nabbout, R., Lounes, R., Syrota, A., and Dulac, O. (1997). The right brain hemisphere is dominant in human infants. *Brain J. Neurol.* 120, 1057–1065.

Choi, I., Lee, J. Y., and Lee, S. H. (2018). Bottom-up and top-down modulation of multisensory integration. *Curr. Opin. Neurobiol.* 52, 115–122. doi: 10.1016/j.conb.2018.05.002

Clay, F. J., Kuriakose, A., Lesche, D., Hicks, A. J., Zaman, H., Azizi, E., et al. (2019). Klüver-Bucy syndrome following traumatic brain injury: A systematic synthesis and review of pharmacological treatment from cases in adolescents and adults. *J. Neuropsychiatry Clin. Neurosci.* 31, 6–16. doi: 10.1176/appi.neuropsych.18050112

Cohen, J. D. (2017). "Cognitive control: Core constructs and current considerations," in *The Wiley handbook of cognitive control*, ed. T. Egner (Hoboken, NJ: Wiley-Blackwell), 1–28. doi: 10.1002/9781118920497.ch1

Cui, G., Jun, S. B., Jin, X., Pham, M. D., Vogel, S. S., Lovinger, D. M., et al. (2013). Concurrent activation of striatal direct and indirect pathways during action initiation. *Nature* 494, 238–242. doi: 10.1038/nature11846

Dalley, J. W., and Robbins, T. W. (2017). Fractionating impulsivity: Neuropsychiatric implications. *Nat. Rev. Neurosci.* 18, 158–171. doi: 10.1038/nrn.2017.8

Desrochers, T. M., Chatham, C. H., and Badre, D. (2015). The necessity of rostrolateral prefrontal cortex for higher-level sequential behavior. *Neuron* 87, 1357–1368. doi: 10.1016/j.neuron.2015.08.026

Douglas, P. K., Gutman, B., Anderson, A., Larios, C., Lawrence, K. E., Narr, K., et al. (2018). Hemispheric brain asymmetry differences in youths with attention-deficit/hyperactivity disorder. *Neuroimage Clin.* 18, 744–752. doi: 10.1016/j.nicl.2018.02.020

Duboc, V., Dufourcq, P., Blader, P., and Roussigné, M. (2015). Asymmetry of the brain: Development and implications. *Annu. Rev. Genet.* 49, 647–672.

Emberson, L. L. (2017). How does experience shape early development? Considering the role of top-down mechanisms. *Adv. Child Dev. Behav.* 52, 1–41. doi: 10.1016/bs.acdb.2016.10.001

Emberson, L. L., Richards, J. E., and Aslin, R. N. (2015). Top-down modulation in the infant brain: Learning-induced expectations rapidly affect the sensory cortex at 6 months. *Proc. Natl. Acad. Sci. U.S.A.* 112, 9585–9590. doi: 10.1073/pnas.1510343112

Fletcher, J. M. (2021). Attention-deficit/hyperactivity disorder (ADHD). *Dev. Psychol.* 89–118. doi: 10.1002/9781118686089.ch5

Fletcher, J. M., and Taylor, H. G. (1984). Neuropsychological approaches to children: Towards a developmental neuropsychology. *J. Clin. Exp. Neuropsychol.* 6, 39–56. doi: 10.1080/01688638408401195

Fransson, P. (2006). How default is the default mode of brain function? Further evidence from intrinsic BOLD signal fluctuations. *Neuropsychologia* 44, 2836–2845. doi: 10.1016/j.neuropsychologia.2006.06.017

Fransson, P., and Marrelec, G. (2008). The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *Neuroimage* 42, 1178–1184. doi: 10.1016/j.neuroimage.2008.05.059

Friedman, N. P., and Robbins, T. W. (2022). The role of prefrontal cortex in cognitive control and executive function. *Neuropsychopharmacology* 47, 72–89. doi: 10.1038/s41386-021-01132-0

Fuster, J. (2015). *The prefrontal cortex*. London: Academic Press. doi: 10.1016/B978-0-12-407815-4.00002-7

Golden, C. J., and Hines, L. J. (2010). "24 Assessment of executive functions in a pediatric population," in *Handbook of pediatric neuropsychology*, ed. E. Davis (New York, NY: Springer), 261.

Guo, Y., Schmitz, T. W., Mur, M., Ferreira, C. S., and Anderson, M. C. (2018). A supramodal role of the basal ganglia in memory and motor inhibition: Meta-analytic evidence. *Neuropsychologia* 108, 117–134. doi: 10.1016/j.neuropsychologia.2017.11.033

Gusnard, D. A., Akbudak, E., Shulman, G. L., and Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proc. Natl. Acad. Sci. U.S.A.* 98, 4259–4264. doi: 10.1073/pnas.071043098

Gusnard, D. A., and Raichle, M. E. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nat. Rev. Neurosci.* 2, 685–694. doi: 10.1038/35094500

Ha, S., Lee, H., Choi, Y., Kang, H., Jeon, S. J., Ryu, J. H., et al. (2020). Maturational delay and asymmetric information flow of brain connectivity in SHR model of ADHD revealed by topological analysis of metabolic networks. *Sci. Rep.* 10:3197. doi: 10.1038/s41598-020-59921-4

Hagiescu, S. M. (2021). The connection between traumatic brain injury (TBI) and attention-deficit/hyperactivity disorder, therapeutic approaches. *Psychology* 12, 1287–1305. doi: 10.4236/psych.2021.128081

Hall-McMaster, S., Millar, J., Ruan, M., and Ward, R. D. (2017). Medial orbitofrontal cortex modulates associative learning between environmental cues and reward probability. *Behav. Neurosci.* 131:1.

Hanć, T., Szwed, A., Słopień, A., Wolańczyk, T., Dmitrzak-Węglarz, M., and Ratajczak, J. (2018). Perinatal risk factors and ADHD in children and adolescents: A hierarchical structure of disorder predictors. *J. Atten. Disord.* 22, 855–863. doi: 10.1177/1087054716643389

Hannah, R., and Aron, A. R. (2021). Towards real-world generalizability of a circuit for action-stopping. *Nat. Rev. Neurosci.* 22, 538–552. doi: 10.1038/s41583-021-00485-1

Hauser, T. U., Fiore, V. G., Moutoussis, M., and Dolan, R. J. (2016). Computational psychiatry of ADHD: Neural gain impairments across Marrian levels of analysis. *Trends Neurosci.* 39, 63–73. doi: 10.1016/j.tins.2015.12.009

Helfer, B., Maltezos, S., Liddle, E., Kuntsi, J., and Asherson, P. (2020). Lateralization of attention in adults with ADHD: Evidence of pseudoneglect. *Eur. Psychiatry* 63:e68. doi: 10.1192/j.eurpsy.2020.68

Hiratani, N., and Fukai, T. (2018). Redundancy in synaptic connections enables neurons to learn optimally. *Proc. Natl. Acad. Sci. U.S.A.* 115, E6871–E6879. doi: 10.1073/pnas.1803274115

Hikosaka, O., Kim, H. F., Amita, H., Yasuda, M., Isoda, M., Tachibana, Y., et al. (2019). Direct and indirect pathways for choosing objects and actions. *Eur. J. Neurosci.* 49, 637–645.

Janssen, T. W. P., Hillebrand, A., Gouw, A., Geladé, K., Van Mourik, R., Maras, A., et al. (2017). Neural network topology in ADHD; Evidence for maturational delay and default-mode network alterations. *Clin. Neurophysiol.* 128, 2258–2267. doi: 10.1016/j.clinph.2017.09.004

Janssen, M. L., Temel, Y., Delaville, C., Zwartjes, D. G., Heida, T., De Deurwaerdere, P., et al. (2017). Cortico-subthalamic inputs from the motor, limbic, and associative areas in normal and dopamine-depleted rats are not fully segregated. *Brain Struct. Funct.* 222, 2473–2485. doi: 10.1007/s00429-016-1351-5

Janssen, T. W., Heslenfeld, D. J., van Mourik, R., Geladé, K., Maras, A., and Oosterlaan, J. (2018). Alterations in the ventral attention network during the stop-signal task in children with ADHD: An event-related potential source imaging study. *J. Atten. Disord.* 22, 639–650. doi: 10.1177/1087054715580847

Jang, S. H., and Kwon, H. G. (2015). The direct pathway from the brainstem reticular formation to the cerebral cortex in the ascending reticular activating system: A diffusion tensor imaging study. *Neurosci. Lett.* 606, 200–203. doi: 10.1016/j.neulet.2015.09.004

Joensson, M., Thomsen, K. R., Andersen, L. M., Gross, J., Mouridsen, K., Sandberg, K., et al. (2015). Making sense: Dopamine activates conscious self-monitoring through medial prefrontal cortex. *Hum. Brain Mapp.* 36, 1866–1877. doi: 10.1002/hbm.22742

Kamali, A., Karbasian, N., Sherbaf, F. G., Wilken, L. A., Aein, A., Sair, H. I., et al. (2020). Uncovering the dorsal thalamo-hypothalamic tract of the human limbic system. *Neuroscience* 432, 55–62. doi: 10.1016/j.neuroscience.2020.02.021

Kerns, J. G., Cohen, J. D., MacDonald, A. W. III, Johnson, M. K., Stenger, V. A., Aizenstein, H., et al. (2005). Decreased conflict-and error-related activity in the anterior cingulate cortex in subjects with schizophrenia. *Am. J. Psychiatry* 162, 1833–1839.

Koirala, N., Fleischer, V., Glaser, M., Zeuner, K. E., Deuschl, G., Volkmann, J., et al. (2018). Frontal lobe connectivity and network community characteristics are associated with the outcome of subthalamic nucleus deep brain stimulation in patients with Parkinson's disease. *Brain Topogr.* 31, 311–321. doi: 10.1007/s10548-017-0597-4

Kutscheidt, K., Dresler, T., Hudak, J., Barth, B., Blume, F., Ethofer, T., et al. (2019). Interoceptive awareness in patients with attention-deficit/hyperactivity disorder (ADHD). *ADHD Atten. Deficit Hyperact. Disord.* 11, 395–401.

Kwak, S., and Jung, M. W. (2019). Distinct roles of striatal direct and indirect pathways in value-based decision making. *Elife* 8:e46050. doi: 10.7554/eLife.46050

Lanier, J., Noyes, E., and Biederman, J. (2021). Mind wandering (internal distractibility) in ADHD: A literature review. *J. Atten. Disord.* 25, 885–890. doi: 10.1177/1087054719865781

Laubach, M., Caetano, M. S., and Narayanan, N. S. (2015). Mistakes were made: Neural mechanisms for the adaptive control of action initiation by the medial prefrontal cortex. *J. Physiol Paris* 109, 104–117.

Leisman, G., and Melillo, R. (2012). "The development of the frontal lobes in infancy and childhood: Asymmetry and the nature of temperament and affect," in *Frontal lobe: Anatomy, functions and injuries*, ed. A. Cavanna (Hauppauge, NY: Nova Scientific Publishers).

Leisman, G., and Sheldon, D. (2022). Tics and emotions. *Brain Sci.* 12, 242. doi: 10.3390/brainsci12020242

Longo, M. R., Trippier, S., Vagnoni, E., and Lourenco, S. F. (2015). Right hemisphere control of visuospatial attention in near space. *Neuropsychologia* 70, 350–357.

Luria, A. R. (2012). *Higher cortical functions in man*. New York, NY: Springer.

Macpherson, T., Morita, M., and Hikida, T. (2014). Striatal direct and indirect pathways control decision-making behavior. *Front. Psychol.* 5:1301. doi: 10.3389/fpsyg.2014.01301

Martella, D., Aldunate, N., Fuentes, L. J., and Sánchez-Pérez, N. (2020). Arousal and executive alterations in attention deficit hyperactivity disorder (ADHD). *Front. Psychol.* 11:1991. doi: 10.3389/fpsyg.2020.01991

McKiernan, K. A., Kaufman, J. N., Kucera-Thompson, J., and Binder, J. R. (2003). A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *J. Cogn. Neurosci.* 15, 394–408. doi: 10.1162/089892903321593117

Melillo, R., and Leisman, G. (2015). "Functional brain imbalance and autistic spectrum disorder," in *The science and pseudoscience of children's mental illness: Cutting edge research and practice. Childhood in america book series*, ed. S. Olfman (Santa Barbara, CA: Praeger), 65–91.

Melillo, R., and Leisman, G. (2009). Autistic spectrum disorders as functional disconnection syndrome. *Rev. Neurosci.* 20, 111–132.

Melillo, R., and Leisman, G. (2010). *Neurobehavioral disorders of childhood: An evolutionary perspective*. New York, NY: Springer.

Melillo, R., Leisman, G., Mualem, R., Ornai, A., and Carmeli, E. (2020). Persistent childhood primitive reflex reduction effects on cognitive, sensorimotor, and academic performance in ADHD. *Front. Public Health* 8:431835. doi: 10.3389/fpubh.2020.431835

Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends Cogn. Sci.* 15, 483–506. doi: 10.1016/j.tics.2011.08.0

Middleton, F. A., and Strick, P. L. (2000). Basal ganglia and cerebellar loops: Motor and cognitive circuits. *Brain Res. Rev.* 31, 236–250.

Miller, E. K., and Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* 24, 167–202.

Monk, A. M., Dalton, M. A., Barnes, G. R., and Maguire, E. A. (2021). The role of hippocampal-ventromedial prefrontal cortex neural dynamics in building mental representations. *J. Cogn. Neurosci.* 33, 89–103.

Nambu, A., Tokuno, H., and Takada, M. (2002). Functional significance of the cortico–subthalamo–pallidal 'hyperdirect'pathway. *Neurosci. Res.* 43, 111–117.

Narayanan, N. S., Wessel, J. R., and Greenlee, J. D. (2020). The fastest way to stop: Inhibitory control and IFG-STN hyperdirect connectivity. *Neuron* 106, 549–551. doi: 10.1016/j.neuron.2020.04.017

Nekovarova, T., Fajnerova, I., Horacek, J., and Spaniel, F. (2014). Bridging disparate symptoms of schizophrenia: A triple network dysfunction theory. *Front. Behav. Neurosci.* 8:171. doi: 10.3389/fnbeh.2014.00171

Neely, K. A., Wang, P., Chennavasin, A. P., Samimy, S., Tucker, J., Merida, A., et al. (2017). Deficits in inhibitory force control in young adults with ADHD. *Neuropsychologia* 99, 172–178.

Norbom, L. B., Rokicki, J., Alnćs, D., Kaufmann, T., Doan, N. T., Andreassen, O. A., et al. (2020). Maturation of cortical microstructure and cognitive development in childhood and adolescence: A T1w/T2w ratio MRI study. *Hum. Brain Mapp.* 41, 4676–4690.

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., and Panksepp, J. (2006). Self-referential process- ing in our brain — a meta-analysis of imaging studies on the self. *Neuroimage* 31, 440–457. doi: 10.1016/j.neuroimage.2005.12.002

Olulade, O. A., Seydell-Greenwald, A., Chambers, C. E., Turkeltaub, P. E., Dromerick, A. W., Berl, M. M., et al. (2020). The neural basis of language development: Changes in lateralization over age. *Proc. Natl. Acad. Sci.U.S.A.* 117, 23477–23483.

Onofrj, V., Chiarelli, A. M., Wise, R., Colosimo, C., and Caulo, M. (2022). Interaction of the salience network, ventral attention network, dorsal attention network and default mode network in neonates and early development of the bottom-up attention system. *Brain Struct. Funct.* 227, 1843–1856. doi: 10.1007/s00429-022-02477-y

Pagliaccio, D., Wiggins, J. L., Adleman, N. E., Curhan, A., Zhang, S., Towbin, K. E., et al. (2017). Behavioral and neural sustained attention deficits in disruptive mood dysregulation disorder and attention-deficit/hyperactivity disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 56, 426–435. doi: 10.1016/j.jaac.2017.02.008

Paniukov, D., Lebel, R. M., Giesbrecht, G., and Lebel, C. (2020). Cerebral blood flow increases across early childhood. *Neuroimage* 204:116224. doi: 10.1016/j.neuroimage.2019.116224

Postema, M. C., Hoogman, M., Ambrosino, S., Asherson, P., Banaschewski, T., Bandeira, C. E., et al. (2021). Analysis of structural brain asymmetries in attention-deficit/hyperactivity disorder in 39 datasets. *J. Child Psychol. Psychiatry* 62, 1202–1219. doi: 10.1111/jcpp.13396

Petrovic, P., and Castellanos, F. X. (2016). Top-down dysregulation—from ADHD to emotional instability. *Front. Behav. Neurosci.* 10:70. doi: 10.3389/fnbeh.2016.00070

Posner, M. I., Rothbart, M. K., Thomas-Thrapp, L., and Gerardi, G. (1998). "The development of orienting to locations and objects," in *Visual attention*, Vol. 8, ed. R. D. Wright (New York, NY: Oxford University Press), 269–288.

Puts, N. A., Harris, A. D., Mikkelsen, M., Tommerdahl, M., Edden, R. A., and Mostofsky, S. H. (2017). Altered tactile sensitivity in children with attention-deficit hyperactivity disorder. *J. Neurophysiol.* 118, 2568–2578. doi: 10.1152/jn.00087.2017

Raichle, M. E., MacLeod, A. M., and Snyder, A. Z. (2001). A default mode of brain function. *Proc. Natl. Acad. Sci. U.S.A.* 98, 676–682. doi: 10.1073/pnas.98.2.676

Raichle, M. E., and Gusnard, D. A. (2005). Intrinsic brain activity sets the stage for expression of motivated behavior. *J. Comp. Neurol.* 493, 167–176. doi: 10.1002/cne.20752

Rozzi, S., and Fogassi, L. (2017). Neural coding for action execution and action observation in the prefrontal cortex and its role in the organization of socially driven behavior. *Front. Neurosci.* 11:492. doi: 10.3389/fnins.2017.00492

Rubia, K. (2007). Neuro-anatomic evidence for the maturational delay hypothesis of ADHD. *Proc. Natl. Acad. Sci. U.S.A.* 104, 19663–19664. doi: 10.1073/pnas.0710329105

Rubia, K., Alegria, A., and Brinson, H. (2014). Imaging the ADHD brain: Disorder-specificity, medication effects and clinical translation. *Expert Rev. Neurother.* 14, 519–538. doi: 10.1586/14737175.2014.907526

Sanz-Cervera, P., Pastor-Cerezuela, G., González-Sala, F., Tárraga-Mínguez, R., and Fernández-Andrés, M. I. (2017). Sensory processing in children with autism spectrum disorder and/or attention deficit hyperactivity disorder in the home and classroom contexts. *Front. Psychol.* 8:1772. doi: 10.3389/fpsyg.2017.01772

Schneider, W., and Shiffrin, R. M. (1977). Controlled and automatic human information processing: I. Detection, search, and attention. *Psychol. Rev.* 84:1. doi: 10.1037/0033-295X.84.1.1

Schneider, F., Bermpohl, F., Heinzel, A., Rotte, M., Walter, M., Tempelmann, C., et al. (2008). The resting brain and our self: Self-relatedness modulates resting state neural activity in cortical midline structures. *Neuroscience* 157, 120–131. doi: 10.1016/j.neuroscience.2008.08.014

Schuck, N. W., Gaschler, R., Wenke, D., Heinzle, J., Frensch, P. A., Haynes, J. D., et al. (2015). Medial prefrontal cortex predicts internally driven strategy shifts. *Neuron* 86, 331–340. doi: 10.1016/j.neuron.2015.03.015

Seidman, L. J., Valera, E. M., and Makris, N. (2005). Structural brain imaging of attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 57, 1263–1272. doi: 10.1016/j.biopsych.2004.11.019

Seli, P., Smallwood, J., Cheyne, J. A., and Smilek, D. (2015). On the relation of mind wandering and ADHD symptomatology. *Psychon. Bull. Rev.* 22, 629–636. doi: 10.3758/s13423-014-0793-0

Serrien, D. J., and Sovijärvi-Spapé, M. M. (2015). Hemispheric asymmetries and the control of motor sequences. *Behav. Brain Res.* 283, 30–36. doi: 10.1016/j.bbr.2015.01.021

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D., et al. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc. Natl. Acad. Sci. U.S.A.* 104, 19649–19654. doi: 10.1073/pnas.0707741104

Shaw, P., and Rabin, C. (2009). New insights into attention-deficit/hyperactivity disorder using structural neuroimaging. *Curr. Psychiatry Rep.* 11, 393–398. doi: 10.1007/s11920-009-0059-0

Sherman, S. M. (2011). Functioning of circuits connecting thalamus and cortex. *Compr. Physiol.* 7, 713–739. doi: 10.1002/cphy.c160032

Sigafoos, J., Roche, L., O'Reilly, M. F., and Lancioni, G. E. (2021). Persistence of primitive reflexes in developmental disorders. *Curr. Dev. Disord. Rep.* 8, 98–105. doi: 10.1007/s40474-021-00232-2

Silk, T. J., Vilgis, V., Adamson, C., Chen, J., Smit, L., Vance, A., et al. (2016). Abnormal asymmetry in frontostriatal white matter in children with attention deficit hyperactivity disorder. *Brain Imaging Behav.* 10, 1080–1089. doi: 10.1007/s11682-015-9470-9

Singer, H. S., Mink, J. W., Gilbert, D. L., and Jankovic, J. (2015). *Movement disorders in childhood*. London: Academic Press.

Sival, D. A., van Noort, S. A., Tijssen, M. A., de Koning, T. J., and Verbeek, D. S. (2022). Developmental neurobiology of cerebellar and Basal Ganglia connections. *Eur. J. Paediatr. Neurol.* 36, 123–129. doi: 10.1016/j.ejpn.2021.12.001

Spagna, A., Martella, D., Fuentes, L. J., Marotta, A., and Casagrande, M. (2016). Hemispheric modulations of the attentional networks. *Brain Cogn.* 108, 73–80.

Spreng, R. N., Mar, R. A., and Kim, A. S. (2009). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: A quantitative meta-analysis. *J. Cogn. Neurosci.* 21, 489–510. doi: 10.1162/jocn.2008.21029

Spreng, R. N., and Grady, C. L. (2010). Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *J. Cogn. Neurosci.* 22, 1112–1123. doi: 10.1162/jocn.2009.21282

Sridharan, D., Levitin, D. J., and Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc. Natl. Acad. Sci U.S.A.* 105, 12569–12574. doi: 10.1073/pnas.0800005105

Sripada, C., Kessler, D., Fang, Y., Welsh, R. C., Prem Kumar, K., and Angstadt, M. (2014). Disrupted network architecture of the resting brain in attention-deficit/hyperactivity disorder. *Hum. Brain Mapp.* 35, 4693–4705. doi: 10.1002/hbm.22504

Tarbanie, H. H. (2020). *Proprioceptive processing in ASD and ADHD children*. Doctoral dissertation. Haifa: University of Haifa.

Temiz, G., Sébille, S. B., Francois, C., Bardinet, E., and Karachi, C. (2020). The anatomo-functional organization of the hyperdirect cortical pathway to the subthalamic area using in vivo structural connectivity imaging in humans. *Brain Struct. Funct.* 225, 551–565. doi: 10.1007/s00429-019-02012-6

Tucker, D. M., and Luu, P. (2021). Motive control of unconscious inference: The limbic base of adaptive Bayes. *Neurosci. Biobehav. Rev.* 128, 328–345. doi: 10.1016/j.neubiorev.2021.05.029

Tseng, Y. T., Tsai, C. L., Chen, F. C., and Konczak, J. (2018). Wrist position sense acuity and its relation to motor dysfunction in children with developmental coordination disorder. *Neurosci. Lett.* 674, 106–111. doi: 10.1016/j.neulet.2018.03.031

Tzourio-Mazoyer, N., Perrone-Bertolotti, M., Jobard, G., Mazoyer, B., and Baciu, M. (2017). Multi-factorial modulation of hemispheric specialization and plasticity for language in healthy and pathological conditions: A review. *Cortex* 86, 314–339. doi: 10.1016/j.cortex.2016.05.013

Uda, S., Matsui, M., Tanaka, C., Uematsu, A., Miura, K., Kawana, I., et al. (2015). Normal development of human brain white matter from infancy to early adulthood: A diffusion tensor imaging study. *Dev. Neurosci.* 37, 182–194.

Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. *Nat. Rev. Neurosci.* 16, 55–61.

Uddin, L. Q., Supekar, K., Amin, H., Rykhlevskaia, E., Nguyen, D. A., Greicius, M. D., et al. (2010). Dissociable connectivity within human angular gyrus and intraparietal sulcus: Evidence from functional and structural connectivity. *Cereb. Cortex* 20, 2636–2646.

Uddin, L. Q., Kelly, A. C., Biswal, B. B., Margulies, D. S., Shehzad, Z., Shaw, D., et al. (2008). Network homogeneity reveals decreased integrity of default-mode network in ADHD. *J. Neurosci. Methods* 169, 249–254. doi: 10.1016/j.jneumeth.2007.11.031

Uddin, L. Q., Clare Kelly, A. M., Biswal, B. B., Xavier Castellanos, F., and Milham, M. P. (2009). Functional connectivity of default mode network components: Correlation, anticorrelation, and causality. *Hum. Brain Mapp.* 30, 625–637.

Uddin, L. Q. (2021). Cognitive and behavioural flexibility: Neural mechanisms and clinical considerations. *Nat. Rev. Neurosci.* 22, 167–179.

Vetter, N. C., Buse, J., Backhausen, L. L., Rubia, K., Smolka, M. N., and Roessner, V. (2018). Anterior insula hyperactivation in ADHD when faced with distracting negative stimuli. *Hum. Brain Mapp.* 39, 2972–2986. doi: 10.1002/hbm.24053

Vizzini, L., Popovic, M., Zugna, D., Vitiello, B., Trevisan, M., Pizzi, C., et al. (2019). Maternal anxiety, depression and sleep disorders before and during pregnancy, and preschool ADHD symptoms in the NINFEA birth cohort study. *Epidemiol. Psychiatr. Sci.* 28, 521–531. doi: 10.1017/S2045796018000185

Vossel, S., Geng, J. J., and Fink, G. R. (2014). Dorsal and ventral attention systems: Distinct neural circuits but collaborative roles. *Neuroscientist* 20, 150–159. doi: 10.1177/1073858413494269

Wang, J., Xiao, L., Wilson, T. W., Stephen, J. M., Calhoun, V. D., and Wang, Y. P. (2020). Examining brain maturation during adolescence using graph Laplacian learning based fourier transform. *J. Neurosci. Methods* 338:10864. doi: 10.1016/j.jneumeth.2020.108649

Wasserstein, J., and Stefanatos, G. A. (2016). Re-examining ADHD as corticostriatal disorder: Implications for understanding common comorbidities. *ADHD Rep.* 24, 1–10.

Wiersema, J. R., and Godefroid, E. (2018). Interoceptive awareness in attention deficit hyperactivity disorder. *PLoS One* 13:e0205221. doi: 10.1371/journal.pone.0205221

Williams, N. H., and Das, J. P. (2021). "Variations of the orienting response in learning-disabled children," in *The orienting reflex in humans*, eds H. D. Kimmel, E. H. van Olst, and J. F. Orlebeke (London: Routledge), 639–645.

Wolff, N., Rubia, K., Knopf, H., Hölling, H., Martini, J., Ehrlich, S., et al. (2016). Reduced pain perception in children and adolescents with ADHD is normalized by methylphenidate. *Child Adolesc. Psychiatry Ment. Health* 10, 1–10. doi: 10.1186/s13034-016-0112-9

Xi, T., and Wu, J. (2021). A review on the mechanism between different factors and the occurrence of autism and ADHD. *Psychol. Res. Behav. Manag.* 14:393.

Yasumura, A., Omori, M., Fukuda, A., Takahashi, J., Yasumura, Y., Nakagawa, E., et al. (2019). Age-related differences in frontal lobe function in children with ADHD. *Brain Dev.* 41, 577–586.

Zelazo, P. D. (2015). Executive function: Reflection, iterative reprocessing, complexity, and the developing brain. *Dev. Rev.* 38, 55–68.

Zhang, Y., Suo, X., Ding, H., Liang, M., Yu, C., and Qin, W. (2019). Structural connectivity profile supports laterality of the salience network. *Hum. Brain Mapp.* 40, 5242–5255.

Ziegler, S., Pedersen, M. L., Mowinckel, A. M., and Biele, G. (2016). Modelling ADHD: A review of ADHD theories through their predictions for computational models of decision-making and reinforcement learning. *Neurosci. Biobehav. Rev.* 71, 633–656. doi: 10.1016/j.neubiorev.2016.09.002

Zikopoulos, B., and Barbas, H. (2007). Parallel driving and modulatory pathways link the prefrontal cortex and thalamus. *PLoS One* 2:e848. doi: 10.1371/journal.pone.0000848

Zou, H., and Yang, J. (2021). Temporal variability–based functional brain lateralization study in ADHD. *J. Atten. Disord.* 25, 839–847. doi: 10.1177/1087054719859074

frontiers | Frontiers in Neuroanatomy

TYPE Perspective
PUBLISHED 24 November 2022
DOI 10.3389/fnana.2022.1028546

OPEN ACCESS

EDITED BY
Basilis Zikopoulos,
Boston University, United States

REVIEWED BY
Casimiro Cabrera Abreu,
Queens University, Canada

*CORRESPONDENCE
Dorit Ben Shalom
doritb@bgu.ac.il

RECEIVED 26 August 2022
ACCEPTED 09 November 2022
PUBLISHED 24 November 2022

CITATION
Ben Shalom D (2022) The amygdala–insula–medial prefrontal cortex–lateral prefrontal cortex pathway and its disorders.
Front. Neuroanat. 16:1028546.
doi: 10.3389/fnana.2022.1028546

The amygdala–insula–medial prefrontal cortex–lateral prefrontal cortex pathway and its disorders

Dorit Ben Shalom*

School of Brain Sciences and Cognition, Ben-Gurion University of the Negev, Beersheba, Israel

Smith and Lane have suggested a model of emotion processing with at least three stations: areas like the amygdala, which process discrete body features areas like the anterior insula, which process whole-body patterns and areas like the medial prefrontal cortex, which process emotion concepts. Ben Shalom and Bonneh have suggested a model of the prefrontal cortex, in which medial BA 9 integrates emotional states, and lateral BA 9 performs selection/inhibition on these states. Taken together, the current paper suggests a pathway for emotion processing with at least four stations: areas like the amygdala, which process discrete body features areas like the anterior insula, which process whole-body patterns, medial BA 9 which integrates emotion concepts, and lateral BA 9, which performs selection/inhibition on these concepts. Following the existing literature, it then suggest that there is a significant involvement of the amygdala in psychopathy (Blair), of the anterior insula in alexithymia (Bird), of the medial BA 9 in deficits in somatosensory discrimination (Ben Shalom), and of lateral BA 9 in emotional impulsivity (Ronel).

KEYWORDS

amygdala, insula, mPFC, LPFC, emotion

Introduction

The current paper can be seen as either an extension of Smith and Lane (2015) model of emotional processing, or as an application of Ben Shalom and Bonneh (2019) model of the prefrontal cortex. Either way, one ends up with a pathway of four stations: the amygdala, insula, medial prefrontal cortex, and lateral prefrontal cortex. Smith and Lane (2015) model of emotion processing talks about three types of emotion representations: Stage 1 (discrete body features), such as in the posterior insula, and presumably the amygdala; Stage 2 (whole body patterns), such as the anterior

insula; and Stage 3 (emotion concepts), such as in the medial prefrontal cortex. In other words, it proposes a pathway with at least three consecutive stations: the amygdala, the anterior insula, and the medial prefrontal cortex (**Figure 1**).

Ben Shalom and Bonneh (2019) suggest a model of the narrow prefrontal cortex (BA 8, 9, 10, 11) in terms of two divisions: horizontal and vertical. But while their horizontal division is traditional (medial vs. lateral), their vertical division is new: four streams of information, from dorsal to ventral (motor, emotion, memory, and sensory). Within each stream, the medial prefrontal cortex integrates basic cognitive objects, while the lateral prefrontal cortex performs selection/inhibition on these objects. In other words, it proposes a pathway with at least two consecutive stations: the medial prefrontal cortex, and the lateral prefrontal cortex (**Figure 2**).

Putting these two models together, one gets a pathway with at least four consecutive stations: Stage 1 (discrete body features), such as in the posterior insula, and presumably the amygdala; Stage 2 (whole body patterns), such as in the anterior insula; Stage 3 (integration of emotion concepts) such as medial BA 9; and Stage 4 (selection/inhibition of emotion concepts), in lateral BA 9.

The amygdala and psychopathy

Psychopathy is a personality disorder characterized by an emotional dysfunction (reduced guilt and empathy) whose antecedents can be identified in a subgroup of young people showing severe antisocial behavior (Hare, 2003). Even though we now know that it correlates with dysfunction in several brain regions (De Brito et al., 2021), it is still accepted that a major defining feature of the disorder is dysfunction of the amygdala (Blair, 2008; Marsh et al., 2013): the amygdala is involved in the formation of both positive and negative stimulus associations. Individuals with psychopathy show impairment in stimulus reinforcement learning (whether positive or negative), which is crucial for learning that some social things are bad to do. As such, these individuals are more likely to learn to use antisocial strategies to achieve their goals. In addition, the reduced amygdala responsivity leads to reduced empathy. Finally, the impairment in positive stimulus learning may relate to the reduced attachment reported in this disorder (Hare, 2003); individuals with psychopathy may find their carers to be less positive stimuli and thus be less motivated to seek their company.

The anterior insula and alexithymia

Alexithymia has been described as a subclinical phenomenon marked by difficulties in identifying and describing feelings and difficulties in distinguishing feelings from the bodily sensations of emotion (Bird et al., 2010). The argument for connecting alexithymia to dysfunction of the anterior insula comes from both functional and structural sources (Smith et al., 2020). In terms of _function_, alexithymia is associated with reduced anterior insula activation on several emotional tasks, such as when rating the emotional valence of stimuli from the International Affective Pictures System (Silani et al., 2008), or when observing either emotional facial expressions (Kano et al., 2003; Reker et al., 2010) or the sight of others in pain (Bird et al., 2010; Feldmanhall et al., 2013). In terms of _structure_, alexithymia is associated with reduced anterior insula volume (Borsci et al., 2009; Ihme et al., 2013; Bernhardt et al., 2014), and reduced coherence of the structural connections of the anterior insula. A recent study (Hogeveen et al., 2016) found _acquired_ alexithymia following damage to the anterior insula.

Medial BA 9 and deficits in somatosensory discrimination

In contrast, there is considerable evidence that the medial prefrontal cortex is involved in the processing of basic conscious feelings. For example, Phan et al. (2002) reviewed 55 PET

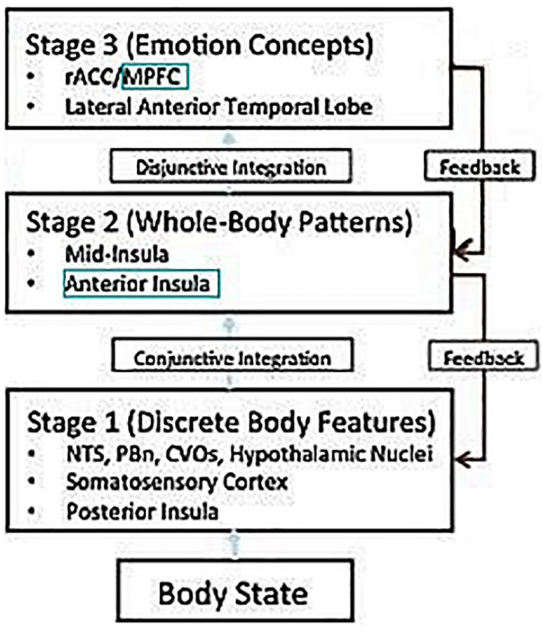


FIGURE 1
Adapted from Smith and Lane (2015). NTS, nucleus of the solitary tract; PBn, parabrachial nucleus; CVOs, circumventricular organs; rACC, rostral ACC; MPFC, medial prefrontal cortex.

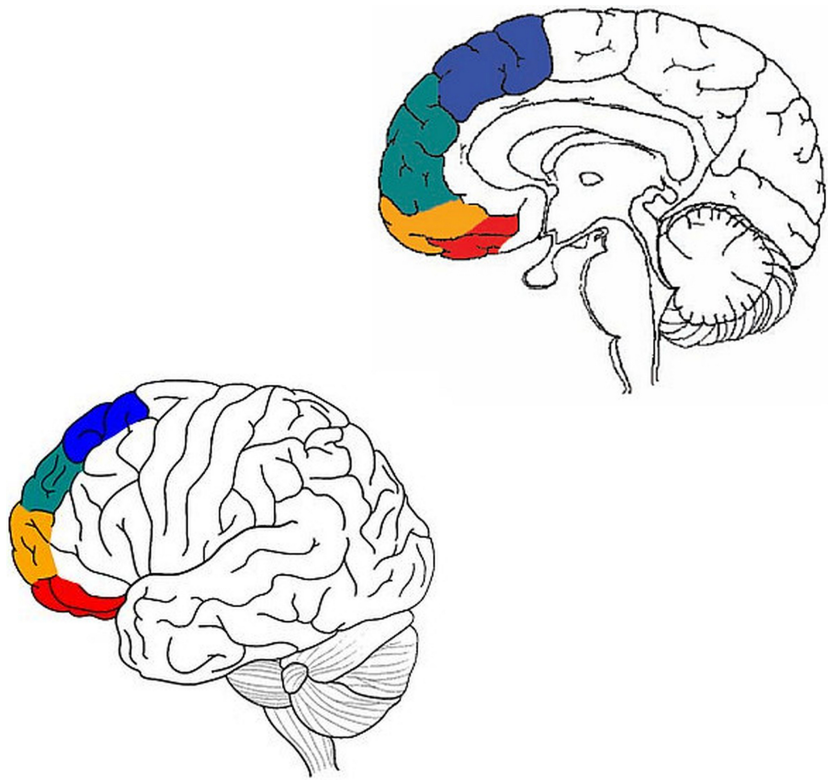


FIGURE 2
Adapted from Ben Shalom (2009) and Ronel (2018). Motor processing in blue, emotion in green, memory in orange, and sensory in red.

and fMRI studies of the processing of basic conscious feelings (happiness, fear, anger, sadness, and disgust), and concluded the following: that while every basic feeling has its own associated areas, the one area that was in common to all of them was the medial prefrontal cortex (BA 9/10). Thus, a problem with medical BA 9 would lead to impaired emotion concepts, and a difficulty in reading the anterior insula body maps, even if the body maps themselves are in fact intact.

But the deficit is probably even more general. For example, somatosensory discrimination relates to the discrimination capacities of the tactile and proprioceptive modalities, derived from somatosensory information regarding touch, pressure, vibration, temperature, texture, pain, and the location and movement of body parts (Bröring et al., 2008).

A recent scoping review (Zetler et al., 2019) found that most studies of people with ASD (a disorder proposed to involve the medial prefrontal cortex, Ben Shalom, 2009; Uddin, 2011) showed atypical somatosensory discrimination, especially among young children. In other words, a difficulty in discriminating basic feelings can be a special case of a difficulty in discriminating body states, whether they are emotional or not.

Lateral BA 9 and emotional impulsivity

Finally, there is much evidence supporting a relation between lateral BA 9 and emotional impulsivity, or, more generally, emotion regulation. One piece of evidence comes from studies of addiction, which is often assumes to be related to emotional impulsivity. For example, a study by Chen and Mo (2017) compared regional homogeneity in nicotine addicts and control participants. The nicotine addicts had lower regional homogeneity values in a prefrontal area whose peak coordinates were in lateral BA 9. Similarly, a post-mortem analysis of individuals with alcohol use disorder demonstrated that DNA methylation alterations in the lateral BA 9 are associated with (and might result in) increased risk of alcohol use disorders (Wang et al., 2016). Another piece of evidence comes from the study of emotion regulation strategies such as reappraisal and suppression (Ronel, 2018): Compared to passive viewing conditions, both reappraisal (Xiong et al., 2013; Hallam et al., 2014; Rabinak et al., 2014), as well as suppression (Hallam et al., 2014), were found to show greater brain activation in lateral BA 9. In addition, two different meta-analyses have been used to examine fMRI studies of emotion regulation. Buhle et al. (2014) found that reappraisal consistently activated lateral BA 9;

Frank et al. (2014) found that such reappraisal was accompanied by increased activation in lateral BA 9 together with reduced activation in the amygdala.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

DB wrote the manuscript, contributed to the article, and approved the submitted version.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Ben Shalom, D. (2009). The medial prefrontal cortex and integration in autism. *Neuroscientist* 15, 589–598.

Ben Shalom, D., and Bonneh, Y. S. (2019). Editorial: The medial prefrontal cortex and integration in ASD and typical cognition. *Front. Hum. Neurosci.* 13:74. doi: 10.3389/fnhum.2019.00074

Bernhardt, B. C., Valk, S. L., Silani, G., Bird, G., Frith, U., and Singer, T. (2014). Selective disruption of sociocognitive structural brain networks in autism and alexithymia. *Cereb. Cortex* 24, 3258–3267. doi: 10.1093/cercor/bht182

Bird, G., Silani, G., Brindley, R., White, S., Frith, U., and Singer, T. (2010). Empathic brain responses in insula are modulated by levels of alexithymia but not autism. *Brain* 133, 1515–1525. doi: 10.1093/brain/awq060

Blair, R. J. (2008). The amygdala and ventromedial prefrontal cortex: Functional contributions and dysfunction in psychopathy. *Philos. Trans. R. Soc. Lond. Series B. Biol. Sci.* 363, 2557–2565.

Borsci, G., Boccardi, M., Rossi, R., Rossi, G., Perez, J., Bonetti, M., et al. (2009). Alexithymia in healthy women: A brain morphology study. *J. Affect. Disorder.* 114, 208–215.

Bröring, T., Rommelse, N., Sergeant, J., and Scherder, E. (2008). Sex differences in tactile defensiveness in children with ADHD and their siblings. *Dev. Med. Child Neurol.* 50, 129–133. doi: 10.1111/j.1469-8749.2007.02024.x

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., et al. (2014). Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. *Cereb. Cortex* 24, 2981–2990.

Chen, H., and Mo, S. (2017). Regional homogeneity changes in nicotine addicts by resting-state fMRI. *PLoS One* 12:e0170143. doi: 10.1371/journal.pone.0170143

De Brito, S. A., Forth, A. E., Baskin-Sommers, A. R., Brazil, I. A., Kimonis, E. R., Pardini, D., et al. (2021). Psychopathy. *Nat. Rev. Dis. Primers* 7:49.

Feldmanhall, O., Dalgleish, T., and Mobbs, D. (2013). Alexithymia decreases altruism in real social decisions. *Cortex* 49, 899–904. doi: 10.1016/j.cortex.2012.10.015

Frank, D. W., Dewitt, M., Hudgens-Haney, M., Schaeffer, D. J., Ball, B. H., Schwarz, N. F., et al. (2014). Emotion regulation: Quantitative meta-analysis of functional activation and deactivation. *Neurosci. Biobehav. Rev.* 45, 202–211.

Hallam, G. P., Webb, T. L., Sheeran, P., Miles, E., Niven, K., Wilkinson, I. D., et al. (2014). The neural correlates of regulating another person's emotions: An exploratory fMRI study. *Front. Hum. Neurosci.* 8:376. doi: 10.3389/fnhum.2014.00376

Hare, R. D. (2003). *Hare Psychopathy Checklist-Revised (PCL-R)*, 2nd Edn. Toronto: Multi Health Systems.

Hogeveen, J., Bird, G., Chau, A., Krueger, F., and Grafman, J. (2016). Acquired alexithymia following damage to the anterior insula. *Neuropsychologia* 82, 142–148. doi: 10.1016/j.neuropsychologia.2016.01.021

Ihme, K., Dannlowski, U., Lichev, V., Stuhrmann, A., Grotegerd, D., Rosenberg, N., et al. (2013). Alexithymia is related to differences in gray matter volume: A voxel-based morphometry study. *Brain Res.* 1491, 60–67.

Kano, M., Fukudo, S., Gyoba, J., Kamachi, M., Tagawa, M., Mochizuki, H., et al. (2003). Specific brain processing of facial expressions in people with alexithymia: An H2 15O-PET study. *Brain* 126, 1474–1484. doi: 10.1093/brain/awg131

Marsh, A. A., Finger, E. C., Fowler, K. A., Adalio, C. J., Jurkowitz, I. T., Schechter, J. C., et al. (2013). Empathic responsiveness in amygdala and anterior cingulate cortex in youths with psychopathic traits. *J. Child Psychol. Psychiatry* 54, 900–910. doi: 10.1111/jcpp.12063

Phan, K. L., Wager, T., Taylor, S. F., and Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 16, 331–348. doi: 10.1006/nimg.2002.1087

Rabinak, C. A., MacNamara, A., Kennedy, A. E., Angstadt, M., Stein, M. B., Liberzon, I., et al. (2014). Focal and aberrant prefrontal engagement during emotion regulation in veterans with posttraumatic stress disorder. *Depress. Anxiety* 31, 851–861. doi: 10.1002/da.22243

Reker, M., Ohrmann, P., Rauch, A. V., Kugel, H., Bauer, J., Dannlowski, U., et al. (2010). Individual differences in alexithymia and brain response to masked emotion faces. *Cortex* 46, 658–667.

Ronel, Z. (2018). The Lateral Prefrontal Cortex and Selection/Inhibition in ADHD. *Front. Hum. Neurosci.* 12:65. doi: 10.3389/fnhum.2018.00065

Silani, G., Bird, G., Brindley, R., Singer, T., Frith, C., and Frith, U. (2008). Levels of emotional awareness and autism: An fMRI study. *Social Neurosci.* 3, 97–112.

Smith, R., and Lane, R. D. (2015). The neural basis of one's own conscious and unconscious emotional states. *Neurosci. Biobehav. Rev.* 57, 1–29. doi: 10.1016/j.neubiorev.2015.08.003

Smith, R., Steklis, H. D., Steklis, N. G., Weihs, K. L., and Lane, R. D. (2020). The evolution and development of the uniquely human capacity for emotional awareness: A synthesis of comparative anatomical, cognitive, neurocomputational, and evolutionary psychological perspectives. *Biol. Psychol.* 154:107925. doi: 10.1016/j.biopsycho.2020.107925

Uddin, L. Q. (2011). The self in autism: An emerging view from neuroimaging. *Neurocase* 17, 201–208. doi: 10.1080/13554794.2010.509320

Wang, F., Xu, H., Zhao, H., Gelernter, J., and Zhang, H. (2016). DNA co-methylation modules in postmortem prefrontal cortex tissues of European Australians with alcohol use disorders. *Sci. Rep.* 6:19430. doi: 10.1038/srep19430

Xiong, K., Zhang, Y., Qiu, M., Zhang, J., Sang, L., Wang, L., et al. (2013). Negative emotion regulation in patients with posttraumatic stress disorder. *PLoS One* 8:e81957. doi: 10.1371/journal.pone.0081957

Zetler, N. K., Cermak, S. A., Engel-Yeger, B., and Gal, E. (2019). Somatosensory discrimination in people with autism spectrum disorder: A scoping review. *Am. J. Occup. Ther.* 73, 7305205010p1–7305205010p14 doi: 10.5014/ajot.2019.029728

frontiers | Frontiers in Neuroanatomy

TYPE Perspective
PUBLISHED 27 February 2023
DOI 10.3389/fnana.2023.1076095

OPEN ACCESS

EDITED BY
Dorit Ben Shalom,
Ben-Gurion University of the Negev, Israel

REVIEWED BY
Bethany Plakke,
Kansas State University, United States

*CORRESPONDENCE
Odelia Elkana
✉ odelia.elkana@gmail.com
Orin Segal
✉ orinseg@gmail.com

RECEIVED 21 October 2022
ACCEPTED 24 January 2023
PUBLISHED 27 February 2023

CITATION
Segal O and Elkana O (2023) The ventrolateral prefrontal cortex is part of the modular working memory system: A functional neuroanatomical perspective.
Front. Neuroanat. 17:1076095.
doi: 10.3389/fnana.2023.1076095

The ventrolateral prefrontal cortex is part of the modular working memory system: A functional neuroanatomical perspective

Orin Segal* and Odelia Elkana*

School of Behavioral Sciences, The Academic College of Tel Aviv Yaffo, Tel Aviv, Israel

For many years, the functional role of the ventrolateral Pre-Frontal Cortex (PFC) was associated with executive functions, specifically in the context of non-affective cognitive processes. However, recent research has suggested that the ventrolateral PFC is also involved in the attention system. The Ben Shalom model of the functional organization of the prefrontal cortex (2019) posits that the ventrolateral PFC selects perceptual stimuli after integration by the adjacent ventromedial PFC. This article reviews the state-of-the-art findings to better understand the role of the ventrolateral PFC in the selection of perceptual information as grounded in the Ben Shalom model. Numerous studies have reported converging evidence for the selective role of this area. However, most argue that this perceptual selection takes place through the active updating of information values linked to goal-oriented actions. These studies thus view the ventrolateral PFC as part of a system that actively manipulates and changes processed information such as the working memory function, rather than being part of the attention system. In agreement with this view, this review suggests that this area is part of a complex and modular working memory system and illustrates with reference to Diamond's work on ADD. This working memory system is functionally and anatomically dispersed and includes the dorsolateral PFC, the ACC, the parietal cortex, the basal ganglia, and the cerebellum. Hence, future research should continue to explore the specific neurofunctional roles of these areas in working memory systems, and the connections between the different subareas in this complex array.

KEYWORDS

vlPFC, ventrolateral prefrontal cortex, working memory, functional neuroanatomical framework, lateral OFC, inattentiveness, PFC, selective attention

Introduction

The frontal lobes and specifically the Pre-Frontal Cortex (PFC) are considered to mediate executive functions; i.e., the range of mental functions guiding human behavior *via* the coordination, operation, and integration of more basic mental processes (Ward, 2020). Although there is a general consensus that the PFC plays a major role that underlies these executive functions, the ways in which they are related to the anatomical structure of the PFC is still hotly debated. Different models have been put forward to clarify this functional neuroanatomical association. Most theories derive from one broader model that makes a horizontal distinction between the lateral PFC and the medial PFC (Ward, 2020) which distinguishes between affective and nonaffective executive functions. The medial PFC, which includes the ventral orbitofrontal

cortex, is thought to be involved in the processing of emotional and social stimuli, and reward-related stimuli in particular, whereas the lateral PFC is believed to be involved in pure emotionally-neutral cognitive, sensory-related stimuli processing (Ward, 2020).

However, other models have been proposed, suggesting different hierarchies of information processing along different axses, such as anterior-posterior or dorsal-ventral (Ben Shalom and Bonneh, 2019; e.g., Koechlin and Summerfield, 2007). Ben Shalom (2009) and Ben Shalom and Bonneh (2019) proposed a framework including both a horizontal and a vertical distinction. In this model, the PFC is functionally organized in four different subareas where Brodmann areas BA 11 and 47, corresponding to the Orbitofrontal Cortex (OFC) and the inferior frontal gyri, are involved in perception, BA 10 and 46, roughly corresponding to the middle frontal gyri, are involved in memory, BA 9, comprising the dorsal regions of the PFC, is involved in emotion and BA 8, in the superior frontal gyri and posterior to BA9, is involved in motor information (Ben Shalom, 2009; Ben Shalom and Bonneh, 2019). While the original model (Ben Shalom, 2009) focused on vertical neuro-functional organization, in 2018, Ronel suggested that while the subareas in both the medial and lateral PFC process similar types of information (sensation perception, memory, emotion, and motor), they also have specific functions, where the medial division integrates subcortical and cortical—sensory and cognitive information, the lateral counterpart is involved in the selection and inhibition of this information (Ronel, 2018).

Here, we extend the Ronel and Ben Shalom model (Ronel, 2018; Ben Shalom and Bonneh, 2019) to explore the role of BA 47 and the lateral BA 11. Ben Shalom's model describes these anatomical subareas using the Brodmann classification. However, most current functional neuroanatomical literature on the PFC uses other taxonomies, such as cerebral divisions into sulci and gyri, or a simple division of the PFC into the four ventromedial, ventrolateral, dorsomedial, and dorsolateral areas. We use this definition when referring to BA 11 and 47. In what follows the more general term PFC or the specific term OFC is used when appropriate.

The lateral OFC: selection and inhibition of perceptual information or goal-directed guidance?

Ronel presents experimental evidence for the role of the ventrolateral PFC, and especially the lateral OFC, in perceptual selection processes (Ronel, 2018). Ronel suggests that the lateral OFC is involved in assigning and updating selection criteria according to stimulus values, rejecting irrelevant stimuli, and maintaining relevant information in working memory.

There is evidence that the lateral OFC plays a role in task-specific and goal-directed information selection (Gremel and Costa, 2013; Zsuga et al., 2016; Ronel, 2018; Malvaez et al., 2019). However, it is difficult to clearly distinguish between selection functions and the other more integrative perceptual processes needed for the goal-directed guidance in which this subarea is involved. For example, recent studies have indicated that the lateral OFC is involved in the updating of outcome values and integrating specific external and internal perceptual presentations to achieve a goal (Baltz et al., 2018; Stayte et al., 2021). These studies lend weight to its putative perceptual role but do not differentiate the lateral and medial parts with respect to the integrative role that was suggested to be under the control of the medial areas in Ben Shalom's model. Moreover, many studies on the functional properties of this area continue to stress its role in goal-directed behavior, including its involvement in goal-directed cognitive control processes, but put forward different mechanisms to underlie this function (e.g., Tang et al., 2016; Sadacca et al., 2018; Wallis, 2019; Tripathi et al., 2021). Although the literature tends to confirm Ronel and Ban Shalom's claim that the ventral PFC, including both the medial and lateral OFC, is closely involved in the processing of perceptual information, the role of the lateral OFC in goal-directed behavior, and how the processing of perceptual information is related to this, remain unclear.

What further complicates the issue is that the OFC is hypothesized to be involved in acquiring information to infer the subjective and emotional value of actions (Rich and Wallis, 2016). That is, its selection properties are part of a learning process where action values are constantly updated by preferring or rejecting the perceptual stimulus related to the updated value outcomes. To do so, the OFC's main function is thought to be driven by behavior-reward associative learning (Kennerley and Wallis, 2009; Zsuga et al., 2016; Sadacca et al., 2018; Knudsen and Wallis, 2020). Studies have reported the existence of neural connections between the OFC, the ventral striatum, and the thalamus in humans and primates, thus suggesting that the OFC plays a role in reward learning (Balleine and O'Doherty, 2010). It is further hypothesized that in this cortico-striatum learning loop, the ventral striatum enables a fast reward learning route while the cortex balances this route in a slower, more gradual learning route, integrating different past and present representations (Buschman et al., 2014). Other studies that have recorded neurons in the rat indicate neural activation in the OFC subsequent to reward training but also after non-rewarding stimulus associations (Sadacca et al., 2018). Following this line, some studies, suggest that while the OFC, in general, represents and updates the emotional value of information, there is a different function between the medial the lateral sub area's functions. While the medial OFC represents expected rewards, the lateral OFC represents non-reward and punishment values (Rolls et al., 2020; Xie et al., 2021). It is important to note that while many studies agree that the lateral OFC has an important role in updating values, many believe it holds both reward and non-reward values (Sescousse et al., 2010; Malvaez et al., 2019).

While many studies have dealt with the role of OFC in the association between value and action during goal-directed behavior and consider that the lateral OFC is involved in the selection or rejection of sensory-perceptual information, they do not suggest that this is its main role. Instead, most have pointed to higher functions such as action selection, memory, and information integration. One possible explanation for the apparent discrepancy with Ben Shalom and Ronel's perceptual processing hypothesis of the broader ventral PFC area is that the lateral OFC, which is a subarea of the ventrolateral PFC, may reciprocally select and process sensory-perceptual information, and update its value through Pavlovian and operant associations, thus actively seeking value-related information. In this reciprocal selection-updating-selection process, the lateral OFC would not function as a passive filter of sensory information, but rather as an active work pad that continuously examines the information passing through its "multimedia" recorders, by comparing it to internal, stored data

and evaluating its relevance to possible actions. This more elaborate active selective function is similar in many ways to working memory. Indeed, there is some evidence that the ventrolateral PFC, including the lateral OFC, is active during specific working memory tasks in which information is associated with rewards (Kennerley and Wallis, 2009; Ronel, 2018; Wallis, 2019). Here, we suggest that the ventrolateral PFC, unlike the dorsolateral PFC, is the locus of specific reward-based working memory which serves as the foundation for its other goal-directed selection functions. Clearly, however, this hypothesis needs to be tested. Diamond's (2005) view of ADHD without hyperactivity, and the evidence supporting her view may help ground this notion of the association between working memory functions and active selection properties of the ventrolateral PFC.

Inattentiveness, working memory, and ventrolateral PFC

Based on her accumulating research and neurocognitive models, Diamond (2016) characterized the PFC as a key player in the exercise of executive functions. Diamond describes executive functions as the group of skills required for concentration, thinking, problem-solving, and the inhibition of automatic responses when they are evaluated negatively. Diamond argues that executive functions are similar and cooperate with, but are not identical to, self-regulation. She argues that three components constitute the core of executive functions: working memory (updating information), inhibitory control (inhibition of responses), and cognitive flexibility (shifting between responses and cognitive processes). Top-down attention, which includes selective and focused attention, is included in inhibitory control, together with the inhibition of thoughts, memories, and behavior. Working memory is defined as the function of relating a mental representation (number, fact, idea, memory, perception object, etc.) to another, thus manipulating the information to reorder, calculate and compare it. Cognitive flexibility relies on the first two components, which develop earlier in life, and is described as the ability to see something from different perspectives, switch between tasks, and switch or change a planned course of action when needed.

Diamond's model may thus have bearing on the role of the ventrolateral PFC: is it part of inhibitory control, given its selective properties? (e.g., Ronel, 2018; Baytunca et al., 2021), or it is part of working memory, because of its mental manipulation properties? (e.g., Kennerley and Wallis, 2009; Zsuga et al., 2016).

Disentangling these two possibilities is not straightforward, since working memory and inhibition are tightly linked according to Diamond (2005, 2016) and Friedman and Miyake (2017). Working memory and selective attention are also interrelated, and it is almost impossible to differentiate between the two. The functions of working memory; namely, inhibitory control and selective attention, are hard to differentiate during childhood on both the neural and functional levels and continue to share similar neural networks and be functionally related in the adult brain (Nelson et al., 2015). Diamond (2016) reports studies showing that the ability to inhibit distractions, which is a characteristic of selective attention, has a stronger link to working memory than to inhibitory control. Thus, to date, it is difficult to determine whether selective attention is a function in its own right, or a subfunction of working memory or inhibitory control. Moreover, Postle (2006) suggests that maybe the roles are reversed, and working memory is a property of attention.

Although there is a theoretical debate regarding the dissociation and association between attention and working memory, we suggest that although it is involved in perceptual selective attention, the ventrolateral PFC does so under the umbrella of working memory. Further support for the idea that the ventrolateral PFC is engaged in both working memory and selective attention comes from research on Attention-Deficit Hyperactivity Disorder without hyperactivity (ADHD-I), which is commonly known as ADD or inattentiveness. In general, several brain regions and neural pathways were found to be involved in ADHD. Functional MRI studies have found decreased activation in the ventrolateral PFC, cerebellum, and PFC-striatal circuits, and reduced gray matter in the medial OFC (Zang et al., 2007; Cubillo et al., 2012; Norman et al., 2016; Lukito et al., 2020). Few studies, however, have attempted to distinguish between different types of ADHD on a neural basis. The studies that have done so have found a correlation between the difficulty to maintain attention, which is the core complaint of individuals with ADHD-I, and impairments in working memory (Diamond, 2005; Orinstein and Stevens, 2014; Elisa et al., 2016).

Studies comparing the neural correlates of individuals with ADHD-I and controls have failed to identify a different pattern of activity in the PFC but reported slightly higher activity in BA 10, as well as in other non-PFC areas in the brain (Orinstein and Stevens, 2014). Recall that the BA 10 corresponds to the dorsolateral PFC, which is viewed by many as the locus of general working memory processes (Kennerley and Wallis, 2009; Barbey et al., 2013; Wischnewski et al., 2021). However, the activation of a more dorsal area of the PFC could be influenced by the specific functional task or area of interest tested in these studies. For example, in Elkana et al. (in preparation, 2023), dTMS (Deep Trans Magnetic Stimulation) was centered on the dorsolateral PFC in 57 adults with ADHD. In Orinstein and Stevens' (2014) study, the task was to identify an auditory target among distractors but did not include an update or change of this target's value during the task. Hence, the dorsolateral PFC was active and possibly maintained the task demands active but not the neighboring ventrolateral cortex. Thus, whereas the ventrolateral PFC and the OFC are involved in selective attention and working memory, they may only do so for an input whose outcome value needs to be evaluated and updated.

Different types of WM and their corresponding neuroanatomical locations

Although traditionally the literature has focused on the dorsolateral PFC as the locus of working memory processes, current research on the neuroanatomical correlates of these processes has revised this view and posits that different areas mediate different working memory processes (O'Reilly and Frank, 2006; Ward, 2020; Wischnewski et al., 2021). Although the dorsolateral PFC plays a key role in a range of working memory tasks such as computation, the encoding and retrieving of verbal information, and the integration of input needed for decision-making, many other cortical and subcortical areas are considered to be involved in processes related to working memory (Chai et al., 2018). These mainly include the

ACC and parietal cortex at the cortical level, and the basal ganglia and cerebellum at the subcortical level. Recent studies have pointed to the involvement of ACC in adjustments when task demands change, and the role of the basal ganglia nuclei in the focusing of attention, which appear to overlap to some extent with the ventrolateral PFC.

Hence, despite accumulating evidence, there is still no integrative model of working memory. Clearly, this type of model would shed light on the specific role of the ventrolateral PFC in updating perceptual stimuli according to the outcome value. Future research should attempt to pinpoint the specific roles of the dorsolateral PFC, the ventrolateral PFC, the ACC, and the basal ganglia.

Discussion and conclusion

The ventrolateral PFC, and more specifically the lateral OFC, have a number of specific characteristics. The lateral OFC is known to play a role in the goal-directed selection of information. Ronel and Ben Shalom argued that this information was primarily perceptual (Ben Shalom and Bonneh, 2019). We hypothesize that the ventrolateral PFC enters into larger working memory functions and that this area may be responsible for value-based working memory. This hints that working memory may not be divided solely in terms of perceptual information (verbal as compared to spatial), as proposed by many and criticized by many others (Baddeley and Logie, 2012; Diamond, 2016; Ward, 2020). Rather, different forms of working memory with and without perceptual features may be mediated by different subareas of the lateral PFC, as well as across the brain as a whole. While most working memory research tasks correlate with the dorsolateral PFC and have established it as the locus of working memory processes, growing research evidence has revealed that other brain areas are involved with working memory such as the ACC and the cerebellum.

We believe that the ventrolateral PFC and more specifically the lateral OFC participates in, and is the locus of the outcome value of working memory.

We further believe that a new, integrative model of working memory should be explored and developed. We advocate further research focusing on the ventrolateral PFC and its functional and structural links to working memory. This model should distinguish between different working memory tasks, the brain areas involved, and the mediation of the execution of these tasks. Consistent with Diamond's description of the difficulty differentiating between selective attention and other executive functions such as inhibition and working memory, we argue that an integrative and comprehensive neuroanatomical model of working memory should reevaluate areas and tasks that are traditionally viewed as associated with selective attention, and revisit them through the prism of goal-directed working memory processes.

The idea that the lateral OFC plays a major role in a specific working memory task calls for an update of Ben Shalom's model of the PFC's functional organization, and specifically the ventral PFC, which corresponds to BA 11 and 47. In line with Ronel and Ben Shalom's hypothesis, we support the idea that this area is involved in the processing of perceptual stimuli. Nevertheless, we propose that the lateral sub-area does not merely play a role in selection and inhibition of perceptual information, but rather is involved in a more elaborate updating of information, as a function of its relevance and value to achieving an action goal. This does not require rejecting the previous model, but rather revising it. Based on Diamond (2016), we suggest that one possible reason for the confusion between selection and working memory can be attributed to their many shared functional characteristics. Another direction which should be further explored is anatomical. Whereas we focused on the lateral OFC (lateral BA 11), the ventrolateral PFC does also include BA 47. Studies stressing the role of the lateral OFC have not differentiated between these two areas, which may end up having different yet related functions. Future research should continue to examine the processes and neuroanatomical correlates of this intriguing brain area.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

Author contributions

The present manuscript was written together by OS & OE. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Baddeley, A. D., and Logie, R. H. (2012). "Working memory: the multiple-component model," in *Models of Working Memory*, eds A. Miyake and P. Shah (Cambridge: Cambridge University Press), 28–61. doi: 10.1017/CBO9781139174909.005

Balleine, B. W., and O'Doherty, J. P. (2010). Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology* 35, 48–69. doi: 10.1038/npp.2009.131

Baltz, E. T., Yalcinbas, E. A., Renteria, R., and Gremel, C. M. (2018). Orbital frontal cortex updates state-induced value change for decision-making. *eLife* 7:e35988. doi: 10.7554/eLife.35988

Barbey, A. K., Koenigs, M., and Grafman, J. (2013). Dorsolateral prefrontal contributions to human working memory. *Cortex* 49, 1195–1205. doi: 10.1016/j.cortex.2012.05.022

Baytunca, M. B., de Frederick, B., Bolat, G. U., Kardas, B., Inci, S. B., Ipci, M., et al. (2021). Increased cerebral blood flow in the right anterior cingulate cortex and fronto-orbital cortex during go/no-go task in children with ADHD. *Nord. J. Psychiatry* 75, 224–233. doi: 10.1080/08039488.2020.1864775

Ben Shalom, D. (2009). The medial prefrontal cortex and integration in autism. *Neuroscientist* 15, 589–598. doi: 10.1177/1073858409336371

Ben Shalom, D., and Bonneh, Y. S. (2019). Editorial: the medial prefrontal cortex and integration in ASD and typical cognition. *Front. Hum. Neurosci.* 13:74. doi: 10.3389/fnhum.2019.00074

Buschman, T. J., Miller, E. K., and Miller, E. K. (2014). Goal-direction and top-down control. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 369:20130471. doi: 10.1098/rstb.2013.0471

Chai, W. J., Abd Hamid, A. I., and Abdullah, J. M. (2018). Working memory from the psychological and neurosciences perspectives: a review. *Front. Psychol.* 9, 1–16. doi: 10.3389/fpsyg.2018.00401

Cubillo, A., Halari, R., Smith, A., Taylor, E., and Rubia, K. (2012). A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with attention deficit hyperactivity disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. *Cortex* 48, 194–215. doi: 10.1016/j.cortex.2011.04.007

Diamond, A. (2005). Attention deficit disorder (attention/hyperactivity deficit disorder without the hyperactivity). *Dev. Psychopathol.* 17, 807–825. doi: 10.1017/S0954579405050388

Diamond, A. (2016). "Why improving and assessing executive functions early in life is critical," in *Executive Function in Preschool-age Children: Integrating Measurement, Neurodevelopment, and Translational Research*, eds J. A. Griffin, P. McCardle, and L. S. Freund (American Psychological Association), 11–43. Available online at: http://www.jstor.org/stable/j.ctv1chs6kz.5

Elisa, R. N., Balaguer-Ballester, E., and Parris, B. A. (2016). Inattention, working memory and goal neglect in a community sample. *Front. Psychol.* 7:1428. doi: 10.3389/fpsyg.2016.01428

Friedman, N., and Miyake, A. (2017). Unity and diversity of executive functions. *Cortex* 86, 186–204. doi: 10.1016/j.cortex.2016.04.023

Gremel, C. M., and Costa, R. M. (2013). Orbitofrontal and striatal circuits dynamically encode the shift between goal-directed and habitual actions. *Nat. Commun.* 4:2264. doi: 10.1038/ncomms3264

Kennerley, S. W., and Wallis, J. D. (2009). Reward-dependent modulation of working memory in lateral prefrontal cortex. *J. Neurosci.* 29, 3259–3270. doi: 10.1523/JNEUROSCI.5353-08.2009

Knudsen, E. B., and Wallis, J. D. (2020). Closed-loop theta stimulation in the orbitofrontal cortex prevents reward-based learning. *Neuron* 106, 537–547. doi: 10.1016/j.neuron.2020.02.003

Koechlin, E., and Summerfield, C. (2007). An information theoretical approach to prefrontal executive function. *Trends Cogn. Sci.* 11, 229–235. doi: 10.1016/j.tics.2007.04.005

Lukito, S., Norman, L., Carlisi, C., Radua, J., Hart, H., Simonoff, E., et al. (2020). Comparative meta-analyses of brain structural and functional abnormalities during cognitive control in attention-deficit/hyperactivity disorder and autism spectrum disorder. *Psychol. Med.* 50, 894–919. doi: 10.1017/S0033291720000574

Malvaez, M., Shieh, C., Murphy, M. D., Greenfield, V. Y., and Wassum, K. M. (2019). Distinct cortical-amygdala projections drive reward value encoding and retrieval. *Nat. Neurosci.* 22, 762–769. doi: 10.1038/s41593-019-0374-7

Nelson, J. M., James, T. D., Chevalier, N., Clark, C. A. C., and Espy, K. A. (2015). "Structure, measurement and development of preschool executive function," in *Executive Function in Preschool-Age Children: Integrating Measurement, Neurodevelopment and Translational Research*, eds J. A. Griffin, P. McCardle and L. S. Freund (American Psychological Association), 65–89.

Norman, L. J., Carlisi, C., Lukito, S., Hart, H., Mataix-Cols, D., Radua, J., et al. (2016). Structural and functional brain abnormalities in attention-deficit/hyperactivity disorder and obsessive-compulsive disorder: a comparative meta-analysis. *JAMA Psychiatry* 73, 815–825. doi: 10.1001/jamapsychiatry.2016.0700

O'Reilly, R. C., and Frank, M. J. (2006). Making working memory work: a computational model of learning in the prefrontal cortex and basal ganglia. *Neural Comput.* 18, 283–328. doi: 10.1186/s12951-023-01765-x

Orinstein, A. J., and Stevens, M. C. (2014). Brain activity in predominantly-inattentive subtype attention-deficit/hyperactivity disorder during an auditory oddball attention task. *Psychiatry Res.* 223, 121–128. doi: 10.1016/j.pscychresns.2014.05.012

Postle, B. R. (2006). Working memory as an emergent property of the mind and brain. *Neuroscience* 139, 23–38. doi: 10.1016/j.neuroscience.2005.06.005

Rich, E. L., and Wallis, J. D. (2016). Decoding subjective decisions from orbitofrontal cortex. *Nat. Neurosci.* 19, 973–980. doi: 10.1038/nn.4320

Rolls, E. T., Cheng, W., and Feng, J. (2020). The orbitofrontal cortex: reward, emotion and depression. *Brain Commun.* 2:fcaa196. doi: 10.1093/braincomms/fcaa196

Ronel, Z. (2018). The lateral prefrontal cortex and selection/inhibition in ADHD. *Front. Hum. Neurosci.* 12:65. doi: 10.3389/fnhum.2018.00065

Sadacca, B. F., Wied, H. M., Lopatina, N., Saini, G. K., Nemirovsky, D., and Schoenbaum, G. (2018). Orbitofrontal neurons signal sensory associations underlying model-based inference in a sensory preconditioning task. *eLife* 7:e30373. doi: 10.7554/eLife.30373

Sescousse, G., Redouté, J., and Dreher, J. C. (2010). The architecture of reward value coding in the human orbitofrontal cortex. *J. Neurosci.* 30, 13095–13104. doi: 10.1523/JNEUROSCI.3501-10.2010

Stayte, S., Dhungana, A., Vissel, B., and Bradfield, L. A. (2021). Parafascicular thalamic and orbitofrontal cortical inputs to striatum represent states for goal-directed action selection. *Front. Behav. Neurosci.* 15:655029. doi: 10.3389/fnbeh.2021.655029

Tang, H., Yu, H. Y., Chou, C. C., Crone, N. E., Madsen, J. R., Anderson, W. S., et al. (2016). Cascade of neural processing orchestrates cognitive control in human frontal cortex. *eLife* 5:e12352. doi: 10.7554/eLife.12352

Tripathi, A., Sato, S. S., and Medini, P. (2021). Cortico-cortical connectivity behind acoustic information transfer to mouse orbitofrontal cortex is sensitive to neuromodulation and displays local sensory gating: relevance in disorders with auditory hallucinations? *J. Psychiatry Neurosci.* 46, E371–E387. doi: 10.1503/jpn.200131

Wallis, J. D. (2019). "Chapter 15 - Reward," in *Handbook of Clinical Neurology*, Vol. 163, eds M. D'Esposito and J. H. Grafman (Elsevier), 281–294. doi: 10.1016/B978-0-12-804281-6.00015-X

Ward, J. (2020). *The Student's Guide to Cognitive Neuroscience*, 4th Edn. London and New York: Routledge.

Wischnewski, M., Mantell, K. E., and Opitz, A. (2021). Identifying regions in prefrontal cortex related to working memory improvement: a novel meta-analytic method using electric field modeling. *Neurosci. Biobehav. Rev.* 130, 147–161. doi: 10.1016/j.neubiorev.2021.08.017

Xie, C., Jia, T., Rolls, E. T., Robbins, T., Sahakian, B. J., Zhang, J., et al. (2021). Reward versus nonreward sensitivity of the medial versus lateral orbitofrontal cortex relates to the severity of depressive symptoms. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 6, 259–269. doi: 10.1016/j.bpsc.2020.08.017

Zang, Y. F., Yong, H., Chao-Zhe, Z., Qing-Jiu, C., Man-Qiu, S., Meng, L., et al. (2007). Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev.* 29, 83–91. doi: 10.1016/j.braindev.2006.07.002

Zsuga, J., Biro, K., Tajti, G., Szilasi, M. E., Papp, C., Juhasz, B., et al. (2016). "Proactive" use of cue-context congruence for building reinforcement learning's reward function. *BMC Neurosci.* 17:70. doi: 10.1186/s12868-016-0302-7

frontiers | Frontiers in Behavioral Neuroscience

TYPE Opinion
PUBLISHED 05 May 2023
DOI 10.3389/fnbeh.2023.1105168

OPEN ACCESS

EDITED BY
Yoram S. Bonneh,
Bar-Ilan University, Israel

REVIEWED BY
Moti Salti,
Ben-Gurion University of the Negev, Israel

*CORRESPONDENCE
Yifat Faran
✉ yfi@post.bgu.ac.il

RECEIVED 23 November 2022
ACCEPTED 07 April 2023
PUBLISHED 05 May 2023

CITATION
Faran Y (2023) A comment on the connection between BA10 and episodic memory. *Front. Behav. Neurosci.* 17:1105168. doi: 10.3389/fnbeh.2023.1105168

A comment on the connection between BA10 and episodic memory

Yifat Faran*

School of Social Work, Ashkelon College, Ashkelon, Israel

KEYWORDS

Brodmann area 10, episodic memory, posterior hippocampus, knowledge integration, retrieval

Introduction

This article is a commentary on the role of BA10 in episodic memory, as predicted by Ben Shalom and Bonneh's (2019) model of the narrow prefrontal cortex. It aimed to explore whether there is any existing literature on memory that supports a connection between BA10 and episodic memory, and if so, what form this connection might take.

Historical context

Many studies have emphasized the crucial role of the frontal lobes in episodic memory (e.g., Piolino et al., 2007; Coste et al., 2015; for a review, see Vakil, 2023). Based on lesion studies, Stuss and Alexander (2005) suggested that the frontal lobes are involved in multiple strategic processes. Similarly, Moscovitch (1992) suggested that the frontal lobes support the memory system by applying top-down processes, such as the implementation of strategy, organization, and conceptual elaborative encoding and retrieval. However, as Stuss and Alexander contended, the frontal lobe is not a homogenous structure and has to be considered in view of its component parts. The most efficient subdivision is based on histology and is defined by Brodmann areas. This article focused on the prefrontal pole, known as Brodmann area 10 (BA10). Studies have shown the involvement of BA10 in many cognitive tasks, including prospective memory (Burgess et al., 2007; Raskin et al., 2018), planning (Volle et al., 2011), analogy solving (Qiu et al., 2008), multitasking (Gilbert et al., 2007; Roca et al., 2011), and more (for a review, see Snow, 2016).

The current article examined the involvement of BA10 in episodic memory, specifically, the predictions made by Ben Shalom and Bonneh (2019) (i.e., that BA10 is involved in the integration of memory episodes) and by Ben Shalom (2009) (i.e., that medial BA10 is involved in the representation of memory episodes themselves).

On the anatomical level, BA10 shows anatomical connections with brain structures involved in episodic memory. Moayedi et al. (2015) found that BA10 can be divided into two sub-regions: the medial cluster and bilateral lateral clusters. The medial cluster is functionally connected to the bilateral and medial PFC, bilateral precuneus/posterior cingulate cortex, ipsilateral lateral occipital cortex, bilateral parahippocampal gyri, bilateral subgenual cingulate cortex, and bilateral middle temporal gyrus, which are mostly associated with the default mode network (DMN; e.g., Buckner and Krienen, 2013; Mak et al., 2017). The bilateral lateral clusters are connected to the bilateral supplementary motor area, ventrolateral premotor cortex, lateral parietal area, dorsolateral prefrontal cortex, and bilateral anterior insula, which are mostly associated with the central-executive network (CEN; Li et al., 2021). BA10 also shows functional connectivity during memory tasks. For instance, Fritch et al. (2021) found that BA10 was functionally connected to the posterior hippocampus, associated with retrieval, but not with the anterior hippocampus, associated with encoding. This functional connectivity was found during retrieval but not during encoding.

On the functional level, a growing body of substantial evidence supports the involvement of BA10 in episodic memory. Numerous studies have demonstrated the involvement of BA10 in episodic retrieval and, to a lesser extent, in episodic encoding. For example, Lepage et al. (2000) reviewed imaging studies that focused on episodic memory retrieval and found that many of them showed activation in BA10 (e.g., Schacter et al., 1996; Rugg et al., 1998). Since then, a growing body of evidence has supported the role of BA10 in the retrieval of episodic memory, and retrieval efforts. However, studies that focus on encoding found less activation in this region. For instance, Fletcher and Henson (2001) reviewed studies that used imaging to test brain activation during both encoding and retrieval and found that, while only 2 out of 23 studies showed activation in BA10 during encoding, 15 out of 25 studies showed activation in BA10 during retrieval. This region has therefore been labeled as part of the retrieval success network. In a review of research that tested activation in response to repetition, Kim (2017) found that BA10, as part of the retrieval success network, indeed showed increased activation due to repetition.

Similarly, Weymar et al. (2018) reported that repetition enhancement was found in the medial posterior parietal (precuneus/cuneus), lateral parietal cortex (angular gyrus), and left BA10. However, some findings were less consistent with the idea that BA10 is involved in the integration of memory episodes. For example, King et al. (2005) showed that increasing the diversity between the contexts of the events, such as giving each item a different context to make them more distinct, reduced the activation in BA10.

A recent synthesis

Two questions can thus be asked regarding the connection between BA10 and episodic memory. The first question pertains to why BA10 is more active during retrieval than encoding. The second question concerns the nature of the actual connection between BA10 and episodic memory.

Some answers to both questions might lie in a recent study by Bonasia et al. (2018). In this article, the authors tested brain activation during the encoding and retrieval of video clips. Participants saw video clips that were either similar to events people encounter in everyday life, that is, congruent video clips, or video clips that were very unusual and/or dissimilar to anything people encounter in day-to-day life, that is, incongruent video clips. In addition, the authors also used neutral video clips that were neither very similar nor dissimilar to everyday life. As expected, the participants recalled both congruent and incongruent video clips better than neutral ones, indicating that both congruency and incongruity can enhance memory. However, brain activation in medial BA10 during encoding and retrieval was modulated by congruency alone. In a parametric analysis, during encoding, medial BA10 was more activated with increasing congruency. It also showed more functional connectivity during encoding with increasing congruency. Importantly, during retrieval, medial BA10 also showed increased functional connectivity with the increasing congruence of the retrieved material. These findings are consistent with those of other studies that showed increased activation of BA10 during repetition (Kim, 2017; Weymar et al., 2018) and reduced activation when the context between encoding and retrieval was changed (King et al., 2005).

It thus appears that the answer to the first question, i.e., why is BA10 activated more during retrieval than during encoding?, might lie in the fact that studied items are rarely considered in terms of their level of congruency, rather, they are more commonly compared between retrieval and encoding. Thus, when the relevant factor is not the level of congruency but retrieval vs. encoding, retrieved items, which have already been encountered, are, on average, more congruent with prior context than encoded items, resulting in additional BA10 activation. In addition, regarding the second question, what does this synthesis mean for the connection between BA10 and episodic memory? According to Bonasia et al. (2018), the medial BA10 detects congruence between current experiences and prior knowledge before activating relevant prior knowledge to facilitate comprehension and enhance the integration of new event-specific information with prior knowledge.

Discussion

As noted by Bonasia et al. (2018), their synthesis is consistent with Van Kesteren et al.'s (2012) SLIMM model (schema-linked interactions between medial prefrontal and medial temporal regions), according to which event congruence would affect activity and connectivity across the brain during both encoding and retrieval: increased congruence between events and prior knowledge correlating with activity in the medial prefrontal cortex, and increased incongruence between events and prior knowledge correlating with activity in the medial temporal lobe.

More importantly, the connection between BA10 and episodic memory indicates that incoming memory episodes are not represented in medial BA10. Instead, what is represented in medial BA10 is prior knowledge that, when activated, helps the integration of incoming episodes into prior knowledge. Thus, while there is indeed a connection between BA10 and episodic memory, as the Ben Shalom and Bonneh (2019) model predicted, it is not as straightforward as incoming memory episodes represented in medial BA10.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Ben Shalom, D. (2009). The medial prefrontal cortex and integration in autism. *Neuroscientist* 15, 589–598. doi: 10.1177/1073858409336371

Ben Shalom, D., and Bonneh, Y. S. (2019). The medial prefrontal cortex and integration in ASD and typical cognition. *Front. Hum. Neurosci.* 13, 74. doi: 10.3389/fnhum.2019.00074

Bonasia, K., Sekeres, M. J., Gilboa, A., Grady, C. L., Winocur, G., and Moscovitch, M. (2018). Prior knowledge modulates the neural substrates of encoding and retrieving naturalistic events at short and long delays. *Neurobiol. Learn. Mem.* 153, 26–39. doi: 10.1016/j.nlm.2018.02.017

Buckner, R. L., and Krienen, F. M. (2013). The evolution of distributed association networks in the human brain. *Trends Cogn. Sci.* 17, 648–665. doi: 10.1016/j.tics.2013.09.017

Burgess, P. W., Dumontheil, I., Gilbert, S. J., Okuda, J., Schölvinck, M. L., and Simons, J. S. (2007). "On the role of rostral prefrontal cortex (area 10) in prospective memory", in *Prospective Memory: Cognitive, Neuroscience, Developmental, and Applied Perspectives*, eds M. Kliegel, M. A. McDaniel, and G. O. Einstein (Mahwah: Erlbaum).

Coste, C., Navarro, B., Vallat-Azouvi, C., Brami, M., Azouvi, P., and Piolino, P. (2015). Disruption of temporally extended self-memory system following traumatic brain injury. *Neuropsychologia* 71, 133–145. doi: 10.1016/j.neuropsychologia.2015.03.014

Fletcher, P. C., and Henson, R. N. A. (2001). Frontal lobes and human memory: insights from functional neuroimaging. *Brain* 124, 849–881. doi: 10.1093/brain/124.5.849

Fritch, H. A., Spets, D. S., and Slotnick, S. D. (2021). Functional connectivity with the anterior and posterior hippocampus during spatial memory. *Hippocampus* 31, 658–668. doi: 10.1002/hipo.23283

Gilbert, S. J., Williamson, I. D., Dumontheil, I., Simons, J. S., Frith, C. D., and Burgess, P. W. (2007). Distinct regions of medial rostral prefrontal cortex supporting social and nonsocial functions. *Soc. Cogn. Affect. Neurosci.* 2, 217–226. doi: 10.1093/scan/nsm014

Kim, H. (2017). Brain regions that show repetition suppression and enhancement: a meta-analysis of 137 neuroimaging experiments. *Hum. Brain Mapp.* 38, 1894–1913. doi: 10.1002/hbm.23492

King, J. A., Hartley, T., Spiers, H. J., Maguire, E. A., and Burgess, N. (2005). Anterior prefrontal involvement in episodic retrieval reflects contextual interference. *Neuroimage* 28, 256–267. doi: 10.1016/j.neuroimage.2005.05.057

Lepage, M., Ghaffar, O., Nyberg, L., and Tulving, E. (2000). Prefrontal cortex and episodic memory retrieval mode. *Proc. Natl. Acad. Sci.* 97, 506–511. doi: 10.1073/pnas.97.1.506

Li, J., Liu, J., Zhong, Y., Wang, H., Yan, B., Zheng, K., et al. (2021). Causal interactions between the default mode network and central executive network in patients with major depression. *Neuroscience* 475, 93–102. doi: 10.1016/j.neuroscience.2021.08.033

Mak, L. E., Minuzzi, L., MacQueen, G., Hall, G., Kennedy, S. H., and Milev, R. (2017). The default mode network in healthy individuals: a systematic review and meta-analysis. *Brain Connect.* 7, 25–33. doi: 10.1089/brain.2016.0438

Moayedi, M., Salomons, T. V., Dunlop, K. A., Downar, J., and Davis, K. D. (2015). Connectivity-based parcellation of the human frontal polar cortex. *Brain Struct. Funct.* 220, 2603–2616. doi: 10.1007/s00429-014-0809-6

Moscovitch, M. (1992). Memory and working-with-memory: a component process model based on modules and central systems. *J. Cogn. Neurosci.* 4, 257–267. doi: 10.1162/jocn.1992.4.3.257

Piolino, P., Desgranges, B., Manning, L., North, P., Jokic, C., and Eustache, F. (2007). Autobiographical memory, the sense of recollection and executive functions after severe traumatic brain injury. *Cortex* 43, 176–195. doi: 10.1016/S0010-9452(08)70474-X

Qiu, J., Li, H., Chen, A., and Zhang, Q. (2008). The neural basis of analogical reasoning: An event-related potential study. *Neuropsychologia* 46, 3006–3013. doi: 10.1016/j.neuropsychologia.2008.06.008

Raskin, S. A., Williams, J., and Aiken, E. M. (2018). A review of prospective memory in individuals with acquired brain injury. *Clin. Neuropsychol.* 32, 891–921. doi: 10.1080/13854046.2018.1455898

Roca, M., Torralva, T., Gleichgerrcht, E., Woolgar, A., Thompson, R., Duncan, J., et al. (2011). The role of Area 10 (BA10) in human multitasking and in social cognition: a lesion study. *Neuropsychologia* 49, 3525–3531. doi: 10.1016/j.neuropsychologia.2011.09.003

Rugg, M. D., Fletcher, P. C., Allan, K., Frith, C. D., Frackowiak, R. S. J., and Dolan, R. J. (1998). Neural correlates of memory retrieval during recognition memory and cued recall. *Neuroimage* 8, 262–273. doi: 10.1006/nimg.1998.0363

Schacter, D. L., Alpert, N. M., Savage, C. R., Rauch, S. L., and Albert, M. S. (1996). Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. *Proc. Natl. Acad. Sci.* 93, 321–325. doi: 10.1073/pnas.93.1.321

Snow, P. J. (2016). The structural and functional organization of cognition. *Front. Hum. Neurosci.* 10, 501. doi: 10.3389/fnhum.2016.00501

Stuss, D. T., and Alexander, M. P. (2005). Does damage to the frontal lobes produce impairment in memory? *Curr. Direct. Psychol. Sci.* 14, 84–88. doi: 10.1111/j.0963-7214.2005.00340.x

Vakil, E. (2023). "The mnemonic consequences of moderate-to-severe traumatic brain injury," in *Handbook of Human Memory*, eds M. Kahana and A. Wagner (Oxford: Oxford University Press).

Van Kesteren, M. T., Ruiter, D. J., Fernández, G., and Henson, R. N. (2012). How schema and novelty augment memory formation. *Trends Neurosci.* 35, 211–219. doi: 10.1016/j.tins.2012.02.001

Volle, E., Gonen-Yaacovi, G., de Lacy Costello, A., Gilbert, S. J., and Burgess, P. W. (2011). The role of rostral prefrontal cortex in prospective memory: a voxel-based lesion study. *Neuropsychologia* 49, 2185–2198. doi: 10.1016/j.neuropsychologia.2011.02.045

Weymar, M., Bradley, M. M., Sege, C. T., and Lang, P. J. (2018). Neural activation and memory for natural scenes: Explicit and spontaneous retrieval. *Psychophysiology* 55, e13197. doi: 10.1111/psyp.13197

frontiers | Frontiers in Psychiatry

TYPE Review
PUBLISHED 20 June 2023
DOI 10.3389/fpsyt.2023.1205199

OPEN ACCESS

EDITED BY
Lei Xu,
Sichuan Normal University, China

REVIEWED BY
Xiaoxiao Zheng,
Chinese Academy of Sciences, China
Juan Kou,
Sichuan Normal University, China

*CORRESPONDENCE
Alok Nath Mohapatra
✉ thinkalok@gmail.com

RECEIVED 16 April 2023
ACCEPTED 26 May 2023
PUBLISHED 20 June 2023

CITATION
Mohapatra AN and Wagner S (2023) The role of the prefrontal cortex in social interactions of animal models and the implications for autism spectrum disorder.
Front. Psychiatry 14:1205199.
doi: 10.3389/fpsyt.2023.1205199

The role of the prefrontal cortex in social interactions of animal models and the implications for autism spectrum disorder

Alok Nath Mohapatra* and Shlomo Wagner

Sagol Department of Neurobiology, Faculty of Natural Sciences, University of Haifa, Haifa, Israel

Social interaction is a complex behavior which requires the individual to integrate various internal processes, such as social motivation, social recognition, salience, reward, and emotional state, as well as external cues informing the individual of others' behavior, emotional state and social rank. This complex phenotype is susceptible to disruption in humans affected by neurodevelopmental and psychiatric disorders, including autism spectrum disorder (ASD). Multiple pieces of convergent evidence collected from studies of humans and rodents suggest that the prefrontal cortex (PFC) plays a pivotal role in social interactions, serving as a hub for motivation, affiliation, empathy, and social hierarchy. Indeed, disruption of the PFC circuitry results in social behavior deficits symptomatic of ASD. Here, we review this evidence and describe various ethologically relevant social behavior tasks which could be employed with rodent models to study the role of the PFC in social interactions. We also discuss the evidence linking the PFC to pathologies associated with ASD. Finally, we address specific questions regarding mechanisms employed by the PFC circuitry that may result in atypical social interactions in rodent models, which future studies should address.

KEYWORDS

autism, prefrontal cortex, rodent models, social interaction, social behavior

Introduction

The prefrontal cortex (PFC) is critical for various aspects of mammalian social behavior, including social motivation, recognition, and decision-making (1–3). In humans, the medial PFC (mPFC) is involved in high-order aspects of social interaction, such as self-referential processing, mentalizing, and emotional regulation (4–6). At the same time, deficits in PFC function have been implicated in various neuropsychiatric disorders, including autism spectrum disorder (ASD). Individuals with ASD exhibit atypical social behavior and deficits in social cognition, such as an impaired theory of mind and a lack of social interest (7, 8). Neuroimaging studies have revealed altered PFC activity in individuals with ASD during social tasks (9, 10). As such, understanding the molecular, cellular, and network mechanisms underlying the role of the PFC in social behavior and its dysfunction in ASD may be critical for developing effective treatments for individuals diagnosed with this disorder.

Research using animal models has provided significant insight into the neural circuitry underlying social behavior, including the role of the PFC in social interactions (11–14). Anatomically, the PFC is a complex brain structure with multiple sub-regions, each with a distinct function and connectivity pattern (15, 16). In rodents, most studies have focused on the mPFC, including the prelimbic and infralimbic regions and their downstream projections to the

striatum (17), amygdala (18), hypothalamus (19), hippocampus (20) and brainstem (21). These sub-regions were shown to be involved in various aspects of social behavior, including social recognition (22), social approach (23), and aggression (24, 25). Moreover, studies have demonstrated that rodents exhibit complex social behaviors, including social hierarchy (26), empathy (27), and territoriality (28), making them a valuable model for studying the biological mechanisms underlying mammalian social behavior. Accordingly, multiple behavioral tasks have been developed to assess rodent social behavior and the role of the PFC therein, including the three-chamber, social recognition, social habitation/dishabituation, and resident-intruder tests (29–32). Such studies have shown that mPFC lesions or manipulations can lead to deficits in social behavior in rodents (33, 34).

Here, we provide an overview of the role of the PFC in the social behavior of animal models and the implications for understanding possible mechanisms underlying social deficits in ASD. The review discusses anatomical and functional homologies of the PFC in rodents and humans, and its role in various aspects of social interactions. Additionally, current literature on PFC involvement in social behavior deficits that lead to ASD symptoms is highlighted.

Social interactions involve social motivation, recognition, and decision-making

Social interactions involve complex information-processing tasks that can broadly be defined as detecting and interpreting social cues and responding appropriately to evolving social contexts (3). By nature, social interactions are multi-faceted and require the integration of external multi-modal sensory information with internal processes. Here, we aim to focus on the following aspects of the process: (1) the motivation for social interaction, which is an internal process; (2) emotional/empathic reactions in response to social cues; and (3) group dynamics, which involve mutual relationship between the subject and others (4, 35–37). These aspects are not mutually exclusive (38) and together affect behavioral decisions. This is exemplified by going out to dinner at a restaurant. This involves interactions with the staff, the degree to which heavily relies on the internal motivation of the subject to interact. The subject's satisfaction with the food and the staff performance, as well as the subject's perception of their emotions. Will lead the subject to either compliment or complain about the staff. Moreover, verbal and emotional communication between the dining partners during dinner will depend on whether the environment is friendly or professional. Thus, social motivation, emotional perception of self and others, group dynamics, and the social context all integrate to determine social behavior.

Social motivation, or the willingness to pursue social interactions, is a fundamental aspect of the decision-making process in a social context. Such motivation and subsequent rewarding experiences require the subject to approach social partners and engage them (35). Accordingly, approaching a conspecific is a highly conserved phenotype in multiple species (38, 39). This aspect of social behavior and cognition emerges early in development, with young infants tending to recognize and initiate interactions with their parents (40, 41). Infants must thus recognize familiar faces for proper decision-making in their social contexts from a very early age (42, 43). Hence, social motivation serves as the developmental and evolutionary foundation for complex social behaviors.

The ability to interpret others' intentions and mental states heavily governs social interactions in any social context. Emotional comprehension, like evaluating social motivation, recognizing body language and facial cues, as well as interpreting implicit and explicit biases of others, are essential to any social interaction. This social cognition process, termed "theory of mind" (44, 45), heavily influences individual social decision-making (46).

Social interactions require effective group dynamics, allowing individuals to develop healthy and essential group relationships (47). Hierarchical, territorial, cooperative, and interdependent social behavior are observed in multiple species. Studies have highlighted the role of social hierarchy in individual well-being, leading to better availability of resources essential to survival, such as food, space, and mating partners (48, 49). Investing in a territorial or hierarchical structure is also an essential decision-making process in which individuals gauge their metabolic energy before involving themselves in conflicts related to group social structure (48). Moreover, the social context of a conflict weighs heavily on an individual's role in the group dynamics, with an effective change in this role relying on a correct decision-making process.

Social decision-making involves multi-faceted processes, Thus, multiple malfunctions can lead to the atypical social behavior characterizing multiple neuropsychiatric disorders, such as autism spectrum disorder (ASD). Impaired recognition of familiar faces or reduced motivation for social interactions have been reported in ASD (7, 50). Indeed, infants lacking social interest are likely to develop social cognition deficits (51), such as the impaired theory of mind (52, 53). Maladaptive social decision-making capabilities are prevalent in ASD and serve as predictors of overall mortality due to the effects of poor interpersonal relationships on mental and physical health (54). Neuroimaging studies subsequently revealed the involvement of many interconnected brain regions during social decision-making (55). Assigning the process to functionally relevant brain entities is critical for explaining their roles in the atypical behaviors exhibited by individuals diagnosed with ASD.

Evidence for the role of the PFC in human social interactions

The PFC has been linked to various aspects of cognition and behavior, such as working memory, decision-making, goal-directed conduct, and social behavior (32, 56, 57). The PFC presents significant yet variable connections to both cortical and sub-cortical areas of the brain, including the hippocampus, amygdala, hypothalamus, and nucleus accumbens, as well as areas associated with sensory-motor functions (18, 58). Many of these areas were shown to be involved in social decision-making (59, 60). Thus, the PFC contributes to all aspects of social interactions, in collaboration with other cortical and sub-cortical regions.

Various regions of the PFC also process distinct aspects of social information (57, 61). Regions that process social motivation play inherent roles in reward, valence, and affiliation and include the orbitofrontal and perigenual anterior cingulate cortices (ventro-medial prefrontal cortex; vmPFC: BA 10,11,12, 25, and 32; orbito-frontal cortex; OFC: BA 10 and 11; and anterior cingulate cortex;

ACC: BA 25 and 32) (61). Multiple studies have reported a role for the vmPFC in social motivation and reward. Humans with vmPFC lesions exhibit impairments in emotional recognition and making moral decisions (62). They also failed to learn from recent reward history in a pro-social game (63). Other studies concluded that the OFC plays a role in decision-making based on the valence of the stimuli (64, 65). Additionally, the vmPFC is active when subjects feel socially accepted and comprehend rewarding social cues (66). Interestingly, specific impairments in the tendency of ASD patients to find social stimuli incentivizing or motivating are similar to those seen in humans with vmPFC lesions (67).

Social interactions that necessitate knowledge of oneself and others are consistently associated with activation within the PFC (specifically, the medial and dorso-medial prefrontal cortex; dmPFC). The mPFC is effectively activated while comprehending self-bias and those of others (in line with the theory of mind), beliefs, moral decisions, and emotional states while empathizing with others' pain and during cooperation [(4, 68);]. Functional magnetic resonance imaging (fMRI) studies showed this region to be active during cooperative tasks among humans, tasks in which ASD patients perform poorly due to lower attention to social cues (69–71). Evidence of decreased activity and connectivity in the mPFC of ASD patients has been reported and are likely to significantly contribute to the social and behavioral deficits presented by these individuals. Studies also demonstrated that ASD patients lack adaptive control in comprehending and adapting their behavior according to an unfair social context or their partner's emotional expressions (72, 73). Moreover, the infant mPFC is responsive to social cues, like a parent's face and gaze (74). Furthermore, in contrast to patients who sustained damage to their mPFC as adults, patients who sustained damage to this region as children demonstrate anti-social behavior and poor moral decision-making in adulthood (62). Together, these studies point to the mPFC as serving a crucial role in the forming of proper social cognition in humans from early development stages.

There have been attempts to define the role of distinct PFC sub-regions in separating internal from external social reasoning. The mPFC has been reported to be involved in tasks that involve processing of internal states of self and others, such as empathy, self-reflection, and vicarious moral reasoning (75–77). In contrast, the lateral PFC (lPFC) is part of a network activated by externally guided information processing in the social domain, such as imitation, abstract social reasoning, and internal conflict resolution (78, 79). In addition to ASD, there is strong evidence that patients with other neuropsychiatric disorders, like schizophrenia (SCZ), display hypo-activity in the dorsal lPFC during social interactions (80, 81). Recent works using transcranial direct current stimulation with SCZ and ASD patients described improved social and emotional behavior (82, 83). Yet, despite the apparent improvement in patient behavior following treatment, there was a lack of mechanistic links and specific definitions of such interventions for comorbidities like depression and anxiety. Thus, the particular sections of the PFC that implicitly and explicitly affect individual emotional comprehension remain elusive, although solid evidence points toward the mPFC and lPFC.

The third aspect of social interaction, group dynamics, combines social motivation and emotional comprehension of the social context. fMRI studies found neural correlates of social hierarchy and group dynamics to occur in the PFC (84, 85), as well as in sub-cortical regions, like the amygdala and ventral striatum, that demarcate distress from rewarding social experiences (86, 87). lPFC bias to the superior as opposed to the inferior player in a monetary reward task was only observed in a social context, i.e., with other players, implying that involvement of the lPFC in processing hierarchical information is specifically social in nature (88, 89). Patients with dorsal and lateral PFC lesions do not understand changes in social hierarchy and fail to learn them (67, 90). Thus, activity in the PFC and sub-cortical regions coordinates proper behavioral responses when the social hierarchy is changing, with such knowledge having to be constantly updated in these regions.

In summary, the PFC and its connections to sub-cortical brain regions regulate and encode various aspects of human social interactions (Figure 1). PFC sub-divisions contribute to social motivation, reward, cooperation, and mentalizing of self and others' socio-emotional states. In the following sections, we compare the above evidence supporting the role for the PFC in human social interactions with what occurs in rodents.

Social interactions in an animal model: practical tools for studying ASD social deficits

Non-human primates (NHPs) present rich social behaviors, such that studies on these models may directly inform on clinical interventions for neuropsychiatric disorders such as ASD. Relevant studies are, however, restricted by small sample size, lack of effective circuit-specific manipulation tools, and the general difficulty and slowness of experimentation. Furthermore, limitations in specific genetic lines that mimic mutations found in ASD patients hinder efforts aimed at mechanistic understanding of modifications in NHP social interactions. At the same time, rodent models represent effective and valuable systems for addressing specific questions regarding biological mechanisms and brain circuits involved in social behavior and their alterations by ASD-associated genetic mutations.

From rodents to primates and humans, social interactions and their underlying neural processes have been remarkably conserved. Nevertheless, the neurobiological mechanisms and brain circuits contributing to rodent social interactions remain elusive and have been only partially explained to date. The following section highlights the anatomical correlates of rodent social interactions that align with the human PFC.

Anatomy of the rodent PFC

Historically, anatomical similarities between the human and rodent PFC gave rise to multiple controversies (91, 93–96). Studies of functional correlates indicated the rodent PFC as being involved in non-social behavior, like working memory (97), impulse control (98), attention, and goal-directed behavior (99, 100). The rodent prelimbic cortex (Figure 1) seems homologous to human BA 32 that is part of the dorsal and ventral PFC, including the lateral PFC (96, 101). At the same time, the rodent infralimbic cortex is considered to be homologous to BA 25, a part of the ventromedial PFC in humans. The rodent medial OFC and ACC share homologies with the human OFC and dorsomedial PFC, respectively. The granular cortical structure of the rodent PFC does not entirely match its human

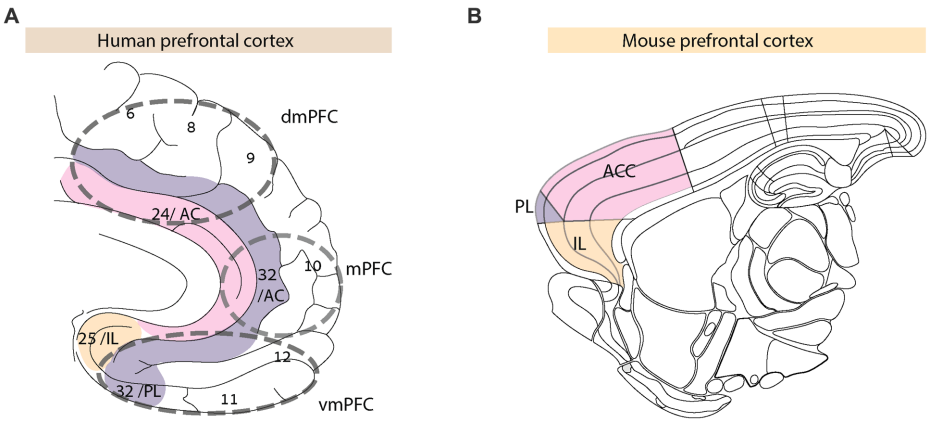


FIGURE 1
Anatomy of prefrontal cortex in human and mouse the human prefrontal cortex **(A)** includes Broca areas (BA) 6, 8, 9, and 24 (comprising the anterior cingulate, AC), 10, 11, 12, 25, and 32. The colored regions define PFC sub-divisions in humans and the corresponding homologous regions in mice (91–93) **(B)**.

counterpart [see (93) for detailed comparisons]. Unlike the human PFC, the rodent PFC receives and projects extensively to other cortical and sub-cortical brain regions, specifically, limbic and midline thalamic regions that densely innervate the PFC.

Previous efforts indicated the existence of a dichotomy between sub-regions of the rodent PFC in processing social interactions (102, 103). Because of this, it is crucial to employ behavioral paradigms that are ethologically appropriate and take advantage of typical rodent actions that are involved in social interactions. In the following section, we discuss how the rodent PFC regulates social interactions in ethologically relevant tasks of social behavior and how specific pre-clinical models of ASD may highlight the role of the PFC in such pathologies. We also review the extensive literature on rodent PFC involvement in numerous social behavior tasks by concentrating on three distinct aspects of social interactions and on studies that specifically explore these aspects.

The role of the PFC in rodent social interactions

Multiple tasks have been developed to gauge rodent social motivation (31). It should be noted that the parameters quantified in these tasks, such as the time spent near social stimuli, reflect traits that are vastly different from those humans employ during social interactions (104, 105). Furthermore, rodents predominantly utilize the olfactory sensory system during social interactions (106), in contrast to predominant dependence of human social interactions on visual and auditory cues (107).

Tasks that assess social motivation and recognition

Multiple tasks have been developed to assess the recognition of conspecifics (social recognition) and the motivation to orient and approach them (see (32) for a detailed list of behavior tasks used to test rodents). The earliest social recognition task, the social habituation/dishabituation test, relied on a series of encounters with the same conspecific (social stimulus) and finally, with an unfamiliar one (108). Such assays reveal that in general, subjects gradually lose the motivation to interact when encountering the same (familiar) social stimulus in subsequent trials (the habituation phase), indicative of recognition of the familiar stimulus. A subject's interaction time returns to the level of the first trial when exposed to an unfamiliar stimulus (dishabituation), thus controlling for changes in general social motivation. This task effectively reports on short-term and long-term memory in rodents, despite exposing confounds of internal state and novelty that cannot be controlled (109).

Social discrimination tasks were devised to probe the motivation to interact with specific stimuli while using appropriate controls that account for the novelty of a stimulus. For example, the social novelty preference task considers the time spent investigating (i.e., sniffing) a novel stimulus as opposed to a familiar cage-mate or a recently encountered conspecific to control for aggression due to male pheromones and general social motivation (110). These discrimination tasks provide information on different behavioral dynamics (111), which cannot be analyzed in the habituation/dishabituation task. Another variation of social recognition task specifically designed for a monogamous species of voles is the partner preference test. These monogamous rodents preferably interact with their partner after pair-bonding, relative to a stranger (112).

Tasks that test affective/emotional behavior

Some of the earliest proof of emotional cognition appears in works where rats (i.e., observers), trained to receive food rewards in lever press tasks, reduced the amount of lever pressing as they observed another rat (i.e., a demonstrator) being exposed to foot shocks. The study reflected the transmission of emotional state between observer and demonstrator rats (113). Similarly, mice and rats demonstrated the social transmission of pain and analgesia (114, 115), fear (116, 117) (Figure 2A), and food preference (118).

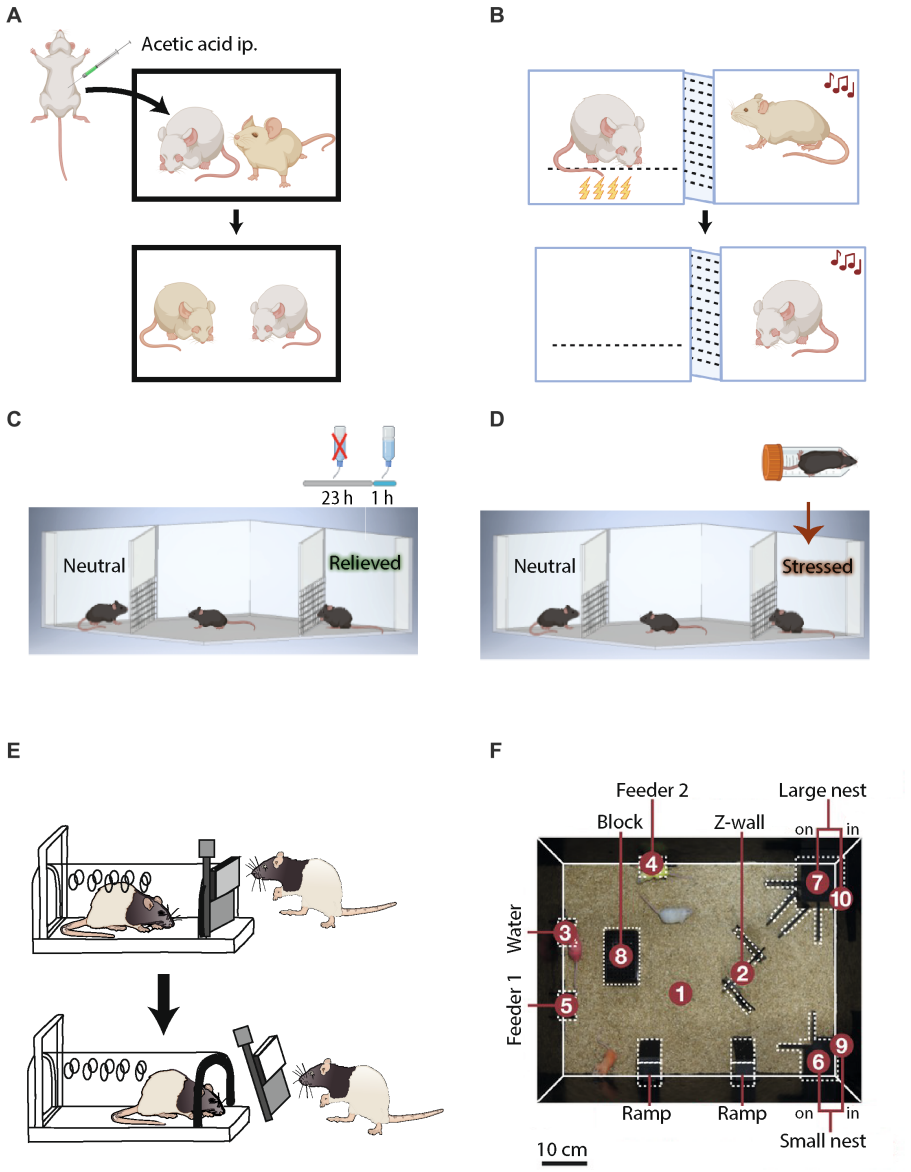


FIGURE 2
Tasks to test affective emotional, empathic and group dynamics in rodents. **(A)** Social transfer of fear in a rodent observing a demonstrator in pain due to acetic acid injection. **(B)** Social transfer of fear in a rodent observing a demonstrator experiencing foot-shock-induced pain. **(C)** Affective emotional state preference of conspecifics experiencing positive emotions, such as relief from thirst or **(D)** negative emotions, such as stress due to being restrained for a while, over neutral conspecifics. **(E)** Pro-social empathic behavior of rats freeing a captive conspecific. **(F)** Semi-natural social box for studying rodent group dynamics.

Several tasks indicate that rodents display emotions, specifically fear, and thus enable social transmission of emotional information. Rodents, moreover, respond to emotional states of other individuals. In transfer learning procedures, such as fear conditioning by proxy, a rat exposed to a novel tone while in the presence of a cage-mate who was previously fear-conditioned to that tone will freeze (119) (Figure 2B). In another procedure, known as social harm aversion, rats avoid a specific task (like lever pressing) if it causes harm to others (120). This behavior is affected by the outcome. For instance, positive outcome behavior occurs more often than does a decrease in negative outcome-related behavior (121).

Recent studies have tested the capability of rodents to recognize and discriminate emotional states of conspecifics (122). In the positive mode of a relevant task, which uses the setup of social discrimination tasks, one of two presented social stimuli is associated with deprivation of water in the home cage for the preceding 23 h and a quenching of thirst for an hour before the experiment. This manipulation of water availability in the home cage induces a "relieved" state in the social stimulus, drawing more attention from the subject than a control stimulus, which remains in neutral conditions (Figure 2C). On the other hand, the negative mode of this test probes discrimination of a negative emotional state, induced in a social stimulus by foot shocks or a short period in a restrainer, as compared to a neutral stimulus. In

both positive and negative conditions, the subject mouse prefers interacting more with the arousing stimuli.

Tasks that test empathic behavior

An behavioral task in which rats persistently try to free a captive conspecific, despite the temptation to instead consume a highly palatable food presented in the same arena, demonstrates empathy in these animals (123) (Figure 2D). Food-sharing tasks also reveal rats to be pro-social and empathic toward cage-mates. For example, Norway rats shared more palatable food with a partner who provided them with a piece of banana than with a partner who provided a less preferred piece of carrot (124). Rats also displayed pro-social behavior by providing food rewards to their cage-mates, even when they did not benefit from the decision to share food (125). In a consolation test of monogamous voles that quantifies the amount of allogrooming of a familiar, as compared to a stranger demonstrator, when the demonstrator was exposed to mild foot-shocks as stress, these rodents performed allogrooming of their stressed familiar partners so as to reduce their stress. The test thus differentiates empathic responses of a vicarious nature from general stress-coping behavior (126). In summary, these studies open ample avenues to study neural mechanisms of emotional recognition and empathy in rodents.

Tasks that test group dynamics behavior

Social hierarchies emerge in mice when they live in densely populated conditions, where competition for territory, housing, mates, and food plays an essential role in the survival of the individual. Introducing pairs of cage-mates from opposing ends of a tube that does not allow sufficient space for a mouse to turn around or for both mice to pass each other offers one way to measure social dominance (127). Alternatively, semi-natural home cages (Figure 2E) that mimic large mouse colonies have been used to study dominance and hierarchical behavior (128, 129). Affective cooperation and altruistic behavior, investigated in rodents using lever pressing tasks, were shown to be influenced by the hierarchal stature of an animal in the group (130).

What role does the rodent PFC play during social interactions?

Animal models support literature implicating the human PFC in social motivation, in conjunction with sub-cortical areas, such as the nucleus accumbens (NAc) and ventral tegmental area (VTA), which mediate the rewarding aspects of social interaction (131, 132). Although lesion studies have provided evidence for the crucial role of the PFC in social motivation (133, 134), such non-specific manipulation may damage nearby regions and axonal projections around the lesioned areas. Still, a comprehensive study examining murine whole-brain c-Fos expression in a social context revealed that social interaction strongly activates the mouse PFC (135).

PFC circuitry is precisely arranged, presenting an array of interneurons that inhibit circuit activity, as well as neuromodulator inputs that rely on acetylcholine, dopamine and oxytocin. In mice, PFC circuitry is characterized by the canonical flow of excitation between cortical layers (Figure 3A), such as thalamo-recipient pyramidal neurons in layer 3 which send excitatory inputs to layer 2 pyramidal neurons. These layer 2 cells descend in turn to layer 5 pyramidal neurons (136). GABAergic interneurons (i.e., parvalbumin (PV+) and somatostatin (SST+) neurons) strongly control the excitatory drive of long-range and local intercortical-projecting pyramidal neurons in the PFC. These PFC interneurons display remarkable selectivity for connections with pyramidal neurons. In superficial layers, the PV+ and SST+ cells preferentially target layer 2 cortico-amygdalar and cortico-striatal pyramidal neurons (137, 138), whereas deeper in the cortex, the interneurons synapse solely with pyramidal neurons that target other pyramidal neurons (136, 139, 140). Many studies of pre-clinical animal models of ASD have reported decreased inhibitory neurotransmission in the PFC (141, 142), leading to low sociability, vocalization, and reciprocal social interactions (143). Excitatory/inhibitory (E/I) balance changes during development are linked to a critical period of plasticity in the PFC (144, 145). Post-mortem studies in ASD patients (146) extensively indicate reduced GABA receptors expression (147–149), increased Glutamatergic receptors expression (150, 151), and a low number of PV+ neurons in prefrontal cortex (152) which could result in the E/I imbalance. ASD patients show decreased gamma oscillation power, indicative of fast-spiking neurons firing at lower rates (153, 154). Studies in ASD patients showed higher numbers of dendritic spines, overall increased within-region connectivity, and a reduction in long-range connections of the PFC (155–157). Moreover, fMRI studies reported hypoactivation of the ACC to social reward in ASD compared to typically developing controls (158, 159), which indicate that these patient process socially rewarding and motivating cues abnormally (160). Therefore, investigating how alterations in the PFC circuitry affect social motivation and behavior may be essential for exposing the underlying mechanism of social deficits seen in ASD (161). Below, we further review the evidence that modified PFC circuitry interferes with social motivation.

Direct intervention in the E/I balance within the PFC circuitry profoundly affects the social motivation of adult mice. In seminal work, researchers optogenetically manipulated the neural activity of specific PFC neuronal populations during reciprocal interaction with juvenile conspecifics and in the three-chamber sociability task (162). Increasing excitatory activity by stimulating pyramidal neurons disrupted social exploration in the unrestricted interaction test and social preference in the three-chamber test. These deficits were brought down by activating inhibitory PV+ interneurons simultaneously with pyramidal cells, emphasizing the crucial role of an appropriate E/I ratio in the PFC for proper social motivation in mice.

Pre-clinical models of E/I balance and its role in social motivation

Multiple synaptic or circuit-level factors establish and tightly regulate neuronal E/I balance (163). The balance between excitatory and inhibitory synapses in the brain is maintained through a complex interplay of several factors. These include the development and functioning of these synapses and the signaling pathways and mechanisms that regulate their plasticity. Homeostatic synaptic

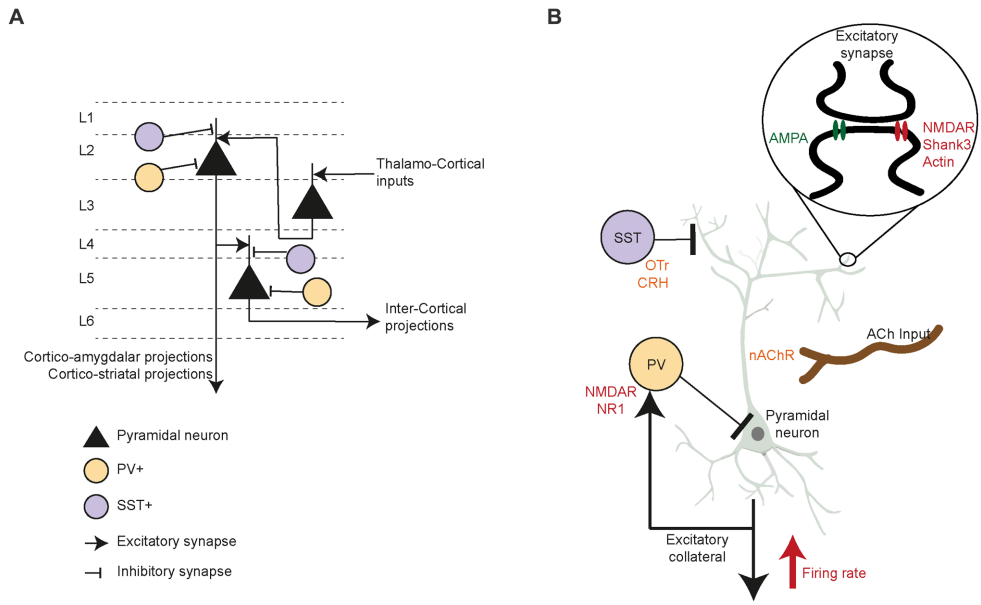


FIGURE 3
Prefrontal circuit's specific components and their role in social interaction. **(A)** PFC circuitry and neuronal cell types driving inter and intra cortical excitatory drive. Specifically, the interneurons PV+ and SST+ inhibitory control over layer 2 (L2) as well as layer 5 (L5) pyramidal neurons. **(B)** Pyramidal neurons firing rate in PFC is modulated by PV+ and SST+ inhibition to the cell body and apical dendrites, respectively. Higher firing rate of the pyramidal neurons correspond to increased social motivation in mice. While the SST+ neurons are reported to be modulated through oxytocin and corticotrophin releasing hormone, specifically during social motivation and novelty preference behavior in rodents. While cholinergic projections into pyramidal neurons regulate social motivation and memory through nicotinic acetylcholine receptors. Further, low NMDA NR1 in PV+ neurons reduce social investigation. Excitatory synapses are specifically affected by structural protein Shank3 deficiency along with disruption actin formation, which cause low social motivation. Similarly, reduced excitatory post-synaptic currents due to low NMDA and AMPA receptors cause significant imbalance in prefrontal circuit E/I imbalance.

plasticity and intrinsic neuronal excitability also play roles in this delicate balance (164). At a higher level, E/I balance is regulated by the activity of different circuits, such as local circuits that involve distinct types of interneurons. These interneurons play a crucial role in regulating the activity of pyramidal neurons and modulating long-range connections (165, 166).

In the context of genetic risk factors for ASD, multiple studies have examined the E/I balance and its disruption in the PFC. Malfunctions of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-D-aspartate (NMDA), and metabotropic glutamate receptors were found to affect the E/I balance in parallel to social behavior. For instance, Gandal et al. (167) showed that mice expressing low levels of the NMDA receptor *NR1* subunit in the PFC display low social motivation, decreased ultrasonic vocalizations, and abnormal gamma synchrony. Studies using genetic pre-clinical models linked reduced interneuronal markers in pre-frontal regions to imbalances in the E/I ratio due to a low level or lack of inhibitory control of pyramidal neuron excitability (168, 169). The maladaptive developmental trajectory of inhibitory interneurons and their role in later dysfunction of the PFC circuit have been widely studied (152, 170–172). While the impact of these deficits is global and affects multiple nodes of the social decision-making network that involves social motivation, the PFC is particularly susceptible. For instance, *Shank3*-deficient mice have been shown to lack social motivation and exhibit specific deficits in PFC circuitry, such as reduced NMDA-based excitatory post-synaptic currents (EPSCs) and a low number of F-actin filaments. These were rescued upon depolymerization of the actin filaments following systemic or focal treatment (173). Recent work involving circuit-specific mutation of *Shank3* in PFC-to-basolateral amygdala-projecting neurons recapitulated social motivation deficits and synaptic hypoactivity (174). In addition, chemogenetic activation of pyramidal neurons in the PFC of these mice rescued social interactions in the three-chamber task, as well as NMDA receptor-dependent EPSCs (175). Thus, PFC circuit dysfunction, especially of excitatory neurons projecting to the amygdala, directs social motivation deficits, at least in *Shank3*-deficient mice. However, mutations of the NMDA receptor *NR1* subunit in the PFC and hippocampus of adult mice did not decrease social novelty preference and sociability in the three-chamber task (176). Taken together, the development and early childhood susceptibility of interneurons may play a significant role in the PFC circuit and E/I balance abnormalities (Figure 3B) seen in ASD models (177, 178).

In addition to excitatory glutamatergic and inhibitory GABAergic activity, many neuromodulators alter PFC activity. Specific lesions of cholinergic projections into the PFC reduced rat social interactions in an open field arena (179). Distinct cholinergic inputs from the basal forebrain seemed to regulate different aspects of social interactions, namely social motivation and memory (180). Moreover, cholinergic signaling through nicotinic receptors in the PFC promoted the exploration of novel social stimuli (133). Oxytocin increased pair bonding and pro-social behavior (181–183) through contributions from sub-cortical regions and perhaps *via* their projections to the PFC (39). Social recognition memory is regulated by oxytocin-mediated

modulation of prefrontal cortex plasticity, which is impaired when juvenile rats eat a high-fat diet (184). Moreover, oxytocin receptor (OTr)-expressing SST+ neurons in the murine PFC present sex-specific responses to oxytocin (185). These neurons regulate female motivation to interact with males during the estrus phase, yet do not affect interactions with other females. In another study, chronic activation of pyramidal neurons of rat PFC reduced social motivation to interact with novel stimuli in a three-chamber task (186). These motivation deficits were ameliorated by systemic OTr agonist injections. Recently, Riad et al. (187) showed that corticotrophin-releasing hormone (CRH)-expressing neurons inhibit OTr-positive neurons and layer 2/3 in the mPFC when stimulated *in vitro* at low frequency. When activated chemo-genetically, these CRH neurons increase novelty preference in male but not female mice. Moreover, a recent study showed that PFC infralimbic CRH+ neurons that project to the lateral septum modulate social novelty preference (188). In summary, more detailed studies on the effects of PFC neuromodulators are required to reveal the intricate mechanisms through which they modulate E/I balance and circuitry in this brain region and regulate its activity during specific social behaviors (Figure 3B).

Does the PFC regulate social and affective emotional state recognition in rodents?

Social recognition and memory of socially relevant events are essential to social interactions. Early social recognition is impaired in children with ASD (189, 190). A study in rats reported that lesions in the ACC reduced social recognition, while OFC lesions did not affect this behavior (134). Activation of pyramidal neurons in *Cntnap2* knockout mice [corresponding to a pre-clinical model of cortical dysplasia focal epilepsy syndrome, a type of ASD (191)] balanced the E/I ratio and alleviated deficits in social recognition of novel juveniles (192). Mice that lack Fgf17, a signaling molecule essential for rostral forebrain development (193), show difficulties in social recognition and low c-Fos activity in the PFC during exploration of opposite sex conspecifics (194).

As discussed above, NMDA receptor hypo-function is a characteristic feature of many ASD mouse models. These deficits in glutamatergic synaptic activity also cause a loss of social recognition and memory. Moreover, acute systemic administration of the NMDA receptor antagonist MK801 reduces recognition of novel juvenile stimulus (195). Specifically, mice with NR1 subunit-deficient GABAergic neurons in the PFC do not distinguish a novel stimulus over a familiar one in a short-term social memory test (196). Collectively, PFC NMDA receptor synaptic activity contributes to social recognition and memory.

Works on empathy behavior in rats, which preferred to rescue a restrained conspecific over getting more food rewards, indicated a role of ACC projections to the Nac shell in regulating such behavior (197). Works from the Hong group (198) showed that dmPFC neuronal activity is related to the sex of the conspecific during social exploration. Furthermore, recent works exploring recognition of emotionally affected conspecifics indicated multi-faceted regulation by the PFC (122, 199). In addition, in mice fear-conditioned to avoid specific social stimuli, SST+ neurons inhibited PV+ neurons in the mPFC, thus causing disinhibition of excitatory projections from the region. These results suggest that the PFC regulates social fear conditioning or affective avoidance by increasing the excitatory drive in the circuit (200).

Conclusion

We are rapidly enhancing our understanding of the neural mechanisms underlying social interactions. Here, we considered an ever-growing body of evidence showing that the prefrontal cortex is a hub in this process. Social interactions involve multiple processes, like decision-making, valence, and perception of the emotions of self and others. It is thus no wonder that such high-order and complex social behavior is affected by disorders like ASD and other neuropsychological comorbidities. We accordingly addressed evidence that the prefrontal circuitry is susceptible to synaptic, cellular, and molecular modifications in ASD. Such modifications bring about a myriad of social deficits, despite the majority of the current literature only reporting on deficits in sociability, social recognition, and vocalization. We suggest that studying social deficits through tasks that address affective emotions, empathic behavior, and even group dynamics will enrich our understanding of the causes of ASD in rodent models. Taken together with studies of the mechanisms and roles of various neuromodulators and transmitters in the PFC during social interactions, such explorations can better guide interventions of clinical value.

Author contributions

AM and SW: conceptualization and writing—review and editing. SW: funding, resources, and supervision. AM: writing—original draft. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by ISF-NSFC joint research program (grant No. 3459/20 to SW), the Israel Science Foundation (grants No. 1361/17 and 2220/22 to SW), the Ministry of Science, Technology and Space of Israel (Grant No. 3-12068 to SW), the Ministry of Health of Israel (ERA-NET 2022 grant No. 3-18380), and the United States-Israel Binational Science Foundation (grant No. 2019186 to SW).

Acknowledgments

The authors thank Shai Netser and Renad Jabarin for their help in gathering literature for this review article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Adolphs R, Tranel D, Damasio AR. Neural systems subserving emotion; lesion studies of the amygdala, somatosensory cortices, and ventromedial prefrontal cortices In: *Handbook of neuropsychology*. (eds Gainotti, G.). 2nd Ed., Elsevier Science Amsterdam: (2001). 89–110.

2. Kieckhaefer C, Schilbach L, Bzdok D. Social belonging: brain structure and function is linked to membership in sports teams, religious groups, and social clubs. *Cereb Cortex*. (2023) 33:4405–20. doi: 10.1093/cercor/bhac351

3. Millan MJ, Bales KL. Towards improved animal models for evaluating social cognition and its disruption in schizophrenia: the CNTRICS initiative. *Neurosci Biobehav Rev*. (2013) 37:2166–80. doi: 10.1016/j.neubiorev.2013.09.012

4. Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. *Nat Rev Neurosci*. (2006) 7:268–77. doi: 10.1038/nrn1884

5. Bickart KC, Hollenbeck MC, Barrett LF, Dickerson BC. Intrinsic amygdala–cortical functional connectivity predicts social network size in humans. *J Neurosci*. (2012) 32:14729–41. doi: 10.1523/JNEUROSCI.1599-12.2012

6. Nieves N, von Schroder C. Roles of medial prefrontal cortex activity in human and animal social learning. In: Vonk, J., Shackelford, T.K. (eds) *Encycl Anim Cogn Behav*. Springer Cham. (2022) 6113–20. doi: 10.1007/978-3-319-55065-7_1298

7. Dubey I, Ropar D, Hamilton AF. Measuring the value of social engagement in adults with and without autism. *Mol Autism*. (2015) 6:31. doi: 10.1186/s13229-015-0031-2

8. Morrison KE, DeBrabander KM, Jones DR, Ackerman RA, Sasson NJ. Social cognition, social skill, and social motivation minimally predict social interaction outcomes for autistic and non-autistic adults. *Front Psychol*. (2020) 11:591100. doi: 10.3389/fpsyg.2020.591100

9. Assaf M, Jagannathan K, Calhoun VD, Miller L, Stevens MC, Sahl R, et al. Abnormal functional connectivity of default mode sub-networks in autism Spectrum disorder patients. *NeuroImage*. (2010) 53:247–56. doi: 10.1016/j.neuroimage.2010.05.067

10. Sumiya M, Okamoto Y, Koike T, Tanigawa T, Okazawa H, Kosaka H, et al. Attenuated activation of the anterior rostral medial prefrontal cortex on self-relevant social reward processing in individuals with autism Spectrum disorder. *NeuroImage Clin*. (2020) 26:102249. doi: 10.1016/j.nicl.2020.102249

11. Franklin TB, Silva BA, Perova Z, Marrone L, Masferrer ME, Zhan Y, et al. Prefrontal cortical control of a brainstem social behavior circuit. *Nat Neurosci*. (2017) 20:260–70. doi: 10.1038/nn.4470

12. Frost NA, Haggart A, Sohal VS. Dynamic patterns of correlated activity in the prefrontal cortex encode information about social behavior. *PLoS Biol*. (2021) 19:e3001235. doi: 10.1371/journal.pbio.3001235

13. Lee E, Rhim I, Lee JW, Ghim J-W, Lee S, Kim E, et al. Enhanced neuronal activity in the medial prefrontal cortex during social approach behavior. *J Neurosci*. (2016) 36:6926–36. doi: 10.1523/JNEUROSCI.0307-16.2016

14. Sakamoto T, Yashima J. Prefrontal cortex is necessary for Long-term social recognition memory in mice. *Behav Brain Res*. (2022) 435:114051. doi: 10.1016/j.bbr.2022.114051

15. Haber SN, Liu H, Seidlitz J, Bullmore E. Prefrontal Connectomics: from anatomy to human imaging. *Neuropsychopharmacology*. (2022) 47:20–40. doi: 10.1038/s41386-021-01156-6

16. Ko J. Neuroanatomical substrates of rodent social behavior: the medial prefrontal cortex and its projection patterns. *Front Neural Circuits*. (2017) 11:41. doi: 10.3389/fncir.2017.00041

17. Park G, Ryu C, Kim S, Jeong SJ, Koo JW, Lee Y-S, et al. Social isolation impairs the prefrontal-nucleus Accumbens circuit subserving social recognition in mice. *Cell Rep*. (2021) 35:109104. doi: 10.1016/j.celrep.2021.109104

18. Gangopadhyay P, Chawla M, Dal Monte O, Chang SWC. Prefrontal–amygdala circuits in social decision-making. *Nat Neurosci*. (2021) 24:5–18. doi: 10.1038/s41593-020-00738-9

19. Padilla-Coreano N, Batra K, Patarino M, Chen Z, Rock RR, Zhang R, et al. Cortical ensembles orchestrate social competition through hypothalamic outputs. *Nature*. (2022) 603:667–71. doi: 10.1038/s41586-022-04507-5

20. Phillips ML, Robinson HA, Pozzo-Miller L. Ventral hippocampal projections to the medial prefrontal cortex regulate social memory. *elife*. (2019) 8:e44182. doi: 10.7554/eLife.44182

21. Zhang H, Chaudhury D, Ma SM, Montgomery S, Cao J-L, Han M-H. A key noradrenergic brainstem-mesolimbic circuit: resilience to social stress. *Chronic Stress*. (2019) 3:247054701985018. doi: 10.1177/2470547019850186

22. Tan Y, Singhal SM, Harden SW, Cahill KM, Nguyen D-TM, Colon-Perez LM, et al. Oxytocin receptors are expressed by glutamatergic prefrontal cortical neurons that selectively modulate social recognition. *J Neurosci*. (2019) 39:3249–63. doi: 10.1523/JNEUROSCI.2944-18.2019

23. He L-N, Chen S, Yang Q, Wu Z, Lao Z-K, Tang C-F, et al. EphB2-dependent prefrontal cortex activation promotes Long-range social approach and partner responsiveness. *Proc Natl Acad Sci*. (2023) 120:e2219952120. doi: 10.1073/pnas.2219952120

24. Takahashi A, Nagayasu K, Nishitani N, Kaneko S, Koide T. Control of Intermale aggression by medial prefrontal cortex activation in the mouse. *PLoS One*. (2014) 9:e94657. doi: 10.1371/journal.pone.0094657

25. Zhang Z, Zhang Y, Yuwen T, Huo J, Zheng E, Zhang W, et al. Hyper-excitability of Corticothalamic PT neurons in MPFC promotes irritability in the mouse model of Alzheimer's disease. *Cell Rep*. (2022) 41:111577. doi: 10.1016/j.celrep.2022.111577

26. Williamson CM, Lee W, Romeo RD, Curley JP. Social context-dependent relationships between mouse dominance rank and plasma hormone levels. *Physiol Behav*. (2017) 171:110–9. doi: 10.1016/j.physbeh.2016.12.038

27. du R, Luo W-J, Geng K-W, Li C-L, Yu Y, Wei N, et al. Empathic contagious pain and consolation in laboratory rodents: species and sex comparisons. *Neurosci Bull*. (2020) 36:649–53. doi: 10.1007/s12264-020-00465-y

28. Lee W, Khan A, Curley JP. Major urinary protein levels are associated with social status and context in mouse social hierarchies. *Proc R Soc B Biol Sci*. (2017) 284:20171570. doi: 10.1098/rspb.2017.1570

29. Clipperton-Allen AE, Page DT. Social behavior testing in mice: social interest, recognition, and aggression. *Neuromethods*. (2023) 190:14. doi: 10.1007/978-1-0716-2748-8_14

30. Clipperton-Allen AE, Page DT. Social behavior testing in mice: social interest, recognition, and aggression In: . *Psychiatric vulnerability, mood, and anxiety disorders:* edS. Harro, J. Neuromethods, Humana, New York: NY (2023) 190:279–307.

31. Jabarin R, Netser S, Wagner S. Beyond the three-chamber test: toward a multimodal and objective assessment of social behavior in rodents. *Mol Autism*. (2022) 13:41. doi: 10.1186/s13229-022-00521-6

32. Kietzman HW, Gourley SL. How social information impacts action in rodents and humans: the role of the prefrontal cortex and its connections. *Neurosci Biobehav Rev*. (2023) 147:105075. doi: 10.1016/j.neubiorev.2023.105075

33. Adhikari A, Topiwala MA, Gordon JA. Article single units in the medial prefrontal cortex with anxiety-related firing patterns are preferentially influenced by ventral hippocampal activity. *Neuron*. (2011) 71:898–910. doi: 10.1016/j.neuron.2011.07.027

34. Bicks LK, Koike H, Akbarian S, Morishita H. Prefrontal cortex and social cognition in mouse and man. *Front Psychol*. (2015) 6:1805. doi: 10.3389/fpsyg.2015.01805

35. Kohls G, Chevallier C, Troiani V, Schultz RT. Social 'wanting' dysfunction in autism: neurobiological underpinnings and treatment implications. *J Neurodev Disord*. (2012). doi: 10.1186/1866-1955-4-10

36. Mitchell JP, Neil Macrae C, Banaji MR. Dissociable medial prefrontal contributions to judgments of similar and dissimilar others. *Neuron*. (2006) 50:40. doi: 10.1016/j.neuron.2006.03.040

37. Rees G, Kreiman G, Koch C. Neural correlates of. *Brain*. (2002) 3:1–10. doi: 10.1093/brain/awf181

38. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. *Nat Rev Neurosci*. (2015) 16:620–31. doi: 10.1038/nrn4005

39. Insel TR, Young LJ. Neuropeptides and the evolution of social behavior. *Curr Opin Neurobiol*. (2000) 10:784–9. doi: 10.1016/S0959-4388(00)00146-X

40. Carver LJ, Dawson G. Development and neural bases of face recognition in autism. *Mol Psychiatry*. (2002) 7:1168. doi: 10.1038/sj.mp.4001168

41. Nelson CA. The development and neural bases of face recognition. *Infant Child Dev*. (2001) 10:1–2. doi: 10.1002/icd.239

42. Sakuta Y, Kanazawa S, Yamaguchi MK. Infants prefer a trustworthy person: an early sign of social cognition in infants. *PLoS One*. (2018) 13:3541. doi: 10.1371/journal.pone.0203541

43. Southgate V. Are infants Altercentric? The other and the self in early social cognition. *Psychol Rev*. (2020) 127:182. doi: 10.1037/rev0000182

44. Mier D, Lis S, Neuthe K, Sauer C, Esslinger C, Gallhofer B, et al. The involvement of emotion recognition in affective theory of mind. *Psychophysiology*. (2010) 47:1031. doi: 10.1111/j.1469-8986.2010.01031.x

45. Mitchell RLC, Phillips LH. The overlapping relationship between emotion perception and theory of mind. *Neuropsychologia*. (2015) 70:1–10. doi: 10.1016/j.neuropsychologia.2015.02.018

46. Kumaran D, Banino A, Blundell C, Hassabis D, Dayan P. Computations underlying social hierarchy learning: distinct neural mechanisms for updating and representing self-relevant information. *Neuron*. (2016) 92:52. doi: 10.1016/j.neuron.2016.10.052

47. Wang F, Kessels HW, Hailan H. The mouse that roared: neural mechanisms of social hierarchy. *Trends Neurosci*. (2014) 37:674–82. doi: 10.1016/j.tins.2014.07.005

48. Qu C, Ligneul R, Van JB, Henst D, Dreher JC. An integrative interdisciplinary perspective on social dominance hierarchies. *Trends Cogn Sci*. (2017) 21:893–908. doi: 10.1016/j.tics.2017.08.004

49. Sapolsky RM. The influence of social hierarchy on primate health. *Science*. (2005) 308:648–652 doi: 10.1126/science.1106477

50. Dawson G, Meltzoff AN, Osterling J, Rinaldi J, Brown E. Children with autism fail to orient to naturally occurring social stimuli. *J Autism Dev Disord*. (1998) 28:479–85. doi: 10.1023/A:1026043926488

51. Rosello B, Berenguer C, Baixauli I, García R, Miranda A. Theory of mind profiles in children with autism Spectrum disorder: adaptive/social skills and pragmatic competence. *Front Psychol*. (2020) 11:7401. doi: 10.3389/fpsyg.2020.567401

52. Brewer N, Young RL, Barnett E. Measuring theory of mind in adults with autism Spectrum disorder. *J Autism Dev Disord*. (2017) 47:3080. doi: 10.1007/s10803-017-3080-x

53. Senju A. Spontaneous theory of mind and its absence in autism Spectrum disorders. *Neuroscientist*. (2012) 18:108–13. doi: 10.1177/1073858410397208

54. Dempsey EE, Moore C, Johnson SA, Stewart SH, Smith IM. Morality in autism Spectrum disorder: a systematic review. *Dev Psychopathol*. (2020) 32:3. doi: 10.1017/S0954579419001160

55. Assaf M, Hyatt CJ, Wong CG, Johnson MR, Schultz RT, Hendler T, et al. Mentalizing and motivation neural function during social interactions in autism Spectrum disorders. *NeuroImage Clin*. (2013) 3:5. doi: 10.1016/j.nicl.2013.09.005

56. Friedman NP, Robbins TW. The role of prefrontal cortex in cognitive control and executive function. *Neuropsychopharmacology*. (2022) 47:72–89. doi: 10.1038/s41386-021-01132-0

57. Wood JN, Grafman J. Human prefrontal cortex: processing and representational perspectives. *Nat Rev Neurosci*. (2003) 4:1033. doi: 10.1038/nrn1033

58. Hiser J, Koenigs M. The multifaceted role of the ventromedial prefrontal cortex in emotion, decision making, social cognition, and psychopathology. *Biol Psychiatry*. (2018) 83:638–47. doi: 10.1016/j.biopsych.2017.10.030

59. Arioli M, Crespi C, Canessa N. Social cognition through the Lens of cognitive and clinical neuroscience. *Biomed Res Int*. (2018) 2018:4283427. doi: 10.1155/2018/4283427

60. Martin-Cortecero J, Nuñez A. Sensory responses in the medial prefrontal cortex of anesthetized rats. Implications for sensory processing. *Neuroscience*. (2016) 339:45. doi: 10.1016/j.neuroscience.2016.09.045

61. Merritt CC, Maccormack JK, Stein AG, Lindquist KA, Muscatell KA. The neural underpinnings of intergroup social cognition: an FMRI Meta-analysis. *Soc Cogn Affect Neurosci*. (2021) 16:34. doi: 10.1093/scan/nsab034

62. Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR. Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nat Neurosci*. (1999) 2:1032–7. doi: 10.1038/14833

63. Bechara A, Damasio H, Tranel D, Damasio AR. The Iowa gambling task and the somatic marker hypothesis: some questions and answers. *Trends Cogn Sci*. (2005) 9:159–62. doi: 10.1016/j.tics.2005.02.002

64. Camille N, Tsuchida A, Fellows LK. Double dissociation of stimulus-value and action-value learning in humans with orbitofrontal or anterior cingulate cortex damage. *J Neurosci*. (2011) 31:2011. doi: 10.1523/JNEUROSCI.3164-11.2011

65. Kennerley SW, Behrens TEJ, Wallis JD. Double dissociation of value computations in orbitofrontal and anterior cingulate neurons. *Nat Neurosci*. (2011) 14:2961. doi: 10.1038/nn.2961

66. Grossman M, Eslinger PJ, Troiani V, Anderson C, Avants B, Gee JC, et al. The role of ventral medial prefrontal cortex in social decisions: converging evidence from FMRI and frontotemporal lobar degeneration. *Neuropsychologia*. (2010) 48:3505–12. doi: 10.1016/j.neuropsychologia.2010.07.036

67. Lieberman MD, Straccia MA, Meyer ML, du M, Tan KM. Social, self,(situational), and affective processes in medial prefrontal cortex (MPFC): causal, multivariate, and reverse inference evidence. *Neurosci Biobehav Rev*. (2019) 99:311–28. doi: 10.1016/j.neubiorev.2018.12.021

68. Chris M, Bird. The impact of extensive medial frontal lobe damage on 'Theory of Mind' and cognition. Brain. (2004) 127:914–928. doi: 10.1093/brain/awh108

69. Bloch C, Tepest R, Jording M, Vogeley K, Falter-Wagner CM. Intrapersonal synchrony analysis reveals a weaker temporal coherence between gaze and gestures in adults with autism Spectrum disorder. *Sci Rep*. (2022) 12:20417. doi: 10.1038/s41598-022-24605-8

70. Redcay E, Dodell-Feder D, Mavros PL, Kleiner M, Pearrow MJ, Triantafyllou C, et al. Atypical brain activation patterns during a face-to-face joint attention game in adults with autism Spectrum disorder. *Hum Brain Mapp*. (2013) 34:22086. doi: 10.1002/hbm.22086

71. Rilling JK, Glenn AL, Jairam MR, Pagnoni G, Goldsmith DR, Elfenbein HA, et al. Neural correlates of social cooperation and non-cooperation as a function of psychopathy. *Biol Psychiatry*. (2007) 61:21. doi: 10.1016/j.biopsych.2006.07.021

72. Edmiston EK, Merkle K, Corbett BA. Neural and cortisol responses during play with human and Computer Partners in Children with autism. *Soc Cogn Affect Neurosci*. (2014) 10:159. doi: 10.1093/scan/nsu159

73. Yang L, Li P, Mao H, Wang H, Shu C, Bliksted V, et al. Theory of mind deficits partly mediate impaired social decision-making in schizophrenia. *BMC Psychiatry*. (2017) 17:1313. doi: 10.1186/s12888-017-1313-3

74. Jessen S, Grossmann T. The developmental origins of subliminal face processing. *Neurosci Biobehav Rev*. (2020) 116:454–60. doi: 10.1016/j.neubiorev.2020.07.003

75. Lieberman MD. Social cognitive neuroscience: a review of Core processes. *Annu Rev Psychol*. (2007) 58:259–89. doi: 10.1146/annurev.psych.58.110405.085654

76. Luyten P, Campbell C, Allison E, Fonagy P. The Mentalizing approach to psychopathology: state of the art and future directions. *Annu Rev Clin Psychol*. (2020) 16:297–325. doi: 10.1146/annurev-clinpsy-071919-015355

77. Shamay-Tsoory SG, Aharon-Peretz J, Perry D. Two Systems for Empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain*. (2009) 132:279. doi: 10.1093/brain/awn279

78. Abdallah M, Zanitti GE, Iovene V, Wassermann D. Functional gradients in the human lateral prefrontal cortex revealed by a comprehensive coordinate-based Meta-analysis. *elife*. (2022) 11:76926. doi: 10.7554/eLife.76926

79. Koechlin Etienne. The cognitive architecture of the human lateral prefrontal cortex. *Sensorimotor foundations of higher cognition*. ed. Haggard: Patrick, Oxford, 1993; online edn, Oxford Academic, 22 Mar. (2012) 482–509.

80. Cardinale RC, Shih P, Fishman I, Ford LM, Müller R-A. Pervasive rightward asymmetry shifts of functional networks in autism Spectrum disorder. *JAMA Psychiat*. (2013) 70:975–82. doi: 10.1001/jamapsychiatry.2013.382

81. Shin JE, Choi SH, Lee H, Shin YS, Jang DP, Kim JJ. Involvement of the dorsolateral prefrontal cortex and superior temporal sulcus in impaired social perception in schizophrenia. *Prog Neuro-Psychopharmacol Biol Psychiatry*. (2015) 58:6. doi: 10.1016/j.pnpbp.2014.12.006

82. Osório AAC, Brunoni AR. Transcranial direct current stimulation in children with autism Spectrum disorder: a systematic scoping review. *Dev Med Child Neurol*. (2019) 61:298–304 doi: 10.1111/dmcn.14104

83. Rassovsky Y, Dunn W, Wynn J, Wu AD, Iacoboni M, Hellemann G, et al. The effect of transcranial direct current stimulation on social cognition in schizophrenia: a preliminary study. *Schizophr Res*. (2015) 165:2–3. doi: 10.1016/j.schres.2015.04.016

84. Lau T, Gershman SJ, Cikara M. Social structure learning in human anterior insula. *elife*. (2020) 9:53162. doi: 10.7554/eLife.53162

85. Park SA, Miller DS, Boorman ED. Inferences on a multidimensional social hierarchy use a grid-like code. *Nat Neurosci*. (2021) 24:916. doi: 10.1038/s41593-021-00916-3

86. McCrory E, Foulkes L, Viding E. The lancet psychiatry. *Lancet Psychiatry*. (2022) 9:828, 202–37. doi: 10.1016/S2215-0366(22)00202-4

87. Tabibnia G. An affective neuroscience model of boosting resilience in adults. *Neurosci Biobehav Rev*. (2020) 115:321–350 doi: 10.1016/j.neubiorev.2020.05.005

88. Farrow TFD, Jones SC, Kaylor-Hughes CJ, Wilkinson ID, Woodruff PWR, Hunter MD, et al. Higher or lower? The functional anatomy of perceived Allocentric social hierarchies. *NeuroImage*. (2011) 57:1552–60. doi: 10.1016/j.neuroimage.2011.05.069

89. Zink CF, Tong Y, Chen Q, Bassett DS, Stein JL, Meyer-Lindenberg A. Know your place: neural processing of social hierarchy in humans. *Neuron*. (2008) 58:273–83. doi: 10.1016/j.neuron.2008.01.025

90. Karafin MS, Tranel D, Adolphs R. Dominance attributions following damage to the ventromedial prefrontal cortex. *J Cogn Neurosci*. (2004) 16:1796–804. doi: 10.1162/0898929042947856

91. Carlén M. What constitutes the prefrontal cortex? *Science*. (2017) 358:478–82. doi: 10.1126/science.aan8868

92. Chafee MV, Heilbronner SR. Prefrontal cortex. *Curr Biol*. (2022) 32:R346–51. doi: 10.1016/j.cub.2022.02.071

93. Le MP, Ährlund-Richter S, Carlén M. The mouse prefrontal cortex: unity in diversity. *Neuron*. (2021) 109:1925–44. doi: 10.1016/j.neuron.2021.03.035

94. Laubach M, Amarante LM, Swanson K, White SR. What, if anything, is rodent prefrontal cortex? *ENeuro*. (2018) 5:–2018. doi: 10.1523/ENEURO.0315-18.2018

95. Leonard CM. Finding prefrontal cortex in the rat. *Brain Res*. (2016):1645, 1–3. doi: 10.1016/j.brainres.2016.02.002

96. Uylings HBM, Groenewegen HJ, Kolb B. Do rats have a prefrontal cortex? *Behav Brain Res*. (2003) 146:3–17 doi: 10.1016/j.bbr.2003.09.028

97. Yang ST, Gu E, Lu X, Wang J-H, Li B-M. Essential role of axonal VGSC inactivation in time-dependent deceleration and unreliability of spike propagation at cerebellar Purkinje cells. *Mol Brain*. (2014) 7:1–13. doi: 10.1186/1756-6606-7-1

98. Tamura M, Spellman TJ, Rosen AM, Gogos JA, Gordon JA. Hippocampal-prefrontal Theta-gamma coupling during performance of a spatial working memory task. *Nat Commun*. (2017) 8:2108. doi: 10.1038/s41467-017-02108-9

99. Mederos S, Sánchez-Puelles C, Esparza J, Valero M, Ponomarenko A, Perea G. GABAergic signaling to astrocytes in the prefrontal cortex sustains goal-directed behaviors. *Nat Neurosci*. (2021) 24:752. doi: 10.1038/s41593-020-00752-x

100. Le Merre P, Esmaeili V, Charrière E, Galan K, Salin PA, Petersen CCH, et al. Reward-based learning drives rapid sensory signals in medial prefrontal cortex and dorsal Hippocampus necessary for goal-directed behavior. *Neuron*. (2018) 97:31. doi: 10.1016/j.neuron.2017.11.031

101. Wise SP. Forward frontal fields: phylogeny and fundamental function. *Trends Neurosci*. (2008) 31:8. doi: 10.1016/j.tins.2008.08.008

102. Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci*. (2011) 15:85–93. doi: 10.1016/j.tics.2010.11.004

103. Kesner RP. Subregional analysis of mnemonic functions of the prefrontal cortex in the rat. *Psychobiology*. (2000) 28:219–28. doi: 10.3758/bf03331980

104. Lewkowicz DJ, Bremner AJ. The development of multisensory processes for perceiving the environment and the self In: . *Multisensory perception*. eds K. Sathian, V.S. Ramachandran. Academic Press. (2020) 89–112.

105. Young LJ. The neurobiology of social recognition, approach, and avoidance. *Biol Psychiatry*. (2002) 51:18–26. doi: 10.1016/S0006-3223(01)01268-9

106. Noack J, Richter K, Laube G, Haghgoo HA, Veh RW, Engelmann M. Different importance of the volatile and non-volatile fractions of an olfactory signature for individual social recognition in rats versus mice and short-term versus Long-term memory. *Neurobiol Learn Mem*. (2010) 94:568–75. doi: 10.1016/j.nlm.2010.09.013

107. Frith C. Role of facial expressions in social interactions. *Philos Trans R Soc B*. (2009) 364:3453–8. doi: 10.1098/rstb.2009.0142

108. Thor DH, Holloway WR. Social memory of the male laboratory rat. *J Comp Physiol Psychol*. (1982) 96:1000–6. doi: 10.1037/0735-7036.96.6.1000

109. Yang M, Crawley JN. Simple behavioral assessment of mouse olfaction. *Curr Protoc Neurosci*. (2009) 48:8–24. doi: 10.1002/0471142301.ns0824s48

110. Moy SS, Nadler JJ, Perez A, Barbaro RP, Johns JM, Magnuson TR, et al. Sociability and preference for social novelty in five inbred strains: an approach to assess autistic-like behavior in mice. *Genes Brain Behav*. (2004) 3:287–302. doi: 10.1111/j.1601-1848.2004.00076.x

111. Netser S, Meyer A, Magalnik H, Zylbertal A, de la Zerda SH, Briller M, et al. Distinct dynamics of social motivation drive differential social behavior in laboratory rat and mouse strains. *Nat. Commun* (2020) 11. 5908. doi: 10.1038/s41467-020-19569-0

112. Insel TR, Hulihan TJ. A gender-specific mechanism for pair bonding: oxytocin and partner preference formation in monogamous voles. *Behav Neurosci*. (1995) 109:782–9. doi: 10.1037/0735-7044.109.4.782

113. Church RM. Emotional reactions of rats to the pain of others. *J Comp Physiol Psychol*. (1959) 52:132–4. doi: 10.1037/h0043531

114. Langford DJ, Crager SE, Shehzad Z, Smith SB, Sotocinal SG, Levenstadt JS, et al. Social modulation of pain as evidence for empathy in mice. *Science*. (2006) 312:1967–70. doi: 10.1126/science.1128322

115. Toyoshima M, Okuda E, Hasegawa N, Kaseda K, Yamada K. Socially transferred stress experience modulates social affective behaviors in rats. *Neuroscience*. (2022) 502:68–76. doi: 10.1016/j.neuroscience.2022.08.022

116. Jones CE, Riha PD, Gore AC, Monfils M-H. Social transmission of Pavlovian fear: fear-conditioning by-proxy in related female rats. *Anim Cogn*. (2014) 17:827–34. doi: 10.1007/s10071-013-0711-2

117. Kim S, Mátyás F, Lee S, Acsády L, Shin H-S. Lateralization of observational fear learning at the cortical but not thalamic level in mice. *Proc Natl Acad Sci*. (2012) 109:15497–501. doi: 10.1073/pnas.1213903109

118. Choleris E, Guo C, Liu H, Mainardi M, Valsecchi P. The effect of demonstrator age and number on duration of socially-induced food preferences in house mouse (*Mus Domesticus*). *Behav Process*. (1997) 41:69–77. doi: 10.1016/S0376-6357(97)00029-6

119. Bruchey AK, Jones CE, Monfils M-H. Fear conditioning by-proxy: social transmission of fear during memory retrieval. *Behav Brain Res*. (2010) 214:80–4. doi: 10.1016/j.bbr.2010.04.047

120. Hernandez-Lallement J, Attah AT, Soyman E, Pinhal CM, Gazzola V, Keysers C. Harm to others acts as a negative Reinforcer in rats. *Curr Biol*. (2020) 30:949–961.e7. doi: 10.1016/j.cub.2020.01.017

121. Hernandez-Lallement J, Van Wingerden M, Marx C, Srejic M, Kalenscher T. Rats prefer mutual rewards in a prosocial choice task. *Front Neurosci*. (2015) 8:443. doi: 10.3389/fnins.2014.00443

122. Scheggia D, Managò F, Maltese F, Bruni S, Nigro M, Dautan D, et al. Somatostatin interneurons in the prefrontal cortex control affective state discrimination in mice. *Nat Neurosci*. (2020) 23:47–60. doi: 10.1038/s41593-019-0551-8

123. Bartal IB-A, Decety J, Mason P. Empathy and pro-social behavior in rats. *Science*. (2011) 334:1427–30. doi: 10.1126/science.1210789

124. Dolivo V, Taborsky M. Norway rats reciprocate help according to the quality of help they received. *Biol Lett*. (2015) 11:20140959. doi: 10.1098/rsbl.2014.0959

125. Márquez C, Rennie SM, Costa DF, Moita MA. Prosocial choice in rats depends on food-seeking behavior displayed by recipients. *Curr Biol*. (2015) 25:1736–45. doi: 10.1016/j.cub.2015.05.018

126. Burkett JP, Andari E, Johnson ZV, Curry DC, de Waal FBM, Young LJ. Oxytocin-dependent consolation behavior in rodents. *Science*. (2016) 351:375–8. doi: 10.1126/science.aac4785

127. Lindzey G, Manosevitz M, Winston H. Social dominance in the mouse. *Psychon Sci*. (1966) 5:451–2. doi: 10.3758/BF03331044

128. Shemesh Y, Sztainberg Y, Forkosh O, Shlapobersky T, Chen A, Schneidman E. High-order social interactions in groups of mice. *elife*. (2013) 2:e00759. doi: 10.7554/eLife.00759

129. Weissbrod A, Shapiro A, Vasserman G, Edry L, Dayan M, Yitzhaky A, et al. Automated Long-term tracking and social Behavioural phenotyping of animal colonies within a semi-natural environment. *Nat Commun*. (2013) 4:2018. doi: 10.1038/ncomms3018

130. Scheggia D, la Greca F, Maltese F, Chiacchierini G, Italia M, Molent C, et al. Reciprocal Cortico-amygdala connections regulate prosocial and selfish choices in mice. *Nat Neurosci*. (2022) 25:1505–18. doi: 10.1038/s41593-022-01179-2

131. Gunaydin LA, Grosenick L, Finkelstein JC, Kauvar IV, Fenno LE, Adhikari A, et al. Natural neural projection dynamics underlying social behavior. *Cells*. (2014) 157:1535–51. doi: 10.1016/j.cell.2014.05.017

132. Kas MJ, Modi ME, Saxe MD, Smith DG. Advancing the discovery of medications for autism Spectrum disorder using new technologies to reveal social brain circuitry in rodents. *Psychopharmacology*. (2014) 231:1147–65. doi: 10.1007/s00213-014-3464-y

133. Avale ME, Chabout J, Pons S, Serreau P, De Chaumont F, Olivo-Marin J-C, et al. Prefrontal nicotinic receptors control novel social interaction between mice. *FASEB J*. (2011) 25:2145–55. doi: 10.1096/fj.10-178558

134. Rudebeck PH, Walton ME, Millette BHP, Shirley E, Rushworth MFS, Bannerman DM. Distinct contributions of frontal areas to emotion and social behaviour in the rat. *Eur J Neurosci*. (2007) 26:2315–26. doi: 10.1111/j.1460-9568.2007.05844.x

135. Kim Y, Venkataraju KU, Pradhan K, Mende C, Taranda J, Turaga SC, et al. Mapping social behavior-induced brain activation at cellular resolution in the mouse. *Cell Rep*. (2015) 10:292–305. doi: 10.1016/j.celrep.2014.12.014

136. Collins DP, Anastasiades PG, Marlin JJ, Carter AG. Reciprocal circuits linking the prefrontal cortex with dorsal and ventral thalamic nuclei. *Neuron*. (2018) 98:366–379.e4. doi: 10.1016/j.neuron.2018.03.024

137. Lu J, Tucciarone J, Padilla-Coreano N, He M, Gordon JA, Josh Huang Z. Selective inhibitory control of pyramidal neuron ensembles and cortical subnetworks by chandelier cells. *Nat Neurosci*. (2017) 20:1377–83. doi: 10.1038/nn.4624

138. McGarry LM, Carter AG. Inhibitory gating of basolateral amygdala inputs to the prefrontal cortex. *J Neurosci*. (2016) 36:9391–406. doi: 10.1523/JNEUROSCI.0874-16.2016

139. Anastasiades PG, Marlin JJ, Carter AG. Cell-type specificity of Callosally evoked excitation and feedforward inhibition in the prefrontal cortex. *Cell Rep*. (2018) 22:679–92. doi: 10.1016/j.celrep.2017.12.073

140. Lee AT, Gee SM, Vogt D, Patel T, Rubenstein JL, Sohal VS. Pyramidal neurons in prefrontal cortex receive subtype-specific forms of excitation and inhibition. *Neuron*. (2014) 81:61–8. doi: 10.1016/j.neuron.2013.10.031

141. Gogolla N, LeBlanc JJ, Quast KB, Südhof TC, Fagiolini M, Hensch TK. Common circuit defect of excitatory-inhibitory balance in mouse models of autism. *J Neurodev Disord*. (2009) 1:172–81. doi: 10.1007/s11689-009-9023-x

142. Gonçalves J, Violante IR, Sereno J, Leitão RA, Cai Y, Abrunhosa A, et al. Testing the excitation/inhibition imbalance hypothesis in a mouse model of the autism Spectrum disorder: *in vivo* Neurospectroscopy and molecular evidence for regional phenotypes. *Mol Autism*. (2017) 8:1–8. doi: 10.1186/s13229-017-0166-4

143. Sacai H, Sakoori K, Konno K, Nagahama K, Suzuki H, Watanabe T, et al. Autism Spectrum disorder-like behavior caused by reduced excitatory synaptic transmission in pyramidal neurons of mouse prefrontal cortex. *Nat Commun*. (2020) 11:5140. doi: 10.1038/s41467-020-18861-3

144. Hensch TK. Critical period plasticity in local cortical circuits. *Nat Rev Neurosci*. (2005) 6:877–88. doi: 10.1038/nrn1787

145. Nelson SB, Valakh V. Excitatory/inhibitory balance and circuit homeostasis in autism Spectrum disorders. *Neuron*. (2015) 87:684–98. doi: 10.1016/j.neuron.2015.07.033

146. Fetit R, Hillary RF, Price DJ, Lawrie SM. The neuropathology of autism: a systematic review of post-mortem studies of autism and related disorders. *Neurosci Biobehav Rev*. (2021) 129:35–62. doi: 10.1016/j.neubiorev.2021.07.014

147. Fatemi SH, Folsom TD, Kneeland RE, Liesch SB. Metabotropic glutamate receptor 5 upregulation in children with autism is associated with Underexpression of both fragile X mental retardation protein and GABAA receptor Beta 3 in adults with autism. *Anat Rec*. (2011) 294:1635–45. doi: 10.1002/ar.21299

148. Fatemi SH, Reutiman TJ, Folsom TD, Thuras PD. GABA a receptor downregulation in brains of subjects with autism. *J Autism Dev Disord*. (2009) 39:223–30. doi: 10.1007/s10803-008-0646-7

149. Oblak A, Gibbs TT, Blatt GJ. Decreased GABAA receptors and benzodiazepine binding sites in the anterior cingulate cortex in autism. *Autism Res*. (2009) 2:205–19. doi: 10.1002/aur.88

150. Kolodny T, Schallmo M-P, Gerdts J, Edden RAE, Bernier RA, Murray SO. Concentrations of cortical GABA and glutamate in young adults with autism spectrum disorder. *Autism Res*. (2020) 13:1111–29. doi: 10.1002/aur.2300

151. Lohith TG, Osterweil EK, Fujita M, Jenko KJ, Bear MF, Innis RB. Is metabotropic glutamate receptor 5 upregulated in prefrontal cortex in fragile X syndrome? *Mol Autism*. (2013) 4:15–8. doi: 10.1186/2040-2392-4-15

152. Hashemi E, Ariza J, Rogers H, Noctor SC, Martínez-Cerdeño V. The number of Parvalbumin-expressing interneurons is decreased in the prefrontal cortex in autism. *Cereb Cortex*. (2017) 27:1931–43. doi: 10.1093/cercor/bhw021

153. Bartos M, Vida I, Jonas P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nat Rev Neurosci*. (2007) 8:45–56. doi: 10.1038/nrn2044

154. Sohal VS, Rubenstein JLR. Excitation-inhibition balance as a framework for investigating mechanisms in neuropsychiatric disorders. *Mol Psychiatry*. (2019) 24:1248–57. doi: 10.1038/s41380-019-0426-0

155. O'Reilly C, Lewis JD, Elsabbagh M. Is functional brain connectivity atypical in autism? A systematic review of EEG and MEG studies. *PLoS One*. (2017) 12:e0175870. doi: 10.1371/journal.pone.0175870

156. Wass S. Distortions and disconnections: disrupted brain connectivity in autism. *Brain Cogn*. (2011) 75:18–28. doi: 10.1016/j.bandc.2010.10.005

157. Zikopoulos B, Barbas H. Altered neural connectivity in excitatory and inhibitory cortical circuits in autism. *Front Hum Neurosci*. (2013) 7:609. doi: 10.3389/fnhum.2013.00609

158. Carlisi CO, Norman L, Murphy CM, Christakou A, Chantiluke VG, Giampietro V, et al. Comparison of neural substrates of temporal discounting between youth with autism Spectrum disorder and with obsessive-compulsive disorder. *Psychol Med*. (2017) 47:2513–27. doi: 10.1017/S0033291717001088

159. Kohls G, Antezana L, Mosner MG, Schultz RT, Yerys BE. Altered reward system reactivity for personalized circumscribed interests in autism. *Mol Autism*. (2018) 9:1–12. doi: 10.1186/s13229-018-0195-7

160. Clements CC, Zoltowski AR, Yankowitz LD, Yerys BE, Schultz RT, Herrington JD. Evaluation of the social motivation hypothesis of autism: a systematic review and Meta-analysis. *JAMA Psychiat*. (2018) 75:797–808. doi: 10.1001/jamapsychiatry.2018.1100

161. Ferguson BR, Gao W-J. PV interneurons: critical regulators of E/I balance for prefrontal cortex-dependent behavior and psychiatric disorders. *Front Neural Circuits*. (2018) 12:37. doi: 10.3389/fncir.2018.00037

162. Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'Shea DJ, et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*. (2011) 477:171–8. doi: 10.1038/nature10360

163. Wu J, Aton SJ, Booth V, Zochowski M. Network and cellular mechanisms underlying heterogeneous excitatory/inhibitory balanced states. *Eur J Neurosci*. (2020) 51:1624–41. doi: 10.1111/ejn.14669

164. Chen L, Li X, Tjia M, Thapliyal S. Homeostatic plasticity and excitation-inhibition balance: the good, the bad, and the ugly. *Curr Opin Neurobiol*. (2022) 75:102553. doi: 10.1016/j.conb.2022.102553

165. Isaacson JS, Scanziani M. How inhibition shapes cortical activity. *Neuron*. (2011) 72:231–43. doi: 10.1016/j.neuron.2011.09.027

166. Tremblay R, Lee S, Rudy B. GABAergic interneurons in the neocortex: from cellular properties to circuits. *Neuron*. (2016) 91:260–92. doi: 10.1016/j.neuron.2016.06.033

167. Gandal MJ, Anderson RL, Billingslea EN, Carlson GC, Roberts TPL, Siegel SJ. Mice with reduced NMDA receptor expression: more consistent with autism than schizophrenia? *Genes Brain Behav*. (2012) 11:740–50. doi: 10.1111/j.1601-183X.2012.00816.x

168. Contractor A, Ethell IM, Portera-Cailliau C. Cortical interneurons in autism. *Nat Neurosci*. (2021) 24:1648–59. doi: 10.1038/s41593-021-00967-6

169. Vogt D, Cho KKA, Lee AT, Sohal VS, Rubenstein JLR. The Parvalbumin/somatostatin ratio is increased in Pten mutant mice and by human PTEN ASD alleles. *Cell Rep*. (2015) 11:944–56. doi: 10.1016/j.celrep.2015.04.019

170. Filice F, Vörckel KJ, Sungur AÖ, Wöhr M, Schwaller B. Reduction in Parvalbumin expression not loss of the Parvalbumin-expressing GABA interneuron subpopulation in genetic Parvalbumin and shank mouse models of autism. *Mol Brain*. (2016) 9:1–17. doi: 10.1186/s13041-016-0192-8

171. Lauber E, Filice F, Schwaller B. Dysregulation of Parvalbumin expression in the Cntnap2−/− mouse model of autism Spectrum disorder. *Front Mol Neurosci*. (2018) 11:262. doi: 10.3389/fnmol.2018.00262

172. Nomura T, Musial TF, Marshall JJ, Zhu Y, Remmers CL, Xu J, et al. Delayed maturation of fast-spiking interneurons is rectified by activation of the TrkB receptor in the mouse model of fragile X syndrome. *J Neurosci*. (2017) 37:11298–310. doi: 10.1523/JNEUROSCI.2893-16.2017

173. Duffney LJ, Zhong P, Wei J, Matas E, Cheng J, Qin L, et al. Autism-like deficits in Shank3-deficient mice are rescued by targeting actin regulators. *Cell Rep*. (2015) 11:1400–13. doi: 10.1016/j.celrep.2015.04.064

174. Kim S, Kim Y-E, Song I, Ujihara Y, Kim N, Jiang Y-H, et al. Neural circuit pathology driven by Shank3 mutation disrupts social behaviors. *Cell Rep*. (2022) 39:110906. doi: 10.1016/j.celrep.2022.110906

175. Qin L, Ma K, Yan Z. Chemogenetic activation of prefrontal cortex in Shank3-deficient mice ameliorates social deficits, NMDAR hypofunction, and Sgk2 downregulation. *IScience*. (2019) 17:24–35. doi: 10.1016/j.isci.2019.06.014

176. Finlay JM, Dunham GA, Isherwood AM, Newton CJ, Nguyen TV, Reppar PC, et al. Effects of prefrontal cortex and hippocampal NMDA NR1-subunit deletion on complex cognitive and social behaviors. *Brain Res*. (2015) 1600:70–83. doi: 10.1016/j.brainres.2014.10.037

177. Robertson CE, Ratai E-M, Kanwisher N. Reduced GABAergic action in the autistic brain. *Curr Biol*. (2016) 26:80–5. doi: 10.1016/j.cub.2015.11.019

178. Ueda S, Niwa M, Hioki H, Sohn J, Kaneko T, Sawa A, et al. Sequence of molecular events during the maturation of the developing mouse prefrontal cortex. *Complex Psychiatry*. (2015) 1:94–104. doi: 10.1159/000430095

179. Savage S, Kehr J, Olson L, Mattsson A. Impaired social interaction and enhanced sensitivity to phencyclidine-induced deficits in novel object recognition in rats with cortical cholinergic denervation. *Neuroscience*. (2011) 195:60–9. doi: 10.1016/j.neuroscience.2011.08.027

180. Okada K, Nishizawa K, Kobayashi T, Sakata S, Hashimoto K, Kobayashi K. Different cholinergic cell groups in the basal forebrain regulate social interaction and social recognition memory. *Sci Rep*. (2021) 11:13589. doi: 10.1038/s41598-021-93045-7

181. Froemke RC, Young LJ. Oxytocin, neural plasticity, and social behavior. *Annu Rev Neurosci*. (2021) 44:359–81. doi: 10.1146/annurev-neuro-102320-102847

182. Oettl LL, Ravi N, Schneider M, Scheller MF, Schneider P, Mitre M, et al. Oxytocin enhances social recognition by modulating cortical control of early olfactory processing. *Neuron*. (2016) 90:609–21. doi: 10.1016/j.neuron.2016.03.033

183. Smeltzer MD, Curtis JT, Aragona BJ, Wang Z. Dopamine, oxytocin, and vasopressin receptor binding in the medial prefrontal cortex of monogamous and promiscuous voles. *Neurosci Lett*. (2006) 394:146–51. doi: 10.1016/j.neulet.2005.10.019

184. Yaseen A, Shrivastava K, Zuri Z, Hatoum OA, Maroun M. Prefrontal oxytocin is involved in impairments in prefrontal plasticity and social memory following acute exposure to high fat diet in juvenile animals. *Cereb Cortex*. (2019) 29:1900–9. doi: 10.1093/cercor/bhy070

185. Nakajima M, Görlich A, Heintz N. Oxytocin modulates female Sociosexual behavior through a specific class of prefrontal cortical interneurons. *Cells*. (2014) 159:295–305. doi: 10.1016/j.cell.2014.09.020

186. Janz P, Knoflach F, Bleicher K, Belli S, Biemans B, Schnider P, et al. Selective oxytocin receptor activation prevents prefrontal circuit dysfunction and social behavioral alterations in response to chronic prefrontal cortex activation in rats. *BioRxiv*. (2022). doi: 10.1101/2022.11.08.515590

187. Riad MH, Park K, Ibañez-Tallon I, Heintz N. Local production of Corticotropin-releasing hormone in prefrontal cortex modulates male-specific novelty exploration. *Proc Natl Acad Sci*. (2022) 119:e2211454119. doi: 10.1073/pnas.2211454119

188. Reyes L, de NS, Diaz PAS, Manas RN, Ruiz-Pino A, Nomura Y, et al. Corticotropin-releasing hormone signaling from prefrontal cortex to lateral septum supports social novelty preference. *BioRxiv*. (2022). doi: 10.1101/2022.03.15.484224

189. Eussen MLJM, Louwerse A, Herba CM, Van Gool AR, Verheij F, Verhulst FC, et al. Childhood facial recognition predicts adolescent symptom severity in autism Spectrum disorder. *Autism Res*. (2015) 8:261–71. doi: 10.1002/aur.1443

190. Webb SJ, Neuhaus E, Faja S. Face perception and learning in autism spectrum disorders. *Q J Exp Psychol*. (2017) 70:970–86. doi: 10.1080/17470218.2016.1151059

191. Strauss KA, Puffenberger EG, Huentelman MJ, Gottlieb S, Dobrin SE, Parod JM, et al. Recessive symptomatic focal epilepsy and mutant Contactin-associated protein-like 2. *N Engl J Med*. (2006) 354:1370–7. doi: 10.1056/NEJMoa052773

192. Selimbeyoglu A, Kim CK, Inoue M, Lee SY, Hong ASOO, Kauvar I, et al. Modulation of prefrontal cortex excitation/inhibition balance rescues social behavior in CNTNAP2-deficient mice. *Sci Transl Med*. (2017) 9:eaah6733. doi: 10.1126/scitranslmed.aah6733

193. Cholfin JA, Rubenstein JLR. Patterning of frontal cortex subdivisions by Fgf17. *Proc Natl Acad Sci*. (2007) 104:7652–7. doi: 10.1073/pnas.0702225104

194. Scearce-Levie K, Roberson ED, Gerstein H, Cholfin JA, Mandiyan VS, Shah NM, et al. Abnormal social behaviors in mice lacking Fgf17. *Genes Brain Behav*. (2008) 7:344–54. doi: 10.1111/j.1601-183X.2007.00357.x

195. Zou H, Zhang C, Xie Q, Zhang M, Shi J, Jin M, et al. Low dose MK-801 reduces social investigation in mice. *Pharmacol Biochem Behav*. (2008) 90:753–7. doi: 10.1016/j.pbb.2008.06.002

196. Belforte JE, Zsiros V, Sklar ER, Jiang Z, Yu G, Li Y, et al. Postnatal NMDA receptor ablation in Corticolimbic interneurons confers schizophrenia-like phenotypes. *Nat Neurosci*. (2010) 13:76–83. doi: 10.1038/nn.2447

197. Ben-Ami Bartal I, Breton JM, Sheng H, Long KLP, Chen S, Halliday A, et al. Neural correlates of Ingroup Bias for Prosociality in rats. *elife*. (2021) 10:e65582. doi: 10.7554/eLife.65582

198. Kingsbury L, Huang S, Raam T, Ye LS, Wei D, Hu RK, et al. Cortical representations of conspecific sex shape social behavior. *Neuron*. (2020) 107:941–953.e7. doi: 10.1016/j.neuron.2020.06.020

199. Levy DR, Tamir T, Kaufman M, Parabucki A, Weissbrod A, Schneidman E, et al. Dynamics of social representation in the mouse prefrontal cortex. *Nat Neurosci*. (2019) 22:2013–22. doi: 10.1038/s41593-019-0531-z

200. Xu H, Liu L, Tian Y, Wang J, Li J, Zheng J, et al. A Disinhibitory microcircuit mediates conditioned social fear in the prefrontal cortex. *Neuron*. (2019) 102:668–682.e5. doi: 10.1016/j.neuron.2019.02.026

frontiers | Frontiers in Neuroanatomy

TYPE Review
PUBLISHED 22 June 2023
DOI 10.3389/fnana.2023.1127143

OPEN ACCESS

EDITED BY
Dorit Ben Shalom,
Ben-Gurion University of the Negev, Israel

REVIEWED BY
Antonio Di Ieva,
Macquarie University, Australia
Christos Koutsarnakis,
Evangelismos Hospital, Greece

*CORRESPONDENCE
Michael E. Sughrue
✉ michael.sughrue@o8t.com

RECEIVED 19 December 2022
ACCEPTED 23 May 2023
PUBLISHED 22 June 2023

CITATION
Dadario NB, Tanglay O and Sughrue ME (2023) Deconvoluting human Brodmann area 8 based on its unique structural and functional connectivity.
Front. Neuroanat. 17:1127143.
doi: 10.3389/fnana.2023.1127143

Deconvoluting human Brodmann area 8 based on its unique structural and functional connectivity

Nicholas B. Dadario[1], Onur Tanglay[2] and Michael E. Sughrue[2]*

[1]Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ, United States, [2]Omniscient Neurotechnology, Sydney, NSW, Australia

Brodmann area 8 (BA8) is traditionally defined as the prefrontal region of the human cerebrum just anterior to the premotor cortices and enveloping most of the superior frontal gyrus. Early studies have suggested the frontal eye fields are situated at its most caudal aspect, causing many to consider BA8 as primarily an ocular center which controls contralateral gaze and attention. However, years of refinement in cytoarchitectural studies have challenged this traditional anatomical definition, providing a refined definition of its boundaries with neighboring cortical areas and the presence of meaningful subdivisions. Furthermore, functional imaging studies have suggested its involvement in a diverse number of higher-order functions, such as motor, cognition, and language. Thus, our traditional working definition of BA8 has likely been insufficient to truly understand the complex structural and functional significance of this area. Recently, large-scale multi-modal neuroimaging approaches have allowed for improved mapping of the neural connectivity of the human brain. Insight into the structural and functional connectivity of the brain connectome, comprised of large-scale brain networks, has allowed for greater understanding of complex neurological functioning and pathophysiological diseases states. Simultaneously, the structural and functional connectivity of BA8 has recently been highlighted in various neuroimaging studies and detailed anatomic dissections. However, while Brodmann's nomenclature is still widely used today, such as for clinical discussions and the communication of research findings, the importance of the underlying connectivity of BA8 requires further review.

KEYWORDS

Brodmann area 8, network, connectivity, cognition, fMRI, neuroimaging

1. Introduction

The human cerebral cortex has been divided into several different cortical maps over previous decades through a variety of analytical methods. Starting in the early 20th century, the human cerebrum was mostly divided by characterizing histological differences between regions according to their function. Brodmann's map, the most widely used traditional map of the human brain, characterized the cerebral cortex into 43 regions according to

regional cytoarchitectural differences in cells and laminar structures (Amunts and Zilles, 2015; **Figure 1A**). Brodmann originally defined BA8 as the posterior aspect of the superior frontal gyrus (SFG), extending medially to the paracingulate sulcus, posteriorly bound by area 6 and anteriorly by areas 9 and 46 (Petrides and Pandya, 2012). Specifically, Brodmann's definition included the following: "Area 8–the intermediate frontal area–consists of a strip-like zone, wide superiorly and narrowing laterally, which, like the agranular frontal area (6), crosses from the callosomarginal sulcus on the medial surface over the upper edge of the hemisphere onto the lateral surface; but there it only reaches to about the middle frontal gyrus before gradually vanishing without distinct borders. Especially on the lateral convexity of the hemisphere it is much less extensive than area 6" (Garey, 1994). Several other cyto- (von Economo and Koskinas, 1925; Bailey, 1951; Sarkissov et al., 1955; Petrides and Pandya, 2012) and myeloarchitectural (Vogt and Vogt, 1919) studies have further divided BA8 into numerous subdivisions. In these studies, BA8 has been separated into area 8A on the middle frontal gyrus (MFG) (commonly said to be the "FEF") (Lanzilotto et al., 2013), later with ventral (area 8Av) and dorsal (area 8Ad) components, as well as area 8B on the superior frontal gyrus (SFG) extending to the paracingulate sulcus (Petrides and Pandya, 2012). Importantly, despite utilizing similar methodology of anatomical delineations, all of the above maps differ significantly in their configuration, size, and number of cortical regions (Zilles and Amunts, 2010). Reasons for the limitations in these purely anatomical schemes have been discussed previously (Zilles and Amunts, 2010), but in general they are largely hindered by their single unit of neurobiological property, mostly cytoarchitectonic, combined with limited sample sizes which increase inter-subject variability.

Advances in neuroimaging capabilities and techniques for structural and functional imaging have led to an improved characterization of Brodmann's maps. Of particular importance has been that of the Human Connectome Project (HCP) given their creation of a multi-modal atlas based on a comprehensive method combining architectural, functional, neural connectivity, and topographical differences between cortical regions in healthy individual brains. The HCP atlas identified a total of 180 fine cortical parcellations per cerebral hemispheres according to these various neurobiological properties (**Figure 1B**).

According to the HCP, the dorsolateral prefrontal cortex contains 4 subdivisions of BA8 (8BL, 8Ad, 8Av, and 8C) and two transitional areas between areas 6 and 8 were also described by the HCP (s6-8 and i6-8), while area 8BM is in the medial prefrontal cortex (**Figure 1B**; Glasser et al., 2016). What becomes particularly important with the new HCP scheme is how they redefined what is generally considered the pre-supplementary motor area (SMA) according to Brodmann, which has been subject to debate by others as well (Ruan et al., 2018). Generally, the dorsal medial frontal cortex contains both the SMA and pre-SMA (Ruan et al., 2018). According to Brodmann, the pre-SMA was included in area 8. However, the HCP authors separated area 8 from the pre-SMA, now anatomically designating the supplementary and cingulate eye field (SCEF) and superior frontal language (SFL) area as the pre-SMA, although they generally refer to these two regions along with areas 6ma and 6mp as the SMA in total (Glasser et al., 2016; Sheets et al., 2021).

2. The new anatomy of BA8–the basic anatomical and structural-functional connectivity patterns

The work by the HCP authors has undoubtedly provided us a significant body of information about structural and functional relationships of the human brain according to a more anatomically specific parcellated atlas. To build off of this work which predominantly explained the atlas using unfamiliar and non-anatomic based maps (e.g., flat maps which do not explain gyri and sulci in depth), we have previously described all 180 HCP parcellations in each hemisphere according to the surrounding cortical anatomy, functional connectivity, and structural connectivity (Baker et al., 2018b).

In our definition, and in accordance with work by the HCP, BA8 can be divided into five regions: areas 8BL and 8AD on the posterior half of the superior frontal gyrus, areas 8AV and 8C on the posterior half of the middle frontal gyrus, and area 8BM in the medial superior frontal gyrus (**Figure 2A**; Baker et al., 2018a,c). Furthermore, two hybrid areas between areas 6 and 8 were also described by the HCP (s6-8 and i6-8) as well as pre-SMA areas SCEF and SFL but are not described in detail in the current work [see Glasser et al. (2016)]. We describe these regions further below in the context of their structural connectivity and speculated functional relevance (**Figures 2B–F**) (Glasser et al., 2016). For additional definitions and reasons for separating these subdivisions from other surrounding areas see the Supplementary material of Glasser et al. (2016) (specifically, Supplementary Figure 25; Glasser et al., 2016).

2.1. Areas 8BL and 8AD

Areas 8BL and 8AD can be found in the superior frontal gyrus. Area 8BL is located at the posterior aspect of the superior SFG surface. It is a lateral division of BA8, bounded medially by area 8BM, anteriorly by areas 9p and 9m, and posteriorly by areas s6-8 and the superior frontal language (SFL) area (**Figure 1B**). Area 8BL demonstrates a wide degree of functional connectivity throughout the frontal lobe, especially to other BA8 subdivisions in the dorsolateral prefrontal cortex, the middle and inferior frontal cortices, as well as the temporal lobe (e.g., temporal area 1 and 2 and the superior temporal sulcus areas) and the parietal lobe (e.g., areas 7 m and divisions of areas 31 and 23). Importantly, area 8B in macaques is commonly believed to be the premotor eye-ear field, and given the role of the posterior aspect of the SFG in working memory, area 8BL has been implicated in spatial working memory (Courtney et al., 1998). We have found that the major fiber bundle connecting area 8BL is also involved in higher visual-cognitive processes, specifically the inferior fronto-occipital fasciculus (IFOF) (Conner et al., 2018). Numerous divisions of the IFOF have been provided, and 8BL may be specifically connected via the IFOF-V which connects with numerous aspects of the occipital and parietal lobes (Wu et al., 2016). Previous work using DTI-tractography have found these connections travel from 8BL through the extreme/external capsule ending at occipital

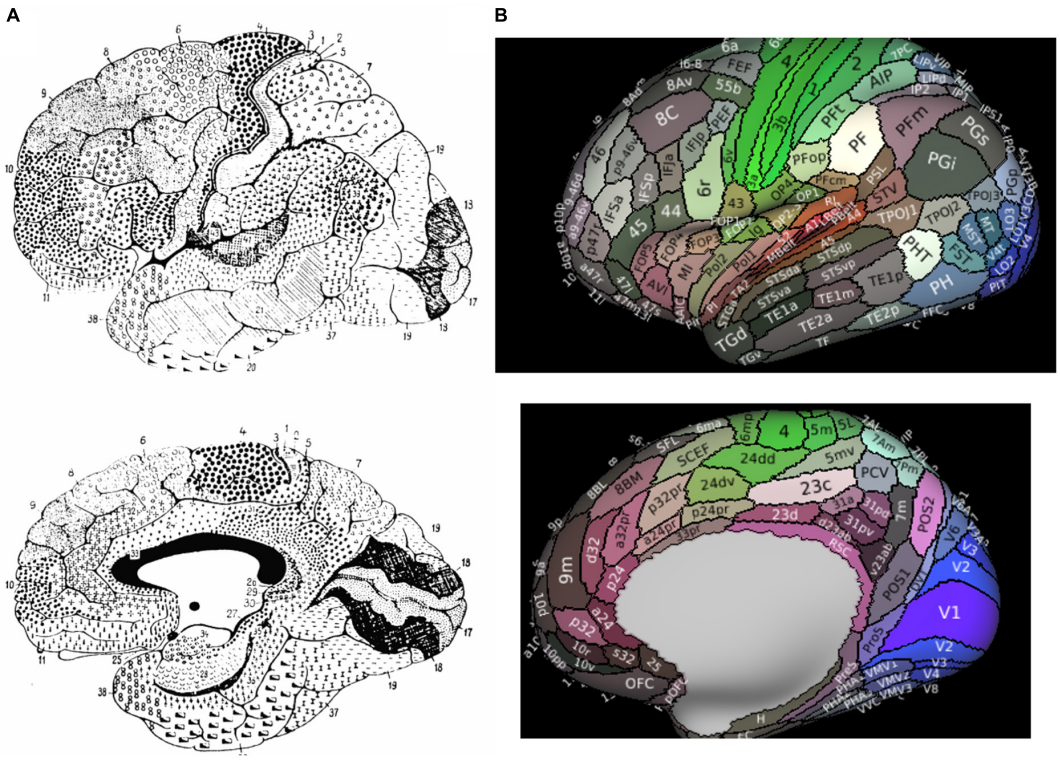


FIGURE 1
Parcellated Human Cerebrum. Panel **(A)** presents Brodmann's original atlas. Panel **(B)** presents the 180 cortical parcellations described by the Human Connectome Project (HCP). The color of each parcellation is based on a 3D color space, reflecting the extent to which each areas is associated in the resting state with auditory (red), somatosensory (green), visual (blue), task positive (white), or task negative (black) groups of areas.

parcellations V2, V3, 7PL, MIP, V6, and V6A (Conner et al., 2018). Another major fiber bundle connecting 8BL are contralateral connections through the genu of the corpus callosum to end at contralateral 8BM and 9m, connections to the medial thalamus via the internal capsule, and frontal aslant tract (FAT) connections to the inferior frontal gyrus to terminate at area 44.

Compared to more medially located area 8BL, area 8Ad is located on the bank of the superior frontal sulcus as it joins the union between the SFS and precentral sulci. It is bordered anterior by areas 9p, 9-46d, and 46, laterally by area 8AV, and posteriorly by the transition areas s6-8 and i6-8. Similar to area 8BL, area 8Ad demonstrates extensive functional connectivity throughout the dorsolateral frontal cortices with area 8 and 10 subdivisions, MFG areas 24 and 32, and numerous temporal and parietal areas (e.g., subdivisions of area 7, 31, 23, and the hippocampal and parahippocampal gyri). However, unlike area 8BL, this region is more locally connected and highly inconsistent between individuals. We discuss the importance of these local connections in the next section, but they reflect the hub like nature of area 8Ad in the SFS, which may integrate visual and auditory information for spatial cognition via short local association bundles with areas 9a, 9p, s6-8, 8Av, and p10p (Reser et al., 2013).

2.2. Areas 8AV and 8C

Areas 8AV and 8C can be found on the middle frontal gyrus, with area 8AV on its most posterior aspect bound laterally by area 8C. Furthermore, area 8AV is bound anteriorly by area 46, posteriorly by areas 55b, FEF, and i6-8, and medially by area 8D. Interestingly, area 8AV demonstrates a number of similar functional connections as seen above with area 8BL, which we later describe as likely being related to their similar functional network associations. However, area 8AV is structurally connected primarily via the arcuate/superior longitudinal fasciculus (SLF), contralateral connections through the body of the corpus callosum to the contralateral superior frontal language area, and local association fibers. Arcuate/SLF fibers can be seen structurally connecting area 8AV to the parietal lobe after wrapping around the sylvian fissure posteriorly, while local association fibers connect it within BA8 with subdivisions area 8C, 8Ad, i6-8, and 46.

Area 8C is also located in the posterior aspect of the MFG, but bordered laterally by inferior frontal sulcus areas (IFSp, IFJa, and IFJp), posteriorly by the precentral eye field and area 55b, and anteriorly areas p9-46v and 46. Similar to medial area 8AV, area 8C can bee seen demonstrating functional connectivity with some similar frontal, temporal, and parietal regions, although some differences become apparent. Namely, area 8C demonstrates less functional connectivity with subdivisions of area 9 and more connectivity with inferior frontal lobe regions (IFSp, IFJp, a47r, p47r, and 44). However, a number of similar structural connections are also found between the two regions as area 8C is connected via the arcuate/SLF as well, but instead terminates in parietal visual areas PH and PHT unlike how the connections of 8AV via the arcuate/SLF terminate in different parietal areas

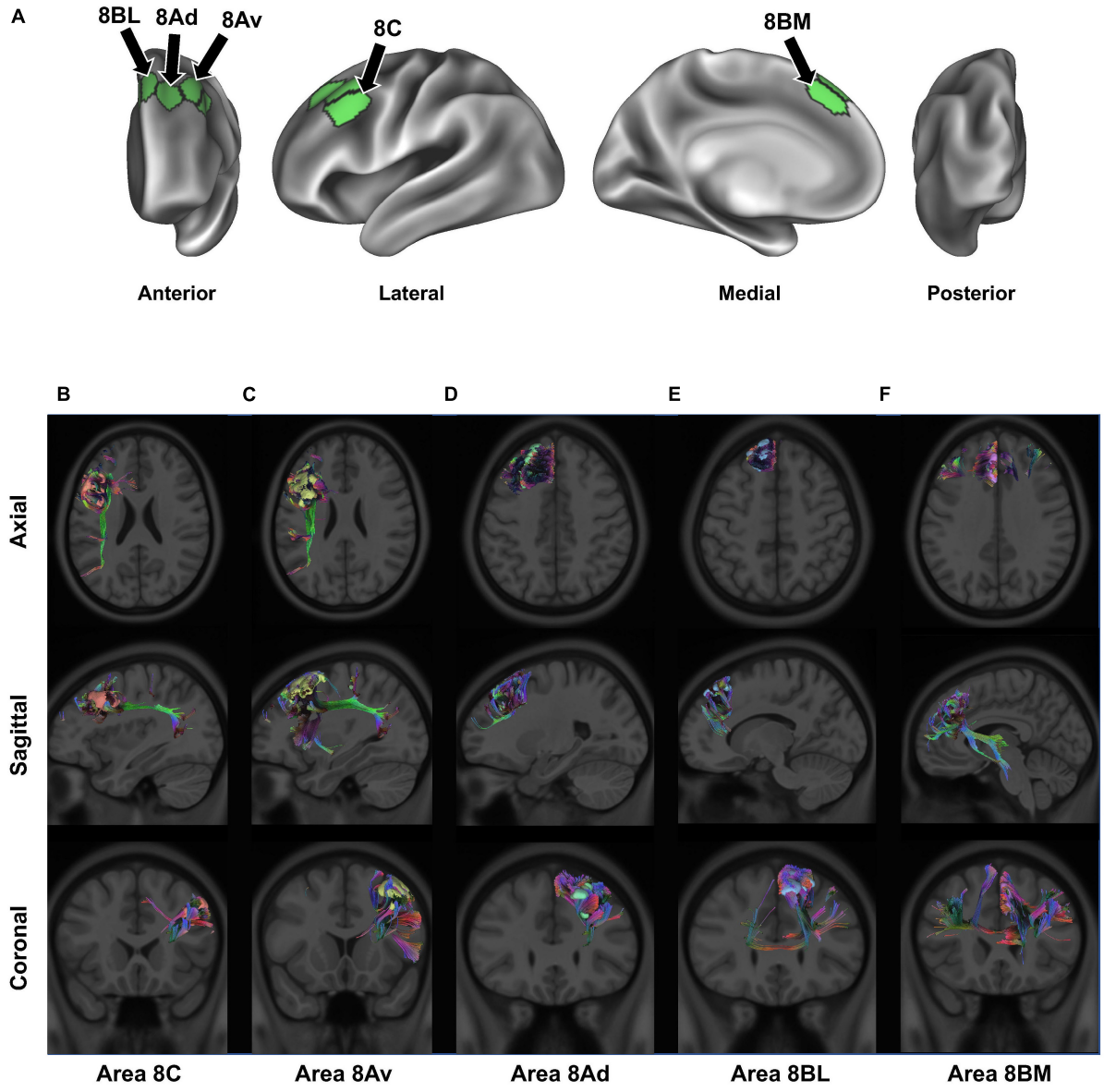


FIGURE 2
Connectivity of BA8. Panel **(A)** details the anatomical location of each BA8 subdivision, projected onto a left-hemispheric model brain. Panels **(B–F)** display the structural connectivity of all 5 area 8 subdivisions through tractography, projected onto a sample MRI image: area 8C **(B)**, area 8Av **(C)**, area 8Ad **(D)**, area 8BL **(E)**, and area 8BM **(F)**. Note that there may be parallax error within the projections, given the two-dimensional nature of the images.

(6a, 7PC, MIP, PFm, 2), which are largely implicated in praxis (Shahab et al., 2022).

2.3. Area 8BM

Area 8BM can be found on the posterior aspect of the medial SFG. Its superior boundary includes subdivision area 8BL and the SFL and area 24 subdivisions, areas d32 and a32pr inferiorly, area 9m anteriorly, and the supplementary and cingulate eye field (SCEF) posteriorly. Area 8BM has a particularly interesting amount of cross-modal functional connectivity as it can be seen linking a variety of different brain regions involved in different brain networks. In particular, area 8BM demonstrates functional connectivity with all area 8 subdivisions as well as areas i6-8, s6-8, a10p, a9-46v, and p9-46 in the dorsolateral frontal lobe, temporal regions TE1p, TE1m, and STSvp, as well as significant functional connectivity with numerous lateral parietal (e.g., LIPv, IP, and PG areas) and medial parietal (e.g., 7pm, 31a, and d23ab) regions. Unsurprisingly, this region is connected to numerous regions by both large fiber bundles and short local association fibers. Large fiber bundles via the IFOF connect area 8BM through the temporal lobe to end at parietal area 7PC and occipital areas V1-3, while FAT fibers connect area 8BM infero-laterally to area 44. Thalamic connections to the brainstem and contralateral connections to area 8BM and 9 m are also appreciated.

3. Connectivity of BA8 subregions determine their behavioral correlates

As a result of the cytoarchitectural boundaries of BA8 and its subdivisions being similar, it is reasonable to consider BA8 and its subdivisions facilitate the same functions. Ultimately, BA8 can generally be considered as a decision maker which is important in weighing uncertainty (Volz et al., 2004, 2005). However, what is important to consider is that the contexts differ in their activations based on who else they are structurally and functionally connected to. According to the literature, beyond traditional views suggesting BA8 is primarily a frontal eye field involved region, its association with a variety of higher-cognitive functions has been recently well-appreciated and well-documented. Neuroimaging based studies have implicated this region in motor learning (Matsumura et al., 2004) and imagery (Malouin et al., 2003), executive functions (Kübler et al., 2006), language (Fox et al., 2000; De Carli et al., 2007), working memory (Rämä et al., 2001), visuospatial attention (Cheng et al., 1995), and a number of other functions.

One major advancement in thinking provided by recent large-scale neuroimaging technology which can address this complex phenomenon is the understanding that higher-order cognitive functions cannot often be reliably linked to single cortical regions, and instead may be better understood based on the underlying connectivity of a region with different areas. From a network perspective, spatially distinct regions are functionally connected within large-scale brain networks to subserve complex human functions. Furthermore, functionally connected regions are commonly structurally connected by white matter connections, which place important constraints on functional connectivity and overall information processing (Bressler and Menon, 2010). This connectomic framework allows us to better understand BA8 and its subdivisions as likely an important hub in mediating different dynamic intra- and inter-network interactions between various large-scale brain networks to facilitate uncertainty driven decision making for processes determined by regions they are connected to. In other words, regardless of the reason for uncertainty (i.e., external or internal stimuli), activation in BA8 increases with increasing uncertainty, but the different ways to resolve or cope with this strategy is facilitated by which additional networks are activated (Volz et al., 2005). We expand on these principles below with common examples provided by recent literature.

3.1. Flexible decision making and memory

The prefrontal cortex has long been implicated in goal-directed behavior (Botvinick and An, 2009; Yang et al., 2022). In particular, the role of BA8 as a decision maker, such as for goal-directed behaviors, can likely be first appreciated by understanding the role of this region in working memory (WM). Important in guiding goal-directed behaviors includes the process of WM, which relies on the quick storage and manipulation of relevant information to guide subsequent behavior. Lesion based and electrophysiological studies including both humans and non-human primates have generally implicated the lateral prefrontal cortex as a predominant area facilitating these processes (Goldman-Rakic, 1987; du Boisgueheneuc et al., 2006; Luria, 2012; Fuster, 2015). WM tasks highlight the activation of SFG, and similarly damage to the SFG causes an impairment in working memory, especially spatially related WM (du Boisgueheneuc et al., 2006). This anatomic region generally corresponds to areas 8AD and 8BL. However, other subdivisions of BA8 have also been implicated by these processes, such as the 2-back test for area 8C and spatial relations for areas 8Av and 8C [see Supplementary Figure 25 in Glasser et al. (2016)]. Importantly, it is likely that BA8 does not facilitate working memory in a single domain (e.g., only visual or spatial), but rather these processes vary according to their specific connections. When examining **Figure 1B** by the HCP atlas, one can see that BA8 subdivisions differ in their functional activation across various cognitive domains. Others have referred to this process as "executive processing" (Postle et al., 2000), where for instance the SFG activates not only for processing of spatially related information, but rather represents a more flexible system for general cognitive control (Duncan and Owen, 2000; du Boisgueheneuc et al., 2006).

One aspect of the connectivity of this region which may explain this functional relevance is the connectivity of BA8 via the IFOF system (**Figure 3A**). The IFOF bundle is a major white matter connection likely to be involved in higher cognitive processing through multiple connectivity related links with many networks. In particular, areas 8BL and 8BM have numerous connections throughout the cerebrum which may be facilitated via this system. As seen in **Figure 3A**, 8BL is primarily connected to earlier visual areas (V2-V4) and also the superior parietal lobe (e.g., 7PC and MIP), while area 8BM primarily sends information to later visual areas. Given the network affiliation of 8BL in the default mode network (DMN), it is possible these connections are likely determining cognitively relevant representations of the visual system (Buckner, 2013), which may subsequently facilitate functions such as praxis (O'Neal et al., 2021). Differently, as we discuss further in the next section, area 8BM is a central executive network (CEN) region which is anatomically located between two SMA regions. Area 8BM may likely facilitate the motor planning and execution of goal-directed behaviors through interacting with numerous higher order networks and the motor system along the medial frontal lobe (Mandonnet et al., 2017; Briggs et al., 2021a). Furthermore, BA8 has been implicated in various language functions, such as speech motor programming (Fox et al., 2000), language processing (De Carli et al., 2007), and translation (Price et al., 1999). Unsurprisingly, language areas such as area 44 show up on the IFOF system, and are connected to BA8 subdivisions like areas 8BL and 8C.

Ultimately, the role of BA8 as a decision maker and in working memory facilitates a number of functions according to this regions connectivity throughout the cerebrum and with the visual system. In particular, the IFOF is a major white matter bundle involved in higher-order cognitive processes beyond basic visual processing, and this system is likely one source of structural connectivity for BA8 which economically supports and constrains these functions. Importantly however, much of the results supporting these connectivity relationships between IFOF and medial area 8 regions (8BL, 8BM) has been provided through neuroimaging based work, such as using DSI tractography (Wu et al., 2016; Conner et al., 2018). With the increase in neuroimaging

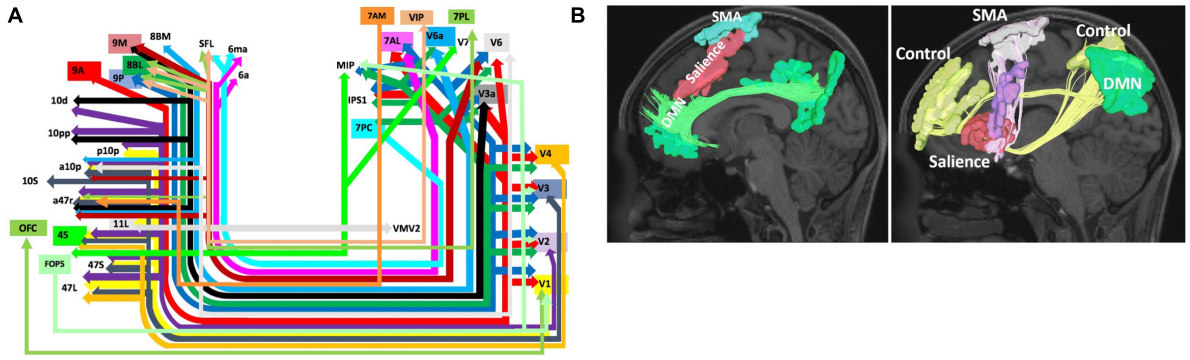


FIGURE 3
Network Interactions of BA8. Higher-order cognitive processes like goal directed behavior and motor planning and initiation are likely supported by the connectivity of BA8 to the visual system via the inferior fronto-occipital fasciculus (IFOF) **(A)** (Conner et al., 2018) and the interaction of BA8 with the salience, default mode, and control networks comprising an initiation axis spanning the middle frontal lobe (Poologaindran et al., 2020) **(B)**. Note that schematic in panel **(A)** shows the entire start and end points of the IFOF, which include areas 8BM and 8BL. Panel A was reproduced with permission from Conner et al. (2018) and Panel **(B)** with permission from Poologaindran et al. (2020).

based techniques to map various aspects of the brain connectome, it is critical that these relationships are also verified with direct anatomic dissection as well, such as post-mortem dissections (Martino et al., 2010; Briggs et al., 2021b). Such direct evidence is lacking with the IFOF and medial BA8 regions to date, and therefore is an important area of future work to better understand the importance of this connectivity or lack thereof.

3.2. Decision making for motor control

A number of studies have implicated BA8 in goal-directed behavior, particularly for motor actions and conflict processing (Usami et al., 2013; Ben Shalom and Bonneh, 2019). A large reason for this focus of study likely originates from the fact that part of the traditional definition of BA8 according to Brodmann includes the pre-supplementary motor area (pre-SMA). However, the pre-SMA was later separated out by the HCP to predominantly include areas SCEF and SFL as discussed previously. Despite these differences in nomenclature, involvement of BA8 in motor planning and actions can be understood based on its underlying neural connectivity. One particular BA8 subdivision, area 8BM, is a CEN region which is strategically placed between these two DMN regions (SCEF and SFL). 8BM has numerous local structural connections with these two regions. This becomes particularly important as multiple lines of evidence have suggested a likely connectomic initiation axis responsible for facilitating motor planning spanning the medial frontal lobe (**Figure 3B**; Darby et al., 2018; Poologaindran et al., 2020; Briggs et al., 2021a). While 8BM is not known to be a direct part of the initiation axis, it likely interacts with other regions within the axis. This initiation axis consists of the DMN linked by the cingulum bundle and the salience network linked by the FAT, and it extends up to the SMA. Damage to the axis causes akinetic mutism and abulia, while sparing the axis prevents these deficits (Briggs et al., 2021a). Given area 8BM's position between both DMN affiliated motor planning areas SCEF and SFL, as well as its major connections via the FAT, area 8BM's role in overall motor planning and the initiation of goal-directed behavior is not entirely surprising. Furthermore, like area 8BM, SMA regions also are connected through the IFOF system further suggesting the importance of these connections in motor planning and execution.

4. Impaired BA8 connectivity and potential therapies

Given the role of BA8 in uncertainty driven decision making, it is important to consider how a lack of this neural correlate, such as in disease or following a lesion, has a notable amount of likely clinical importance. Generally, dysfunction in this region has been implicated in a variety of psychiatric illnesses [i.e., depression (Rogers et al., 2004; Siegle et al., 2007; Holmes and Pizzagalli, 2008) and obsessive-compulsive disorder (OCD) (Rotge et al., 2010; Yun et al., 2017)], behavioral disorders [i.e., ADHD (Hai et al., 2022)], neurodegenerative disorders [i.e., dementia (Godefroy et al., 2022) and Parkinson's disease (Shen et al., 2020)], as well as motor (Bannur and Rajshekhar, 2000; Dadario et al., 2021) and language (Rubens et al., 1976; Freedman et al., 1984; Rapcsak and Rubens, 1994) deficits. Together, these deficits can be thought of as a lack of motivation, apathy, and poor response inhibition (Hu et al., 2016). However, what is important to note is that just considering BA8, or even perhaps its subdivisions, as prominent features in all of these disorders does not create an adequate model to actually better understand, treat, and prevent these symptoms. As an example, preventing damage to the SFG does not always prevent SMA syndrome, characterized by transient hemiparesis and akinetic mutism and abulia, and damage outside the SFG can still cause SMA syndrome (Ruan et al., 2018). Furthermore, not all patients recover and trajectories are unpredictable (Abel et al., 2015). However, as mentioned above, by considering the dynamic underlying structural and functional connectivity of this region and with other brain networks, we may be able to better understand these clinical diseases and also prevent them.

In resective brain surgery around BA8, connectivity features provide a map which may be utilized intraoperatively to avoid critical networks, such as by the SFG bank (Briggs et al., 2021a). Elsewhere, this connectomic architecture may also allow us to

better understand heterogenous clinical symptomology associated with various neuropsychiatric illness related to this region. fMRI analyses have suggested network-based executive dysfunction in OCD is associated with different resting-state connectivity disturbances between an anterior cingulate component of the salience network and (1) the left dorsolateral BA8 (presumably 8C/8AV) for information integration and overall planning and (2) the superior lateral BA8 (presumably 8Ad/8BL) bilaterally for selective attention and response inhibition (Yun et al., 2017). Differently, dysfunctional connectivity in depression is demonstrated between SFG components of BA8 and default mode network nodes in the precuneus (Helm et al., 2018; Tanglay et al., 2022). Importantly in this context, various neuromodulatory treatments targeted in this region are now available to treat psychiatric disorders (Marques et al., 2019) and modulate specific behaviors (Rose et al., 2011), presumably by influencing surrounding the neural connectivity and (re)-synchronizing brain networks. Thus, simultaneously improving our understanding of the specific neural connectivity in this region can provide more precise information to identify anatomically specific targets for neuromodulatory treatments which are now capable of utilizing this level of granular information (Stephens et al., 2021; Einstein et al., 2022; Poologaindran et al., 2022).

5. Conclusion

A significant amount of information has been revealed about the anatomy of BA8 which has both challenged the traditional anatomic boundaries of this region and also expanded our understanding of its functional relevance. BA8 and its subdivisions are generally implicated in uncertainty driven decision making. However, this region is implicated in a variety of higher-order cognitive processes as the context of the decision making, and therefore activation of BA8, depends on its structural and functional connectivity to other brain regions and throughout various large-scale brain networks. These processes are largely evident through underlying multi-network interactions stemming from BA8, especially with the DMN and CEN, and communication through major fiber bundles like the (1) IFOF with the visual system and (2) connectomic initiation axis for goal-directed behavior and motor initiation.

Author contributions

ND, OT, and MS: conception, writing, editing, reviewing, and figures. All authors contributed to the article and approved the submitted version.

Conflict of interest

ND has no disclosures. OT was an employee of Omniscient Neurotechnology. MS was a co-founder of Omniscient Neurotechnology. No aspects related to these products were discussed in the current work.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Abel, T., Buckley, R., Morton, R., Gabikian, P., and Silbergeld, D. (2015). Recurrent supplementary motor area syndrome following repeat brain tumor resection involving supplementary motor cortex. *Neurosurgery* 11, 447–455. doi: 10.1227/NEU.0000000000000847

Amunts, K., and Zilles, K. (2015). Architectonic mapping of the human brain beyond brodmann. *Neuron* 88, 1086–1107. doi: 10.1016/j.neuron.2015.12.001

Bailey, P. (1951). *The isocortex of man*. Urbana, IL: University of Illinois Press.

Baker, C., Burks, J., Briggs, R., Conner, A., Glenn, C., Sali, G., et al. (2018b). A connectomic atlas of the *human* cerebrum-chapter 1: Introduction, methods, and significance. *Oper. Neurosurg.* 15, S1–S9. doi: 10.1093/ons/opy253

Baker, C., Burks, J., Briggs, R., Conner, A., Glenn, C., Morgan, J., et al. (2018a). A connectomic atlas of the human cerebrum-chapter 2: The lateral frontal lobe. *Oper. Neurosurg.* 15, S10–S74. doi: 10.1093/ons/opy254

Baker, C., Burks, J., Briggs, R., Stafford, J., Conner, A., Glenn, C., et al. (2018c). A connectomic atlas of the human cerebrum-chapter 4: The medial frontal lobe, anterior cingulate gyrus, and orbitofrontal cortex. *Oper. Neurosurg.* 15, S122–S174. doi: 10.1093/ons/opy257

Bannur, U., and Rajshekhar, V. (2000). Post operative supplementary motor area syndrome: Clinical features and outcome. *Br. J. Neurosurg.* 14, 204–210. doi: 10.1080/026886900408379

Ben Shalom, D., and Bonneh, Y. (2019). Editorial: The medial prefrontal cortex and integration in ASD and typical cognition. *Front. Hum. Neurosci.* 13:74. doi: 10.3389/fnhum.2019.00074

Botvinick, M., and An, J. (2009). Goal-directed decision making in prefrontal cortex: A computational framework. *Adv. Neural. Inf. Process Syst.* 21, 169–176.

Bressler, S., and Menon, V. (2010). Large-scale brain networks in cognition: Emerging methods and principles. *Trends Cogn. Sci.* 14, 277–290. doi: 10.1016/j.tics.2010.04.004

Briggs, R., Allan, P., Poologaindran, A., Dadario, N., Young, I., Ahsan, S., et al. (2021a). The frontal aslant tract and supplementary motor area syndrome: Moving towards a connectomic initiation axis. *Cancers* 13:1116. doi: 10.3390/cancers13051116

Briggs, R., Lin, Y., Dadario, N., Kim, S., Young, I., Bai, M., et al. (2021b). Anatomy and white matter connections of the middle frontal gyrus. *World Neurosurg.* 150, e520–e529. doi: 10.1016/j.wneu.2021.03.045

Buckner, R. (2013). The brain's default network: Origins and implications for the study of psychosis. *Dialogues Clin. Neurosci.* 15, 351–358. doi: 10.31887/DCNS.2013.15.3/rbuckner

Cheng, K., Fujita, H., Kanno, I., Miura, S., and Tanaka, K. (1995). Human cortical regions activated by wide-field visual motion: An H2(15)O PET study. *J. Neurophysiol.* 74, 413–427. doi: 10.1152/jn.1995.74.1.413

Conner, A., Briggs, R., Sali, G., Rahimi, M., Baker, C., Burks, J., et al. (2018). A connectomic atlas of the human cerebrum-chapter 13: Tractographic description of the inferior fronto-occipital fasciculus. *Oper. Neurosurg.* 15, S436–S443. doi: 10.1093/ons/opy267

Courtney, S., Petit, L., Haxby, J., and Ungerleider, L. (1998). The role of prefrontal cortex in working memory: Examining the contents of consciousness. *Philos. Trans. R. Soc. B Biol. Sci.* 353, 1819–1828. doi: 10.1098/rstb.1998.0334

Dadario, N., Tabor, J., Silverstein, J., Sun, X., and DAmico, R. (2021). Postoperative focal lower extremity supplementary motor area syndrome: Case report and review of the literature. *Neurodiagn. J.* 61, 169–185. doi: 10.1080/21646821.2021.1991716

Darby, R., Joutsa, J., Burke, M., and Fox, M. (2018). Lesion network localization of free will. *Proc. Natl. Acad. Sci. U.S.A.* 115, 10792–10797. doi: 10.1073/pnas.1814117115

De Carli, D., Garreffa, G., Colonnese, C., Giulietti, G., Labruna, L., Briselli, E., et al. (2007). Identification of activated regions during a language task. *Magn. Reson. Imaging* 25, 933–938. doi: 10.1016/j.mri.2007.03.031

du Boisgueheneuc, F., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., et al. (2006). Functions of the left superior frontal gyrus in humans: A lesion study. *Brain* 129, 3315–3328. doi: 10.1093/brain/awl244

Duncan, J., and Owen, A. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci.* 23, 475–483. doi: 10.1016/s0166-2236(00)01633-7

Einstein, E., Dadario, N., Khilji, H., Silverstein, J., Sughrue, M., and D'Amico, R. (2022). Transcranial magnetic stimulation for post-operative neurorehabilitation in neuro-oncology: A review of the literature and future directions. *J. Neurooncol.* 157, 435–443. doi: 10.1007/s11060-022-03987-9

Fox, P., Ingham, R., Ingham, J., Zamarripa, F., Xiong, J., and Lancaster, J. (2000). Brain correlates of stuttering and syllable production. A PET performance-correlation analysis. *Brain* 123, 1985–2004. doi: 10.1093/brain/123.10.1985

Freedman, M., Alexander, M., and Naeser, M. (1984). Anatomic basis of transcortical motor aphasia. *Neurology* 34, 409–417. doi: 10.1212/wnl.34.4.409

Fuster, J. (2015). *The prefrontal cortex*. Cambridge, MA: Academic press.

Garey, L. (1994). *Brodmann's localisation in the cerebral cortex*. Singapore: World Scientific Publishing Company.

Glasser, M., Coalson, T., Robinson, E., Hacker, C., Harwell, J., Yacoub, E., et al. (2016). A multi-modal parcellation of human cerebral cortex. *Nature* 536, 171–178. doi: 10.1038/nature18933

Godefroy, V., Batrancourt, B., Charron, S., Bouzigues, A., Bendetowicz, D., Carle, G., et al. (2022). Functional connectivity correlates of reduced goal-directed behaviors in behavioural variant frontotemporal dementia. *Brain Struct. Funct.* 227, 2971–2989. doi: 10.1007/s00429-022-02519-5

Goldman-Rakic, P. (1987). *Handbook of physiology-The nervous system*. Rockville, MD: American Physiological Society.

Hai, T., Swansburg, R., Kahl, C., Frank, H., Stone, K., Lemay, J., et al. (2022). Right superior frontal gyrus cortical thickness in pediatric ADHD. *J. Atten. Disord.* 26, 1895–1906. doi: 10.1177/10870547221110918

Helm, K., Viol, K., Weiger, T., Tass, P., Grefkes, C., Del Monte, D., et al. (2018). Neuronal connectivity in major depressive disorder: A systematic review. *Neuropsychiatr. Dis. Treat.* 14, 2715–2737. doi: 10.2147/NDT.S170989

Holmes, A., and Pizzagalli, D. (2008). Spatiotemporal dynamics of error processing dysfunctions in major depressive disorder. *Arch. Gen. Psychiatry* 65, 179–188. doi: 10.1001/archgenpsychiatry.2007.19

Hu, S., Ide, J., Zhang, S., and Li, C. (2016). The right superior frontal gyrus and individual variation in proactive control of impulsive response. *J. Neurosci.* 36, 12688–12696. doi: 10.1523/JNEUROSCI.1175-16.2016

Kübler, A., Dixon, V., and Garavan, H. (2006). Automaticity and reestablishment of executive control-an fMRI study. *J. Cogn. Neurosci.* 18, 1331–1342. doi: 10.1162/jocn.2006.18.8.1331

Lanzilotto, M., Perciavalle, V., and Lucchetti, C. (2013). Auditory and visual systems organization in Brodmann Area 8 for gaze-shift control: Where we do not see, we can hear. *Front. Behav. Neurosci.* 7:198. doi: 10.3389/fnbeh.2013.00198

Luria, A. (2012). *Higher cortical functions in man*. Berlin: Springer Science & Business Media.

Malouin, F., Richards, C., Jackson, P., Dumas, F., and Doyon, J. (2003). Brain activations during motor imagery of locomotor-related tasks: A PET study. *Hum. Brain Mapp.* 19, 47–62. doi: 10.1002/hbm.10103

Mandonnet, E., Sarubbo, S., and Duffau, H. (2017). Proposal of an optimized strategy for intraoperative testing of speech and language during awake mapping. *Neurosurg. Rev.* 40, 29–35. doi: 10.1007/s10143-016-0723-x

Marques, R., Vieira, L., Marques, D., and Cantilino, A. (2019). Transcranial magnetic stimulation of the medial prefrontal cortex for psychiatric disorders: A systematic review. *Braz. J. Psychiatry* 41, 447–457. doi: 10.1590/1516-4446-2019-0344

Martino, J., Brogna, C., Robles, S., Vergani, F., and Duffau, H. (2010). Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data. *Cortex* 46, 691–699. doi: 10.1016/j.cortex.2009.07.015

Matsumura, M., Sadato, N., Kochiyama, T., Nakamura, S., Naito, E., Matsunami, K., et al. (2004). Role of the cerebellum in implicit motor skill learning: A PET study. *Brain Res. Bull.* 63, 471–483. doi: 10.1016/j.brainresbull.2004.04.008

O'Neal, C., Ahsan, S., Dadario, N., Fonseka, R., Young, I., Parker, A., et al. (2021). A connectivity model of the anatomic substrates underlying ideomotor apraxia: A meta-analysis of functional neuroimaging studies. *Clin. Neurol. Neurosurg.* 207:106765. doi: 10.1016/j.clineuro.2021.106765

Petrides, M., and Pandya, D. (2012). "Chapter 26 - The frontal cortex," in *The human nervous system (third edition)*, eds J. Mai and G. Paxinos (Berlin: Academic Press), 988–1011.

Poologaindran, A., Lowe, S., and Sughrue, M. (2020). The cortical organization of language: Distilling human connectome insights for supratentorial neurosurgery. *J. Neurosurg.* 134, 1959–1966. doi: 10.3171/2020.5.JNS191281

Poologaindran, A., Profyris, C., Young, I., Dadario, N., Ahsan, S., Chendeb, K., et al. (2022). Interventional neurorehabilitation for promoting functional recovery post-craniotomy: A proof-of-concept. *Sci. Rep.* 12:3039. doi: 10.1038/s41598-022-06766-8

Postle, B., Stern, C., Rosen, B., and Corkin, S. (2000). An fMRI investigation of cortical contributions to spatial and nonspatial visual working memory. *Neuroimage* 11, 409–423. doi: 10.1006/nimg.2000.0570

Price, C., Green, D., and von Studnitz, R. (1999). A functional imaging study of translation and language switching. *Brain* 122, 2221–2235. doi: 10.1093/brain/122.12.2221

Rämä, P., Martinkauppi, S., Linnankoski, I., Koivisto, J., Aronen, H., and Carlson, S. (2001). Working memory of identification of emotional vocal expressions: An fMRI study. *Neuroimage* 13, 1090–1091. doi: 10.1006/nimg.2001.0777

Rapcsak, S., and Rubens, A. (1994). *Localization and neuroimaging in neuropsychology*. San Diego, CA: Academic Press.

Reser, D., Burman, K., Yu, H., Chaplin, T., Richardson, K., Worthy, K., et al. (2013). Contrasting patterns of cortical input to architectural subdivisions of the area 8 complex: A retrograde tracing study in marmoset monkeys. *Cereb. Cortex* 23, 1901–1922. doi: 10.1093/cercor/bhs177

Rogers, M., Kasai, K., Koji, M., Fukuda, R., Iwanami, A., Nakagome, K., et al. (2004). Executive and prefrontal dysfunction in unipolar depression: A review of neuropsychological and imaging evidence. *Neurosci. Res.* 50, 1–11. doi: 10.1016/j.neures.2004.05.003

Rose, J., McClernon, F., Froeliger, B., Behm, F., Preud'homme, X., and Krystal, A. (2011). Repetitive transcranial magnetic stimulation of the superior frontal gyrus modulates craving for cigarettes. *Biol. Psychiatry* 70, 794–799. doi: 10.1016/j.biopsych.2011.05.031

Rotge, J., Langbour, N., Guehl, D., Bioulac, B., Jaafari, N., Allard, M., et al. (2010). Gray matter alterations in obsessive-compulsive disorder: An anatomic likelihood estimation meta-analysis. *Neuropsychopharmacology* 35, 686–691. doi: 10.1038/npp.2009.175

Ruan, J., Bludau, S., Palomero-Gallagher, N., Caspers, S., Mohlberg, H., Eickhoff, S., et al. (2018). Cytoarchitecture, probability maps, and functions of the human supplementary and pre-supplementary motor areas. *Brain Struct. Funct.* 223, 4169–4186. doi: 10.1007/s00429-018-1738-6

Rubens, A., Whitakeer, H., and Whitaker, H. (1976). *Studies in neurolinguistics*. Amsterdam: Elsevier.

Sarkissov, S., Filimonoff, I., Kononowa, E., Preobraschenskaja, I., and Kukuew, L. (1955). *Atlas of the cytoarchitectonics of the human cerebral cortex*. Moscow: Medgiz.

Shahab, Q., Young, I., Dadario, N., Tanglay, O., Nicholas, P., Lin, Y., et al. (2022). A connectivity model of the anatomic substrates underlying Gerstmann syndrome. *Brain Commun.* 4:fcac140. doi: 10.1093/braincomms/fcac140

Sheets, J., Briggs, R., Young, I., Bai, M., Lin, Y., Poologaindran, A., et al. (2021). Parcellation-based modeling of the supplementary motor area. *J. Neurol. Sci.* 421:117322. doi: 10.1016/j.jns.2021.117322

Shen, Y., Yuan, Y., Wang, M., Zhi, Y., Wang, J., Wang, L., et al. (2020). Dysfunction in superior frontal gyrus associated with diphasic dyskinesia in Parkinson's disease. *NPJ Parkinsons Dis.* 6:30. doi: 10.1038/s41531-020-00133-y

Siegle, G., Thompson, W., Carter, C., Steinhauer, S., and Thase, M. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: Related and independent features. *Biol. Psychiatry* 61, 198–209. doi: 10.1016/j.biopsych.2006.05.048

Stephens, T., Young, I., O'Neal, C., Dadario, N., Briggs, R., Teo, C., et al. (2021). Akinetic mutism reversed by inferior parietal lobule repetitive theta burst stimulation: Can we restore default mode network function for therapeutic benefit? *Brain Behav.* 11:e02180. doi: 10.1002/brb3.2180

Tanglay, O., Young, I., Dadario, N., Briggs, R., Fonseka, R., Dhanaraj, V., et al. (2022). Anatomy and white-matter connections of the precuneus. *Brain Imaging Behav.* 16, 574–586. doi: 10.1007/s11682-021-00529-1

Usami, K., Matsumoto, R., Kunieda, T., Shimotake, A., Matsuhashi, M., Miyamoto, S., et al. (2013). Pre-SMA actively engages in conflict processing in human: A combined study of epicortical ERPs and direct cortical stimulation. *Neuropsychologia* 51, 1011–1017. doi: 10.1016/j.neuropsychologia.2013.02.002

Vogt, C., and Vogt, O. (1919). *Allgemeine ergebnisse unserer hirnforschung*. Germany: JA Barth.

Volz, K., Schubotz, R., and von Cramon, D. (2004). Why am I unsure? Internal and external attributions of uncertainty dissociated by fMRI. *Neuroimage* 21, 848–857. doi: 10.1016/j.neuroimage.2003.10.028

Volz, K., Schubotz, R., and von Cramon, D. (2005). Variants of uncertainty in decision-making and their neural correlates. *Brain Res. Bull.* 67, 403–412. doi: 10.1016/j.brainresbull.2005.06.011

von Economo, C., and Koskinas, G. (1925). *Die cytoarchitektonik der hirnrinde des erwachsenen menschen*. Berlin: Springer.

Wu, Y., Sun, D., Wang, Y., and Wang, Y. (2016). Subcomponents and connectivity of the inferior fronto-occipital fasciculus revealed by diffusion spectrum imaging fiber tracking. *Front. Neuroanat.* 10:88. doi: 10.3389/fnana.2016.00088

Yang, C., Hu, Y., Talishinsky, A., Potter, C., Calva, C., Ramsey, L., et al. (2022). Medial prefrontal cortex and anteromedial thalamus interaction regulates goal-directed behavior and dopaminergic neuron activity. *Nat. Commun.* 13:1386. doi: 10.1038/s41467-022-28892-7

Yun, J., Jang, J., Jung, W., Shin, N., Kim, S., Hwang, J., et al. (2017). Executive dysfunction in obsessive-compulsive disorder and anterior cingulate-based resting state functional connectivity. *Psychiatry Investig.* 14, 333–343. doi: 10.4306/pi.2017.14.3.333

Zilles, K., and Amunts, K. (2010). Centenary of Brodmann's map–conception and fate. *Nat. Rev. Neurosci.* 11, 139–145. doi: 10.1038/nrn2776

frontiers | Frontiers in Psychology

TYPE Original Research
PUBLISHED 24 August 2023
DOI 10.3389/fpsyg.2023.1210259

OPEN ACCESS

EDITED BY
Dorit Ben Shalom,
Ben-Gurion University of the Negev, Israel

REVIEWED BY
Zhong-Xu Liu,
University of Michigan–Dearborn, United States
Dermot Bowler,
City University of London, United Kingdom

*CORRESPONDENCE
Marjorie Solomon
✉ marsolomon@ucdavis.edu

RECEIVED 24 April 2023
ACCEPTED 09 August 2023
PUBLISHED 24 August 2023

CITATION
Minor GN, Hannula DE, Gordon A, Ragland JD, Iosif A-M and Solomon M (2023) Relational memory weakness in autism despite the use of a controlled encoding task.
Front. Psychol. 14:1210259.
doi: 10.3389/fpsyg.2023.1210259

Relational memory weakness in autism despite the use of a controlled encoding task

Greta N. Minor[1], Deborah E. Hannula[1], Andrew Gordon[2], J. Daniel Ragland[2], Ana-Maria Iosif[2] and Marjorie Solomon[2]*

[1]Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, WI, United States, [2]Department of Psychiatry & Behavioral Sciences, University of California, Davis, Davis, CA, United States

Introduction: Recent work challenged past findings that documented relational memory impairments in autism. Previous studies often relied solely on explicit behavioral responses to assess relational memory integrity, but successful performance on behavioral tasks may rely on other cognitive abilities (e.g., executive functioning) that are impacted in some autistic individuals. Eye-tracking tasks do not require explicit behavioral responses, and, further, eye movements provide an indirect measure of memory. The current study examined whether memory-specific viewing patterns toward scenes differ between autistic and non-autistic individuals.

Methods: Using a long-term memory paradigm that equated for complexity between item and relational memory tasks, participants studied a series of scenes. Following the initial study phase, scenes were re-presented, accompanied by an orienting question that directed participants to attend to either features of an item (i.e., in the item condition) or spatial relationships between items (i.e., in the relational condition) that might be subsequently modified during test. At test, participants viewed scenes that were unchanged (i.e., repeated from study), scenes that underwent an "item" modification (an exemplar switch) or a "relational" modification (a location switch), and scenes that had not been presented before. Eye movements were recorded throughout.

Results: During study, there were no significant group differences in viewing directed to regions of scenes that might be manipulated at test, suggesting comparable processing of scene details during encoding. However, there was a group difference in explicit recognition accuracy for scenes that underwent a relational change. Marginal group differences in the expression of memory-based viewing effects during test for relational scenes were consistent with this behavioral outcome, particularly when analyses were limited to scenes recognized correctly with high confidence. Group differences were also evident in correlational analyses that examined the association between study phase viewing and recognition accuracy and between performance on the Picture Sequence Memory Test and recognition accuracy.

Discussion: Together, our findings suggest differences in the integrity of relational memory representations and/or in the relationships between subcomponents of memory in autism.

KEYWORDS

ASD, autism, episodic memory, relational memory, eye tracking

1. Introduction

Autism is a neurodevelopmental disorder characterized by persistent difficulties with social interaction and communication, in addition to the presence of restricted and repetitive behaviors, interests, or activities (American Psychiatric Association, 2013). Although these behavioral hallmarks are criterial for an autism diagnosis, other aspects of cognition are also atypical in autism. For example, weaknesses in executive functioning and attention are reliably reported (Wainwright-Sharp and Bryson, 1993; Burack, 1994; Belmonte and Yurgelun-Todd, 2003; Landry and Bryson, 2004; Solomon et al., 2008, 2009; Mostert-Kerckhoffs et al., 2015; Lai et al., 2017; see Demetriou et al. (2018), Keehn et al. (2013) for reviews), and studies indicate that weaknesses in episodic memory are present as well (see Boucher et al. (2012), Cooper and Simons (2019), Desaunay et al. (2020a), Griffin et al. (2021) for reviews). Notably, differences in episodic memory have not always been reported in past work. One reason for contradictory findings may be that tasks used in some prior studies were susceptible to other forms of cognitive dysfunction in autistic individuals. For instance, direct tests of memory (e.g., recognition tasks that require deliberative processing and decision making) may be more reliant on executive functioning abilities than indirect measures of memory (e.g., measures that do not require explicit memory decisions), and executive functioning abilities are a well-documented weakness in autistic individuals. Additionally, some published studies used incidental encoding tasks (i.e., learning tasks without explicit instructions to memorize materials), which are likely to be more challenging for autistic individuals, who often show attentional difficulties relative to their non-autistic peers. Therefore, it is possible that previously reported memory difficulties in autism are a consequence of conflated cognitive requirements of specific tasks that have been used rather than evidence for true memory difficulties. The current study was designed to help adjudicate conflicting findings by employing both direct (i.e., explicit recognition) and indirect (i.e., eye-tracking) measures of memory performance in a task with experimental conditions matched for difficulty and more controlled encoding requirements.

Predicted episodic memory weaknesses in autistic persons are not unwarranted, as there are documented structural and functional connectivity differences in brain regions that contribute to episodic memory in autism. Research conducted with non-autistic participants reports that dissociable regions of the medial temporal lobes (MTL), including the hippocampus and perirhinal cortex, support long-term declarative memory (Eichenbaum et al., 2007; Konkel et al., 2008; Ranganath, 2010). Past studies indicate that the hippocampus is critical for the binding of associative, spatial, and temporal relationships between items in memory (i.e., relational memory), while the perirhinal cortex is identified as a key player in item-specific memory (Ryan et al., 2000; Davachi et al., 2003; Hannula et al., 2006; Staresina and Davachi, 2008; see Davachi (2006) for review). Consistent with behavioral reports of relational memory difficulties in autistic individuals, structural abnormalities in the hippocampus are reported in postmortem studies in this population (Bauman and Kemper, 2005; Fetit et al., 2021) and in structural imaging studies of hippocampal development (Reinhardt et al., 2020).

Neuroimaging studies, conducted with non-autistic individuals, also indicate that structures in the frontal and parietal lobes contribute to episodic memory encoding and retrieval (see Kim (2010), Spaniol et al. (2009) for reviews). The prefrontal cortex supports the organization of information in working memory during encoding, source monitoring during retrieval, post-retrieval selection of goal-relevant information, and self-referential processing that permits the integration of retrieved memories with prior knowledge (e.g., Dobbins and Wagner, 2005; Schlichting and Preston, 2015; see Blumenfeld and Ranganath (2007), Fletcher and Henson (2001) for reviews). Activation in the posterior parietal cortex is associated with the subjective experience of recollection, high confidence source memory judgments, attention to retrieved content, and the online representation and maintenance of retrieved representations over time (Cabeza et al., 2008; Ciaramelli et al., 2017; see Moscovitch et al. (2016), Rugg and Vilberg (2013) for reviews).

Postmortem studies and structural imaging work indicate volumetric differences in frontal and parietal brain regions in autistic individuals relative to controls (Ecker et al., 2010; Fetit et al., 2021; although see Trontel et al., 2015), and functional neuroimaging studies demonstrate abnormalities in functional connectivity between the prefrontal cortex, parietal regions, and the hippocampus in autistic individuals (e.g., Ben Shalom, 2003; Barnea-Goraly et al., 2014; Cooper et al., 2017b; Banker et al., 2021; Li et al., 2022). For example, attenuated functional connectivity between the hippocampus and fronto-parietal networks is reported during retrieval, accompanied by lower levels of retrieval accuracy, in autistic individuals (Cooper et al., 2017b). Another study documents reduced activation in the left posterior hippocampus and enhanced PFC activation during encoding, which may indicate more effortful encoding for these individuals (Gaigg et al., 2015).

The combination of structural and functional differences in memory-associated brain areas observed in autism align with reported weaknesses on long-term memory tasks requiring retrieval of details diagnostic of the encoding experience (Boucher and Warrington, 1976; Boucher, 1981; Bowler et al., 1997). Specifically, autistic individuals make fewer subjective, recollection-related responses (e.g., "remember" responses in remember-know paradigms; e.g., Bowler et al., 2007; Cooper et al., 2015), exhibit reduced confidence in judgments of mnemonic accuracy (i.e., metamemory; e.g., Wojcik et al., 2013; Grainger et al., 2014; Cooper et al., 2016), and demonstrate poorer recall of autobiographical memories (e.g., Lind and Bowler, 2010). Consistent with these observations, individuals diagnosed with autism have a disproportionate weakness in relational memory with relatively intact memory for individual items (Bigham et al., 2010; Bowler et al., 2014; Desaunay et al., 2020b). Indeed, relational memory difficulties are documented across a range of stimuli (e.g., abstract and realistic objects, words, etc.) and across different types of relational memory tasks (e.g., inter-object, object-location, object-color, object-action, and object-voice pairing tasks; Lind and Bowler, 2009; Bigham et al., 2010; Bowler et al., 2014; Cooper et al., 2017b; Desaunay et al., 2020b). Such findings are in line with the *relational binding account* of episodic memory in autism (Bowler et al., 2011), which posits that autistic individuals show a selective weakness in hippocampus-dependent binding of items and contexts but a relative sparing of memory for items alone.

Importantly, the relational binding account has not always been supported by previous findings. Some studies report that autistic individuals show difficulties restricted to item memory (Solomon et al., 2016; Cooper et al., 2017a), weaknesses in both item and relational memory (Cooper et al., 2015; Massand and Bowler, 2015;

Ring et al., 2016; Semino et al., 2018; Mogensen et al., 2020), or intact item and relational memory (Souchay et al., 2013; Lind et al., 2014; Ring et al., 2015, 2017; Hogeveen et al., 2020). One possible explanation for discrepant findings is that task complexity differed across item-specific and relational memory tasks in these experiments (e.g., as in Bowler et al., 2014). Indeed, in past work, tests of item-specific memory have typically required participants to recognize a single item from the encoding phase, while tests of relational memory required participants to remember multiple elements of the encoding scenario. Further supporting the potential influence of this confound on prior work, autistic individuals have shown difficulties with processing "complex" information (e.g., complex conceptual structure/organization of material and/or retrieval tasks that require higher levels of cognitive control) across a range of cognitive tasks (*complex information processing model*; Minshew and Goldstein, 1998, 2001). Thus, it is conceivable that reports from previous studies are in conflict because task demands are typically quite different for item-specific and relational memory tests.

To address this problem, Cooper et al. (2015) utilized a long-term memory task with item-specific and relational memory conditions that were well-matched for task difficulty. During encoding, autistic and non-autistic adults studied computer-generated scenes that contained pre-defined "critical" items. Subsequently, in a corresponding test phase, participants were presented with previously studied and new (i.e., never presented) scenes, and some of the studied scenes were modified. When scenes were modified, rather than repeated, the critical item was either replaced with a different exemplar (i.e., item-specific change) or had moved to a new spatial location (i.e., relational change). Participants were instructed to determine, for each test scene, whether it was repeated, modified, or new. Importantly, the experiment was designed so that memory for item-specific detail and spatial relationships was assessed in the context of the same set of scenes, and pilot testing had confirmed that performance was well-matched across conditions (Hannula et al., 2015). Results indicated that autistic individuals identified significantly fewer modified scenes in both the item-specific and relational memory conditions relative to their non-autistic peers and that autistic participants were less likely to endorse successfully identified scenes as recollected. Thus, when task-difficulty is well-matched across conditions, it appears that the memory weakness is not limited to relational memory (Cooper et al., 2015).

It is important to note, however, that much of the past work investigating long-term episodic memory in autistic individuals, including Cooper et al.'s (2015) study, has relied solely on explicit behavioral responses (e.g., button-press recognition responses). This is problematic because complex instructions and/or button-press mappings in these experiments depend on the integrity of additional cognitive processes (Luck and Gold, 2008) that are impacted in autistic individuals (e.g., cognitive control; Schmitt et al., 2018; see Tonizzi et al. (2021) for review). Moreover, other aspects of previously published studies (e.g., relatively uncontrolled encoding conditions) make it difficult to determine whether results provide evidence of true memory difficulties or are a secondary consequence of attentional and executive processing differences during encoding. For example, in Cooper et al.'s (2015) work, participants were instructed to try and remember the appearance and location of the objects in the scene. However, autistic individuals show difficulties with the disengagement of attention (see Keehn et al. (2013) for review) and inefficient attentional filtering of information (e.g., Burack, 1994; Murphy et al., 2014; Keehn et al., 2019), which may have interfered with the initial exploration and encoding of information in scenes during the study phase and may have led to reported memory weaknesses. In sum, specific task requirements may result in the conflation of cognitive processes that are differentially impacted in autistic individuals, and these differences may account for reported discrepancies in autistic performances on episodic memory tests.

Therefore, other methods may be useful in disentangling contradictory findings. One method used to index memory indirectly is eye tracking. An advantage of this method is that eye movements can be recorded throughout an experiment, which means that researchers can pinpoint when (i.e., at what stage of processing – encoding vs. retrieval) there are differences in performance (e.g., differences in scene exploration) that may contribute to reported memory difficulties in special populations. Past eye-tracking studies with healthy, college-age participants demonstrate that when a stimulus is presented repeatedly, participants make fewer fixations and sample fewer distinct regions of a picture with each repetition (i.e., Althoff and Cohen, 1999; Ryan et al., 2000, 2007; Heisz and Shore, 2008). Additionally, the number of fixations made during encoding is positively correlated with recognition accuracy during test (Pertzov et al., 2009; Molitor et al., 2014; Olsen et al., 2014) and, during retrieval, viewing patterns distinguish previously studied scenes that have been modified from those that are repeated without a change (e.g., Ryan et al., 2000).

In one representative example, Hannula et al. (2010a,b) used the task subsequently adopted by Cooper et al. (2015) but also incorporated a second, controlled encoding phase. During this second encoding phase, participants viewed the same set of scenes that were presented during the first encoding phase, but now each scene was accompanied by an orally-presented "yes/no" question orienting a participant's attention to either the features of a "critical" item (i.e., an 'item-specific' orienting question) or to the spatial location of a "critical" item (i.e., a 'spatial relational' orienting question) that might be modified in the test phase. Use of orienting questions during the encoding task ensured that participants attended to the very same information that might be manipulated subsequently, meaning that any differences in retrieval performance were less likely due to differences in attention to critical objects during encoding. At test, participants spent more time fixating the critical regions of repeated (versus novel) scenes because attention had been directed to these regions by the orienting questions during the second encoding phase. Additionally, a disproportionate amount of time was spent viewing critical regions of modified (versus repeated) scenes, including the *empty* regions of scenes when a relational change had been made (i.e., the location originally occupied by the critical object, now empty). Because eye movements are more likely to be made toward objects than to empty regions of a scene (Yarbus, 1967), these viewing time differences represent particularly compelling evidence for the influence of relational memory on eye-movement behavior (see also Ryan et al. (2000)).

Further evidence for the sensitivity of eye movements to item-specific and relational memory comes from previous work with clinical populations. For instance, in the study described above (Hannula et al., 2010b), individuals diagnosed with schizophrenia showed a disproportionate deficit in the eye-movement-based relational memory effect relative to healthy comparison participants.

This outcome is similar to impairments reported when amnesic patients with MTL damage are tested in comparable experiments. Specifically, amnesic patients show standard effects of stimulus repetition in patterns of viewing, but eye-movement-based relational memory effects are impaired (e.g., Ryan et al., 2000). In studies of autism, eye tracking has been used to examine the exploration of social stimuli (with differences in viewing reported; see Chita-Tegmark (2016); Papagiannopoulou et al. (2014) for reviews), but only a handful of previous studies have used this method to address questions about the integrity of long-term memory (Loth et al., 2011; Ring et al., 2017; Cooper et al., 2017a).

In general, published eye-tracking studies indicate that viewing effects (e.g., gaze time, number of fixations, fixation duration) are similar between autistic and non-autistic individuals during encoding, suggesting attention to scenes during encoding is unaffected in autism (Loth et al., 2011; Cooper et al., 2017a). However, when correlational analyses are conducted to examine associations between viewing patterns and subsequent memory, results suggest that viewing patterns may not predict subsequent memory performance to the same degree in autistic and non-autistic participants (Loth et al., 2011; Ring et al., 2017; Cooper et al., 2017a). It is proposed that these differences point to a problem at the time of retrieval, rather than encoding, in autistic individuals (Cooper et al., 2017a), since differences in memory performance occur during the retrieval phase and are accompanied by similar eye-movement patterns during encoding. Consistent with this conclusion, past work measuring retrieval-related viewing patterns indicate that fixation 'reinstatement' (i.e., extent to which viewing patterns from study are reinstated during test) is reduced for recollected scenes in autistic relative to non-autistic participants, while reinstatement patterns for non-recollected scenes are not different between groups (Cooper et al., 2017a), potentially indicating that memory weaknesses reported in autism are due to a disrupted recollection-related retrieval process (cf. Griffin et al., 2021).

To our knowledge, one eye-tracking study has explicitly used a relational memory task in an autism population (Ring et al., 2017), and results revealed between-groups differences in retrieval-related eye movements. During test phase trials, three locations were marked in previously studied scenes – one corresponding to the location that was occupied by a studied object and two previously unoccupied locations. On every trial, participants were either presented with the originally encoded object or a new, unstudied object. In each case, they were required to place the object in one of the marked scene locations. For "include" trials, they were to put the object in its originally studied location; for "exclude" trials, they were to put the object in one of the two new locations (i.e., process dissociation procedure; Jacoby, 1991). If unable to remember the object or the location, participants were told to choose one of the available locations (i.e., a measure of potential position-based bias for the set of counterbalanced new objects). Results indicated that both groups of participants were equally likely to place the object in its original location on "exclude" trials (a measure of implicit memory) but that individuals with autism were less likely to put the object in its original location on "include" trials (a measure of explicit memory). Eye-tracking results revealed that, during encoding, non-autistic individuals spent more time viewing objects that were subsequently placed correctly during test relative to autistic individuals. In addition, autistic participants spent less time looking at target locations during "include" trials and non-target locations during "exclude" trials compared to the non-autistic participants. Collectively, these results are consistent with reports that relational memory is disrupted in autism, and, further, differences were evident not only in direct measures of performance but also when memory was measured indirectly, using eye movement data.

In a key departure from previously published studies, eye-tracking data was recorded here in a task that examined both item-specific and relational memory. Importantly, as indicated earlier, a norming experiment demonstrated that these experimental conditions were equated for difficulty (Hannula et al., 2010b) to ensure viewing effects could not be attributed to differential task complexity. Specifically, we examined whether memory-specific viewing patterns to realistic, non-social scenes differed between autistic and non-autistic individuals. Participants first viewed a set of scenes while being instructed to memorize the scene. Following the initial study phase, scenes were re-presented, accompanied by an orienting question (e.g., "Is the hat on the chair?"). Participants were told to respond to the question, which encouraged them to attend to specific objects in the scenes that might be subsequently manipulated (i.e., exchanged with different exemplar or moved to different spatial location) during the test phase. This 'orienting' question was intended to reduce the burden on attentional resources and executive functions that may be compromised in autism. During test, participants viewed scenes that were unchanged (i.e., repeated from study), scenes that underwent an "item" change (an exemplar switch) or a "relational" change (a location switch), and scenes that were not presented during the encoding phase. Both direct (i.e., recognition responses) and indirect (i.e., eye movement) measures of memory were recorded.

Consistent with results reported in Cooper et al.'s (2015) study that used the same scenes and a similar task, one possibility was reduced explicit recognition accuracy for modified scenes in the autistic group, whether the change was item-specific or relational. The few studies examining eye-movement behavior in autism suggest that between-group differences in basic viewing patterns might not be evident during encoding. It is possible though that there may be reductions in the positive correlations between encoding-related eye movements and subsequent memory performance, as reported previously in autism (Loth et al., 2011; Ring et al., 2017; Cooper et al., 2017a). During test, eye movement effects sensitive to memory for spatial relationships might be selectively reduced in autism, an outcome consistent with the relational binding hypothesis (Bowler et al., 2011). However, if the problem in autism is related to the initial processing of relational information (e.g., during encoding), then use of an orienting question during the second study block should reduce or eliminate the relational memory difficulty because these questions encourage participants to attend to and process the same relationships that might be modified at test. In sum, use of direct and indirect measures of memory, together with well-matched item-specific and relational memory conditions, was expected to aid in disambiguating contradictory findings reported in the autism episodic memory literature.

2. Method

2.1. Participants

Forty participants (18 autistic, 22 non-autistic) were recruited during the second wave of data collection from a cohort-sequential study (*Neurodevelopment of cognitive control in autism: adolescence to*

TABLE 1 Demographic and clinical characteristics of the sample.

	Autistic (n = 18)	Non-Autistic (n = 20)
Female	7 (39%)	5 (25%)
Male	11 (61%)	15 (85%)
Age	20.68 (2.71; 16.42–24.83)	21.28 (2.39; 17.08–24.92)
FSIQ-4	103.11 (12.22; 76–125)	108.60 (14.20; 79–129)
VCI	102.61 (10.42; 85–120)	105.5 (15.81; 73–137)
PRI	103.11 (16.57; 68–131)	109.35 (14.76; 83–140)
ADOS CSS	7.06 (2.10; 4–10)	–
ADOS SA Severity	7.33 (2.00; 3–10)	–
ADOS RRB Severity	6.5 (2.94; 1–10)	–

Data are reported as frequencies (percentages) for categorical variables and means (standard deviations; ranges) for continuous variables.
FSIQ-4 (Full Scale IQ composed of 4 indices); VCI (Verbal Comprehension Index); PRI (Perceptual Reasoning Index); ADOS (Autism Diagnostic Observation Schedule); ADOS CSS (ADOS Calibrated Severity Score); ADOS SA Severity (ADOS Social Affect Severity); ADOS RRB Severity (ADOS Restricted, Repetitive Behavior Severity).

TABLE 2 NIH toolbox® cognition battery scores for autistic and non-autistic participants.

	Autistic (n = 18)	Non-autistic (n = 20)
Flanker Inhibitory Control and Attention Test (FICA)	103.89 (8.17; 90–114)	111.45 (4.26; 104–117)
Dimensional Change Card Sort Test (DCCS)	105.11 (12.12; 81–120)	113 (6.14; 101–120)
Picture Sequence Memory Test (PSM)	107.17 (11.25; 86–123)	117 (14.54; 95–136)
List Sorting Working Memory Test (LSWM)	110.06 (12.29; 90–136)	112.55 (8.85; 97–128)

Data are reported as means (standard deviations; ranges).

young adulthood; 1R01MH106518) of autistic and non-autistic persons without intellectual disability (IQ ≥ 70) through the University of California (UC) Davis MIND Institute and Imaging Research Center. Two participants in the non-autistic group were removed from analysis because the number of test block trials with unreliable eye-tracking data was more than two standard deviations above the group mean. Therefore, the sample carried forward for analysis included 18 autistic individuals and 20 non-autistic individuals. This sample size was comparable to, or greater than, the sample size from previously published studies using the same task (i.e., Cooper et al. (2015) – 24 participants per group; Hannula et al. (2010b) – 16 participants per group). With this sample size, we had sufficient power (80.4%) to detect large effects for group differences (d = 0.9) with alpha set to 0.05, two-tailed.

Written, informed consent was obtained from participants in accordance with the UC Davis Institutional Review Board. Participants received a gift card for their participation. To be included in the study, all participants were required to be between the ages of 12 and 24 and to have a Full Scale IQ of 70 or above on the Wechsler Abbreviated Scale of Intelligence – 2nd Edition (WASI-II; Wechsler, 2011). Participants were not permitted to be taking psychotropic medications at the time of their enrollment in the study. Participants were also excluded from participation if they had a diagnosis of epilepsy or another neurological disorder and/or if imaging was contraindicated. Autistic participants were required to have a community diagnosis of autism and were required to meet criteria for autism on a DSM-5 Criteria Checklist for autism (American Psychiatric Association, 2013) and on the Autism Diagnostic Observation Schedule – 2nd Edition (ADOS-2; Lord et al., 2000), which were administered by a licensed clinician at the UC Davis MIND Institute. Non-autistic participants were not included in the study if they had a community diagnosis of autism, attention-deficit/hyperactivity disorder, or any neurodevelopmental disorder, had a first-degree family member with autism, had reported Axis I psychopathology, or surpassed a cut-off value of 11 on the Social Communication Questionnaire (SCQ; Rutter et al., 2003), suggestive of an autism diagnosis.

Table 1 provides basic descriptive statistics for each group on the following characteristics: gender, chronological age, WASI-II (Wechsler, 2011) Full Scale IQ (FSIQ-4), and WASI-II index scores (Verbal Comprehension Index [VCI] and Perceptual Reasoning Index [PRI]). There were no significant differences between groups on age, WASI-II FSIQ-4, or WASI-II index scores, F's ≤ 1.61, p's ≥ 0.21. In Table 1, scores on the semi-structured ADOS-2 (Lord et al., 2000) are also provided for individuals in the autistic group, including the calibrated severity score (CSS) and severity scores in the Social Affect (SA) and Restricted, Repetitive Behavior (RRB) domains. Table 2 presents scores on select tests from the NIH Toolbox® Cognition Battery used to assess symptoms related to inattention/impulsivity, executive dysfunction, working memory, and episodic memory (Akshoomoff et al., 2013), including scores on the Flanker Inhibitory Control and Attention Test (FICA), Dimensional Change Card Sort Test (DCCS), Picture Sequence Memory Test (PSM), and List Sorting Working Memory Test (LSWM). There were significant differences between groups on two executive functioning tasks (FICA, DCCS), Welch's F's ≥ 6.20, p's ≤ 0.020, ω^2's ≥ 0.12, and on an episodic memory test (PSM), F (1, 36) = 5.35, p = 0.027, η_p^2 = 0.13, with higher scores in the non-autistic group compared to the autistic group across all three measures. There were no significant group differences on a working memory task (LSWM), F (1, 36) = 0.52, p = 0.47.

2.2. Materials and apparatus

Sixty-four computer-generated indoor and outdoor scenes (800 × 600 pixels) created using Punch! Home Design Software (Encore, Inc., El Segundo, CA) by Hannula et al. (2006, 2010b) were used in the current study. Three versions of each scene were developed – an original version, a version in which a designated critical item was switched with a different exemplar (i.e., an item manipulation), and a version in which that same critical item had been moved to a similarly plausible location (i.e., a relational manipulation; see Figure 1A). The total stimulus sample included 192 scenes. When critical objects switched spatial locations in the relational condition, objects were moved equally often from left, in the original scene, to right, in the manipulated scene, and vice versa. Scenes were presented at a resolution of 1,012 × 762 pixels, and scenes subtended 28.61 (width) by 21.74 (height) degrees of visual angle, from a viewing distance of 70 cm. Scenes were displayed on a monitor with 1,980 × 1,200-pixel

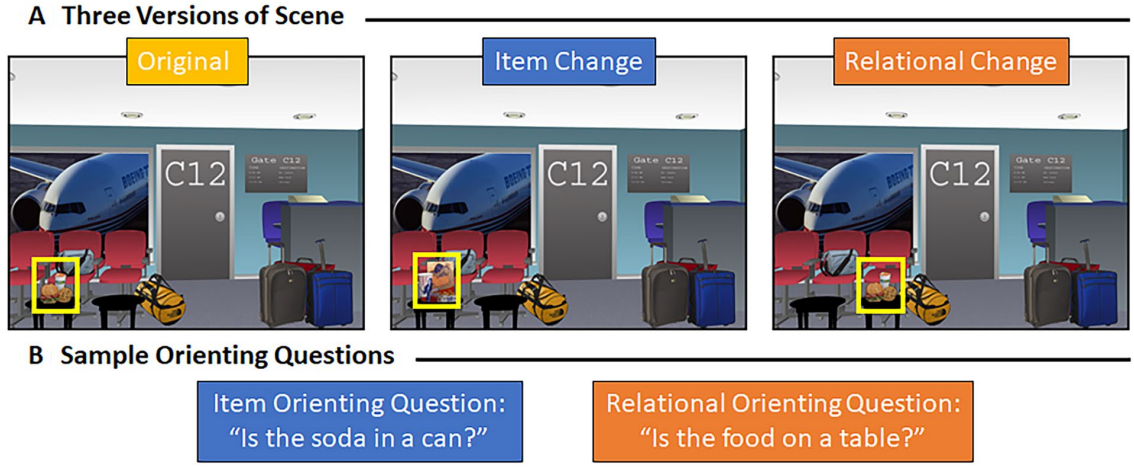


FIGURE 1
Representative scene and associated orienting questions. **(A)** Example of a representative scene – the original scene, the version of that scene with an item manipulation, and the version of that scene with a relational manipulation. **(B)** Item (in blue) and relational (in orange) orienting question for the scene shown above **(A)**.

resolution and a refresh rate of 60 Hz. Additionally, two orienting questions were created for each scene. One question was designed to orient attention to the features of a critical object and the other to the spatial relationship between a critical object and its surroundings (examples are provided in Figure 1B). The purpose of the orienting question was to direct the viewer's attention to critical properties of the scenes that might be manipulated during the subsequent test block.

Eye movements were recorded with an Eyelink 1,000 Plus eye-tracking system (SR Research LTD: Ontario, Canada). This system has a temporal resolution of 1,000 Hz and head-supported spatial resolution of 0.01°. Eye movements were identified as saccades using an automated algorithm that requires a minimum velocity of 30°/s and a minimum acceleration of 8,000°/s^2. Experiment Builder software package (SR Research LTD: Ontario, Canada) was used to display the experiment, and Data Viewer software package (SR Research LTD: Ontario, Canada) was used to extract the eye-tracking data.

2.3. Design and procedure

After participants gave their consent to participate, they were seated 70 cm from the computer monitor and a chinrest was adjusted to a comfortable position. An automated 9-point calibration process was then performed to align fixations with screen coordinates before the experiment began; this process was repeated as necessary until calibration was successful, and a drift correction procedure was used before each trial to ensure accurate tracking throughout the experiment. Prior to completing the experiment, instructions were provided. Twelve practice study trials (six each in Study Blocks 1 and 2) and eight practice test trials were used to ensure that participants understood the task. During the practice test trials, participants were given feedback on their performance. Scenes viewed during study and test were presented side-by-side to afford participants the opportunity to become familiar with the types of scene manipulations they may encounter. Eye movements were recorded in each phase of the experiment.

2.3.1. Study Block 1

Following practice, participants were shown 48 scenes during Study Block 1 (see Figure 2A). Sixteen of these scenes were 'repeated' during test (i.e., same version of the scene was re-presented), 16 underwent an item manipulation at test (i.e., henceforth referred to as the "item" condition), and 16 underwent a relational manipulation at test (i.e., henceforth referred to as the "relational" condition). Participants were instructed to view the scenes and attempt to commit each scene to memory. Every trial began with a central fixation cross; the trial could not be initiated by the experimenter until the participant fixated the center of the screen. Each scene was presented for a duration of 8 s.

2.3.2. Study Block 2

During Study Block 2, the same 48 scenes were presented again in a new random order (see Figure 2B). When participants fixated the center of the screen, the experimenter initiated the trial, and a scene was presented for 5 s. Now, each scene was accompanied by a corresponding orienting question (pre-recorded and presented over speakers), initiated 500 ms after scene onset. The question directed the participant's attention either to features of a critical object (if the scene was assigned to the "item" condition) or to the spatial relationship between a critical object and its surroundings (if the scene was assigned to the "relational" condition). For scenes assigned to the "repeated" condition, half were presented with an item-specific orienting question and half were presented with a relational orienting question. Participants were instructed to respond "yes," "no," or "don't know" to the orienting question via a button press, while the picture was in view.

2.3.3. Test Block

Participants saw 64 scenes during the Test Block (see Figure 2C). Sixteen scenes were the exact image seen during study (i.e., "repeated" scenes), 16 scenes had undergone an item manipulation (i.e., "item" scenes), 16 scenes had undergone a relational manipulation (i.e., "relational" scenes), and 16 scenes were new (i.e., "novel" scenes). Critically, a yoked design was used; three participants saw the exact

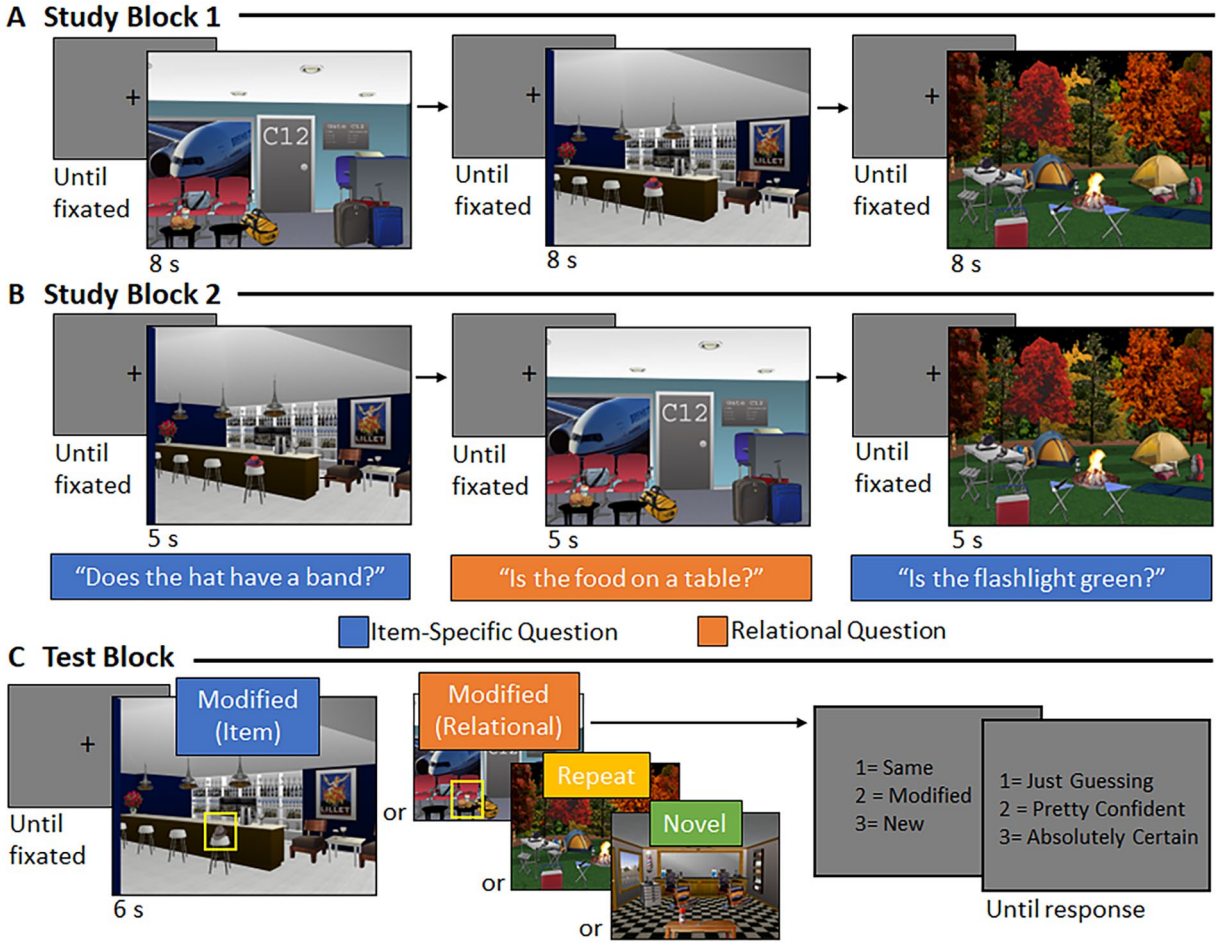


FIGURE 2
Trial structure and event timing. **(A)** During Study Block 1, central fixation was followed by a scene (8 s). **(B)** During Study Block 2, central fixation was followed by a scene (5 s), accompanied by an orally presented orienting question to which participants responded via button press. **(C)** During the test block, central fixation was followed by a scene (6 s). Participants indicated via button press whether the scene was the "same," "modified," or "new" and provided a confidence rating, when prompted.

same version of a scene during test, but different encoding experiences meant the scene was manipulated for one participant, repeated for another, and novel for a third (see Figure 3). This yoked design means that any differences in viewing, across conditions, could not be due to differences in features of the scenes presented during the test phase. Instead, any differences in viewing patterns would be directly attributable to differences in encoding history. Scenes were presented equally often as repeated, manipulated, and novel across participants.

Following central fixation, the experimenter initiated the trial, and a scene was presented for 6 s. After the scene disappeared from the screen, participants were prompted to respond via button press whether the scene was the "same" as one they had studied, had been "modified" somehow, or was "new." Then, participants were asked to rate their recognition confidence on a scale from 1 ("just guessing") to 3 ("absolutely certain") with a button-press response. In each case, response options remained on the screen until a response was made. At the end of the experiment, participants were debriefed.

2.3.4. Data processing and analysis

Trials were flagged and removed from analyses when eye position was lost or unreliable. As in previously published work (e.g., Hannula et al., 2010b), trials were removed if the total viewing time directed to the scene was less than 65% of the trial duration. This resulted in the loss of 2.14% of trials ($SD = 2.98\%$) across autistic and non-autistic participants. Two participants from the non-autistic group were removed from all analyses because the number of test block trials flagged as bad was more than two standard deviations above the group mean (28 and 55% of the trials, respectively). To examine differences in processing of and attention toward critical items, orienting question accuracy was calculated for button-press responses made during Study Block 2. Corrected recognition scores were calculated to determine whether explicit memory performance during the Test Block differed between groups. As was done by Cooper et al. (2015), the percentage of studied (repeated and modified) scenes mistakenly endorsed as "new" (i.e., Novel False Alarms) was subtracted from the percentage of novel scenes that were identified correctly (i.e., Novel Hits) to examine *memory for scenes.* Corrected recognition scores sensitive to *memory for scene detail* were calculated separately for the item and relational conditions by subtracting the percentage of repeated scenes incorrectly endorsed as "modified" from the percentage of item and relational scenes identified correctly, respectively. This measure provides us with information about how effectively participants could

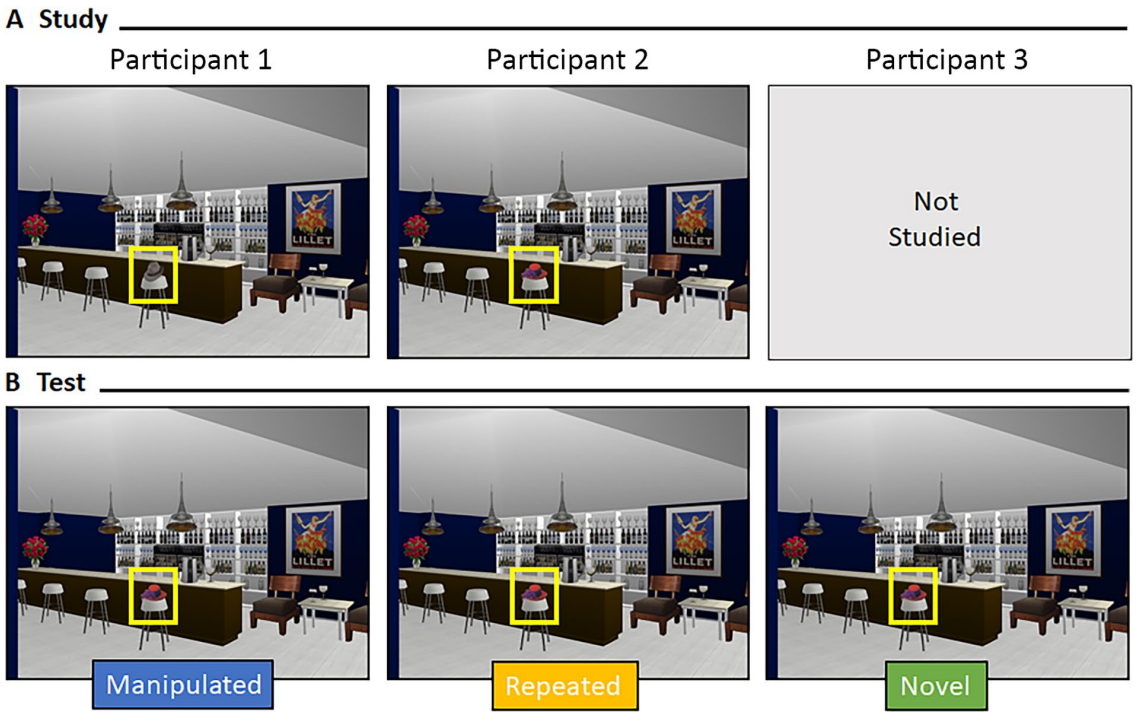


FIGURE 3
Yoking procedure at test. Representative example of a yoked scene during **(A)** study and **(B)** test for three different participants. Scenes during test were identical across participants but varied by encoding history.

discriminate between studied scenes that went on to be manipulated and studied scenes that remained the same.

Three regions of interest were drawn for each scene to examine viewing effects. One of these regions marked the boundaries of the whole scene (i.e., "scene" region), one marked the current location of the critical object (i.e., "filled" region), and one marked the location where the critical object used to be located (i.e., "now-empty" region) when a relational change was made. The boundaries of the "filled" and "empty" regions were drawn in Adobe Photoshop to extend 25 pixels beyond the horizontal and vertical limits of the critical object. Fixations outside the bounds of the "scene" region were discarded from analyses, and total viewing time, used as the denominator in our proportion of total viewing time measures, was the summed duration of fixations made to the scene itself (rather than the full duration of scene presentation; see Hannula et al. (2010a) for details). For the Study Blocks, regions of interest analyses were based on viewing directed to each scene's "filled" location (i.e., location occupied by the critical object). Scenes presented during the study blocks (i.e., scenes in the repeated, item, and relational conditions) were subdivided based on whether they were presented with an item-specific or relational orienting question during Study Block 2. For the Test Block, region of interest analyses were based on viewing directed to the "filled" location for scenes that underwent an *item change* (along with their yoked repeated and novel counterparts) and viewing directed to both the "filled" and "empty" locations for scenes that underwent a *relational change* (along with their yoked repeated and novel counterparts).

To determine whether there were differences in viewing between groups during Study Blocks 1 and 2, the average number of fixations made to whole scenes (collapsed across conditions) was examined, along with the proportion of total viewing time directed to the filled critical region of scenes accompanied by item-specific and relational orienting questions (collapsed across to-be-repeated and to-be-manipulated scenes). As in previous work (Hannula et al., 2010b), we calculated two separate memory indices to examine viewing patterns from the Test Block. Our first index, *memory for repetition*, was used to determine whether there were differences in viewing due to memory for the scenes themselves, absent any modification. Viewing of the critical region(s) within novel scenes (i.e., scenes presented for the first time during test) was subtracted from viewing of the analogous region(s) within repeated scenes (presented during study and test). The second index, *memory for detail*, was used to determine whether item-specific and/or relational changes affected viewing of the critical region(s). In this case, viewing of the critical region(s) within repeated scenes (presented during study and test) was subtracted from viewing of the analogous region(s) within manipulated scenes (in which an item or relational change occurred at test). We utilized these two calculated indices to examine two eye-movement measures: the proportion of total viewing time directed to critical scene region(s) and the duration of the first gaze (in ms) to the filled region. For the first gaze analysis, the durations of consecutive fixations to the filled region in the first gaze following scene presentation were summed. The first gaze began with the first entry into the filled region and ended when the participant looked at a different scene location. Empty locations, in the relational condition, were not included in the first gaze analysis because so few fixations were made to that part of the scene.

2.3.4.1. Statistical contrasts

Analyses were conducted in SPSS Statistics (Version 28.0). All tests were two-sided and p-values <0.05 were considered statistically significant. Levene's test was used to examine

homogeneity of variances before conducting independent samples *t*-tests and repeated measures ANOVAs. Age and gender were included as covariates when marginal or significant group differences were documented. Partial eta-squared (η_p^2) and Cohen's *d* were calculated as effect size indices.

Additionally, Bayes factors, giving evidence for the null hypothesis over the alternative hypothesis (BF_{01}), were calculated to determine whether reported results were likely to have been obtained under the null or alternative hypothesis or whether results did not favor either hypothesis. A Bayes factor (BF_{01}) greater than 3 provides evidence for the null hypothesis, and a value less than 0.33 provides evidence for the alternative hypothesis, while any value between 3 and 0.33 is inconclusive.

Finally, Pearson's correlations were calculated to examine associations between viewing patterns during study (i.e., proportion of total viewing time to filled regions in studied scenes), viewing patterns during test (i.e., detailed-based proportion of total viewing time and first gaze duration), and recognition memory performance (i.e., corrected recognition scores). Specifically, we examined four types of associations: 1) association between critical region viewing for scenes paired with *item* orienting questions during study and detail-based viewing for scenes with an *item* change during test, 2) association between critical region viewing for scenes paired with *relational* orienting questions during study and detail-based viewing for scenes with a *relational* condition during test, 3) association between critical region viewing for scenes paired with *item* orienting questions during study and *item* corrected recognition scores, and 4) association between critical region viewing for scenes paired with *relational* orienting questions during study and *relational* corrected recognition scores. Additionally, Pearson's correlations were calculated between Picture Sequence Memory Test (PSM) scores, corrected recognition scores, and viewing during test (i.e., detail-based proportion of total viewing time and first gaze duration). Two-tailed *p*-values are reported for each correlation. We used Fisher's *r*-to-*z* transformation to statistically compare correlations between groups. Pearson's correlation coefficients were transformed into *z*-scores using Fisher's transformation formula: $z = ½*\ln((1+r)/(1-r))$. *Z*-scores for each group were then statistically compared using the test statistic: $z_{observed} = (z_1 - z_2)/\text{sqrt}((1/(N_1-3)) + (1/(N_2-3))$. Using a *p*-value of 0.05 to determine statistical significance, a $z_{observed}$ value > +1.96 or < −1.96 was considered significant.

3. Results

3.1. Behavioral performance

3.1.1. Orienting questions (Study Block 2)

Two autistic participants were removed from the orienting question analysis because they used the wrong buttons to make responses on a subset of trials; therefore, analyses were based on data from 16 autistic participants and 20 non-autistic participants. Most often, participants made correct responses to the orienting questions (autistic participants: $M = 89.32\%$, $SD = 7.97\%$; non-autistic participants: $M = 89.90\%$, $SD = 7.41\%$). There was no significant difference in orienting question response accuracy between autistic and non-autistic participants, $t\,(34) = 0.22$, $p = 0.83$, Cohen's $d = 0.08$, $BF_{01} = 4.01$.

3.1.2. Recognition

On average, scenes were most often identified correctly at test (autistic participants: $M = 81.16\%$ correct, $SD = 11.54\%$; non-autistic participants: $M = 87.03\%$ correct, $SD = 7.14\%$). Further evaluation of the data indicated that more than half of the scenes were recognized correctly and with high confidence by both groups (autistic participants: $M = 51.56\%$ correct high confidence trials, $SD = 18.86\%$; non-autistic participants: $M = 60.31\%$ correct high confidence trials, $SD = 18.04\%$). Table 3 provides a full accounting of accuracy and confidence across scene types, for both groups.

3.1.2.1. Memory for scenes

To determine whether there were general differences in memory for scenes, corrected recognition scores were calculated by subtracting novel false alarms (repeated and modified scenes called "new") from novel hits for each group of participants (see Figure 4A). Results from an independent samples *t*-test indicated that there was not a significant between-groups difference in the ability to distinguish new from old scenes, $t\,(36) = 1.31$, $p = 0.20$, Cohen's $d = 0.43$, $BF_{01} = 2.01$.

3.1.2.2. Memory for scene detail

Two corrected recognition scores sensitive to memory for detail were calculated by subtracting the percentage of modified false alarms (i.e., repeated scenes called "modified") from the percentage of modified hits, one for scenes with item changes and one for scenes with relational changes (see Figure 4B). A repeated measures ANOVA, with factors for the group (autistic, non-autistic), scene type (item change, relational change), and their interaction, was calculated. There was a marginal effect of group, $F\,(1, 36) = 3.53$, $p = 0.07$, $\eta_p^2 = 0.09$, but neither the main effect of scene type nor the interaction was significant, F's ≤ 1.53, p's ≥ 0.22, η_p^2's ≤ 0.04. As was done by Cooper et al. (2015), independent samples *t*-tests were calculated to determine whether the group difference was significant for item changes, relational changes, or both. There was no significant group difference in corrected recognition scores sensitive to memory for item changes, $t\,(36) = 1.46$, $p = 0.15$, Cohen's $d = 0.48$, $BF_{01} = 1.69$. There was, however, a significant group difference in corrected recognition scores sensitive to relational memory, $t\,(36) = 2.10$, $p = 0.04$, Cohen's $d = 0.68$, $BF_{01} = 0.67$. This group difference in relational memory was marginal after adjusting for age and gender, $F\,(1, 34) = 3.83$, $p = 0.059$, $\eta_p^2 = 0.10$.

3.1.2.3. High confidence recognition

Since specific weaknesses in recollection and high-confidence responding are reported in autism (e.g., Bowler et al., 2007; Cooper et al., 2015), we also examined whether group differences in memory for scenes and memory for scene detail were evident when analyses were limited to trials with high-confidence responses (see Figure 5). Two participants, one from each group, were excluded from the memory for scenes analysis because there were either no high-confidence hits for novel scenes or no high-confidence false alarms for repeated and modified scenes. Results from an independent samples *t*-test indicated that there was not a significant group difference in memory for scenes, $t\,(34) = 1.20$, $p = 0.24$, Cohen's $d = 0.40$, $BF_{01} = 2.22$ (see Figure 5A).

Next, we examined high-confidence memory for scene detail. Two autistic participants were excluded from this analysis. One participant did not have any high-confidence hits for scenes with an item change, and the other participant did not have any high-confidence hits for

TABLE 3 Scene recognition accuracy and confidence ratings for autistic and non-autistic participants.

	Autistic (n = 18)					Non-autistic (n = 20)				
	Correct Low	Correct Mid	Correct High	Incorrect Low	IncorrectMid	Incorrect High	Correct Low	Correct Mid	Correct High	Incorrect Low	Incorrect Mid	Incorrect High
Repeat	11.46 (13.77)	37.15 (27.41)	26.39 (26.82)	5.21 (7.50)	11.81 (11.72)	7.99 (15.58)	2.81 (6.87)	48.75 (25.94)	31.56 (24.29)	3.75 (5.88)	8.44 (9.78)	4.69 (9.70)
Item	2.78 (6.15)	21.88 (28.70)	53.47 (25.92)	4.86 (6.63)	7.29 (6.52)	9.72 (15.93)	1.88 (4.58)	15.00 (11.54)	65.94 (21.12)	2.19 (4.19)	10.94 (11.63)	4.06 (6.81)
Relation	3.82 (11.77)	22.22 (24.27)	53.47 (29.80)	2.43 (3.80)	10.07 (11.37)	7.99 (13.86)	3.75 (4.71)	13.75 (14.28)	70.00 (19.72)	1.25 (4.35)	9.69 (12.08)	1.56 (3.99)
Novel	2.43 (3.80)	16.67 (18.19)	72.92 (24.06)	1.74 (2.88)	4.51 (7.05)	1.74 (3.59)	4.69 (6.69)	16.25 (20.72)	72.75 (27.70)	1.88 (2.94)	2.81 (5.16)	0.063 (1.92)
Overall	5.12 (6.96)	24.48 (19.20)	51.56 (18.86)	3.56 (2.39)	8.41 (5.95)	6.85 (11.27)	3.28 (4.39)	23.44 (13.50)	60.31 (18.04)	2.27 (2.75)	7.97 (6.08)	2.73 (4.56)

Data are reported as mean percentages (standard deviations) for test trials identified correctly or incorrectly, subdivided by confidence, and organized by group and scene type.

either type of manipulated scene. In addition, because several participants did not have any high-confidence false alarms to repeated scenes (i.e., repeated scenes called "modified), the false alarm rate was calculated by including novel scenes (i.e., both repeated and novel scenes called "modified" with high confidence were included in the calculated false alarm rate). Results from a repeated measures ANOVA revealed marginal effects of scene type (item change, relational change), F (1, 34) = 3.07, p = 0.09, η_p^2 = 0.08, and group (autistic, non-autistic), F (1, 34) = 3.86, p = 0.06, η_p^2 = 0.10, but the interaction was not significant, F (1, 34) = 0.08, p = 0.79, η_p^2 = 0.002. As above, results from independent samples t-tests indicated that there was a significant group difference in relational memory, t (34) = 2.16, p = 0.04, Cohen's d = 0.72, BF_{01} = 0.60, but not item memory, t (34) = 1.67, p = 0.11, Cohen's d = 0.56, BF_{01} = 1.27 (see Figure 5B). In this case, the group difference for relational memory remained significant after adjusting for age and gender, F (1, 32) = 4.49, p = 0.042, η_p^2 = 0.12.

3.2. Viewing behavior

3.2.1. Study blocks

One objective of this work was to determine whether there were group differences in viewing behavior during encoding that might correspond to differences in the operation of cognitive processes that can affect memory performance (e.g., attention to critical scene regions). Two measures were used to examine between-groups differences in scene viewing during the study blocks: number of scene fixations and proportion of total viewing time directed to the filled critical region of encoded scenes.

3.2.1.1. Number of fixations to studied scenes

First, we calculated the average number of fixations to whole scenes, collapsed across conditions, and without considering specific regions of interest. For Study Block 1, there was not a significant difference in the average number of scene fixations between autistic (M = 24.44, SD = 3.59) and non-autistic participants (M = 22.98, SD = 2.70), t (36) = 1.43, p = 0.16, Cohen's d = 0.46, BF_{01} = 1.75. However, for Study Block 2, autistic participants (M = 15.39, SD = 1.41) made significantly more fixations to scenes than non-autistic participants (M = 13.87, SD = 1.69), t (36) = 2.98, p = 0.005, Cohen's d = 0.98, BF_{01} = 0.12. The overall decrease (for both groups) in the number of fixations across study blocks is at least in part due to the reduction in scene presentation time (i.e., 8 s in Study Block 1 versus 5 s in Study Block 2).

3.2.1.2. Proportion of total viewing time to the filled critical region of studied scenes

Next, we examined whether there were differences in the proportion of total viewing time directed to the *filled* critical region of studied scenes – the location occupied by an object. We did not examine the proportion of total viewing time to empty critical regions because they were not meaningful (i.e., had never been occupied by an object) at this point in the experiment. For this analysis, all of the studied scenes, regardless of whether they went on to be repeated or manipulated during test, were subdivided by the type of orienting question (item-specific, relational) they were paired with during Study Block 2. Repeated measures ANOVAs with the

10.3389/fpsyg.2023.1210259

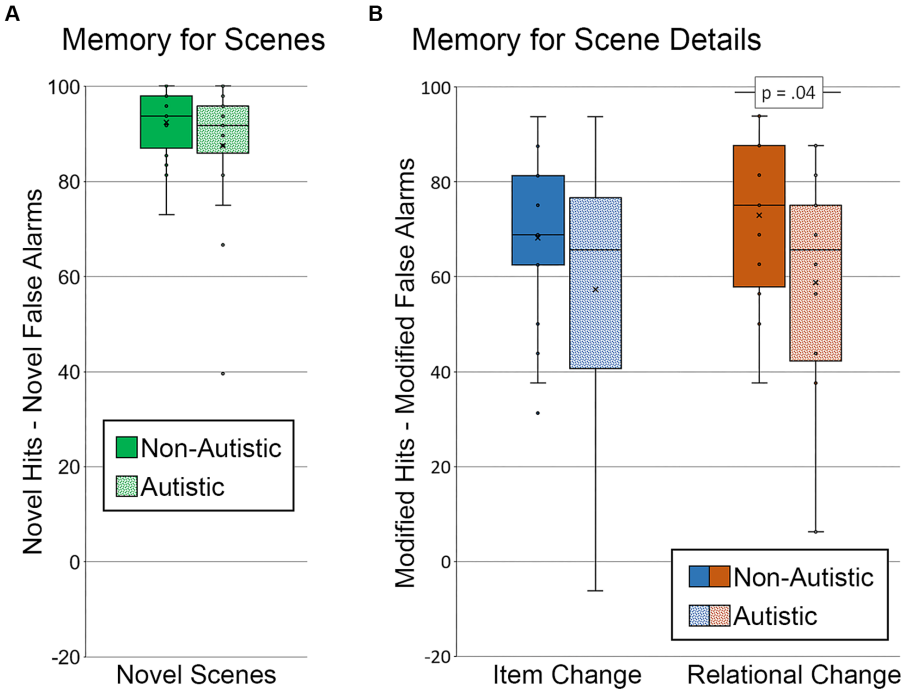


FIGURE 4
Recognition memory for scenes and scene details. Corrected recognition accuracy for **(A)** memory for scenes index (percentage of novel hits – percentage of novel false alarms) by group. Corrected recognition accuracy for **(B)** memory for scene details index (percentage of modified hits – percentage of modified false alarms) by group and scene type. Error bars represent standard error of the mean.

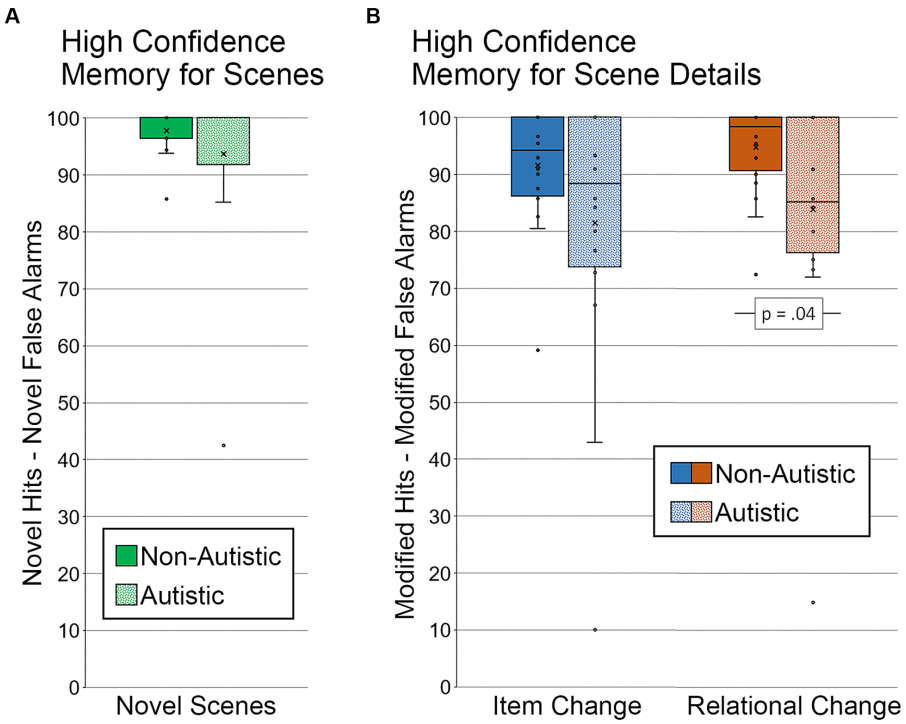


FIGURE 5
Recognition memory for scenes and scene details for high confidence correct trials. **(A)** Memory for scenes (percentage of novel hits – percentage of novel false alarms) by group, limited to scenes identified correctly and with high confidence. **(B)** Memory for scene details (percentage of modified hits – percentage of modified false alarms) by group and scene type, limited to scenes identified correctly and with high confidence. Error bars represent standard error of the mean.

factors group (autistic, non-autistic) and question type (item-specific, relational) were calculated separately for Study Block 1 and Study Block 2.

In Study Block 1 (see Figure 6A), there were no significant main effects or interactions, F's ≤ 1.15, p's ≥ 0.29, η_p^2's ≤ 0.031. Bayes factors were in favor of the null hypothesis – i.e., no group differences in the proportion of total viewing time directed to the filled region of scenes paired with item-specific or relational questions, $BF_{01} = 3.65$ and $BF_{01} = 3.23$, respectively.

In Study Block 2 (see Figure 6B), there was a significant main effect of question type, $F\,(1, 36) = 41.56$, $p < 0.001$, $\eta_p^2 = 0.54$, with more viewing directed to the filled region for scenes paired with item-specific than relational questions. There was no significant main effect of group and no significant interaction, F's ≤ 0.80, p's ≥ 0.38, η_p^2's ≤ 0.022. Bayes factors indicated that the data were inconclusive regarding group differences in viewing directed to the filled region of scenes paired with item-specific questions, $BF_{01} = 2.66$, but were in favor of the null hypothesis for scenes paired with relational questions, $BF_{01} = 3.54$.

As can be seen in Figure 6, the proportion of total viewing time directed to the filled critical region was greater in Study Block 2 than in Study Block 1. This is because orienting questions, used in Study Block 2, required participants to inspect the critical objects and/or their relative locations. Reduced viewing of the filled critical region for scenes paired with relational (versus item-specific) orienting questions in Study Block 2 likely occurs because these questions encouraged exploration of an object relative to something else in the scene. In contrast, item-specific orienting questions asked about characteristics of the object itself.

3.2.1.3. High confidence proportion of total viewing time to the filled critical region

To determine whether there were any between-groups differences in viewing directed to the filled critical region of studied scenes that went on to be correctly recognized and endorsed with high confidence, we backsorted the study phase data by test block performance. In other words, we binned study trials by subsequent test phase accuracy (i.e., correct, incorrect) and recognition confidence (i.e., high, middle, low). This analysis was limited to scenes that would go on to be modified in the test block. Repeated scenes were excluded because several participants did not have any high-confidence correct recognition responses in the repeated scene condition. In addition, two participants from the autistic group were excluded from these backsorted analyses. In one case, there were no high-confidence correct responses to scenes with item changes; in the other case, there were no high-confidence correct responses to any of the manipulated scenes. Repeated measures ANOVAs with the factors scene type (item, relational) and group (autistic, non-autistic) were calculated separately for Study Block 1 and Study Block 2.

In Study Block 1 (see Figure 7A), there was no difference in the proportion of total viewing time directed to the filled region across question types or groups, F's ≤ 0.06, p's ≥ 0.81, η_p^2's ≤ 0.002, nor was there a significant interaction, $F\,(1, 34) = 0.009$, $p = 0.92$, $\eta_p^2 < 0.0001$. As when analyses were based on all trials, Bayes factors were in favor of the null hypothesis – i.e., no group differences in the proportion of total viewing time directed to the filled region of scenes accompanied by item-specific or relational questions, $BF_{01} = 4.02$ and $BF_{01} = 4.08$, respectively.

In Study Block 2 (see Figure 7B), there was a significant effect of question type, $F\,(1, 34) = 26.05$, $p < 0.001$, $\eta_p^2 = 0.43$, but there was not a significant group effect or a question type by group interaction, F's ≤ 2.45, p's ≥ 0.13, η_p^2's ≤ 0.067. As when analyses were based on all trials, Bayes factors indicated that the data were inconclusive regarding group differences in viewing directed to the filled region of scenes associated with item-specific questions, $BF_{01} = 2.16$, but were in favor of the null hypothesis for scenes paired with relational questions, $BF_{01} = 3.94$.

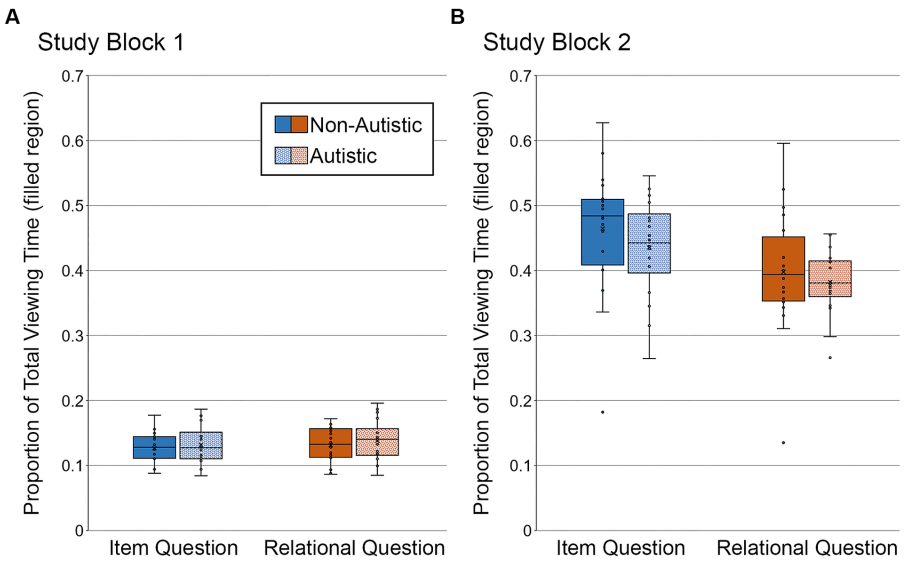


FIGURE 6
Proportion of total viewing time directed to the filled critical region of to-be-manipulated scenes in **(A)** Study Block 1 and **(B)** Study Block 2, subdivided by group and question type. Error bars represent standard error of the mean.

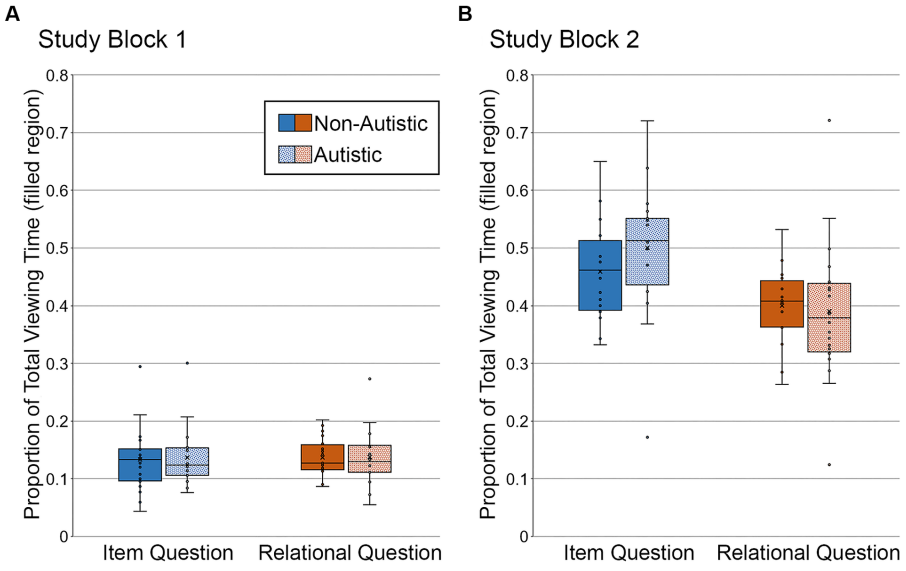


FIGURE 7
Proportion of total viewing time directed to the filled critical region of to-be-manipulated scenes in **(A)** Study Block 1 and **(B)** Study Block 2, subdivided by group and question type, and limited to the subset of scenes identified correctly and with high confidence. Error bars represent standard error of the mean.

Once again, more time was spent looking at the filled region of scenes paired with item-specific questions than with relational questions, likely due to differences in processing requirements associated with these types of questions (see Figure 7).

3.2.2. Test block

Another major objective of this work was to assess group differences in viewing behavior during the test phase. As described above, we calculated two difference scores – *memory for repetition* (repeated scene viewing minus novel scene viewing) and *memory for detail* (modified scene viewing minus repeated scene viewing) – to examine viewing patterns during test. Difference scores were calculated for two eye-movement measures: proportion of total viewing time directed to critical scene region(s) and the duration of the first gaze (in ms) made to the filled region. Independent samples *t*-tests were calculated to compare the proportion of total viewing time directed to the filled critical region in item scenes, the filled critical region in relational scenes, and the empty critical region in relational scenes for the proportion of viewing time measure. First gaze analyses were limited to the filled region.

3.2.2.1. Proportion of viewing time to filled and empty critical regions of test scenes

First, we examined differences in the proportion of total viewing time to critical regions of test scenes. For scenes in the item condition, there were no significant group differences in repetition- or detail-based proportion of total viewing time to the filled critical region, t's ≤ 1.26, p's ≥ 0.22, Cohen's d's ≤ 0.43, $BF_{01} = 3.36$ and 2.13, respectively. Likewise, for scenes in the relational condition, there were no significant group differences in repetition- or detail-based proportion of total viewing time to either the filled or empty critical region, t's ≤ 1.14, p's ≥ 0.26, Cohen's d's ≤ 0.38, BF_{01} repetition filled = 4.17, BF_{01} repetition empty = 3.82, BF_{01} detail filled = 2.40, BF_{01} detail empty = 4.21. As can be seen in Figure 8A, participants from both groups spent more time looking at the critical region(s) of repeated scenes than the same region(s) of novel scenes (i.e., positive-going difference scores), a likely consequence of the orienting questions during encoding. Participants from both groups also spent more time looking at the critical region(s) of manipulated scenes than the same region(s) of repeated scenes (i.e., positive-going difference scores), an index of memory for scene detail, as illustrated in Figure 8B.

3.2.2.1.1. High confidence proportion of total viewing time to filled and empty regions

Targeted analyses were performed to examine whether there were any viewing time differences for scenes correctly recognized and endorsed with high confidence (see Figure 9). For this analysis, like before, data from 16 autistic participants and 20 non-autistic participants were included. As above, two autistic participants were dropped from the analysis because there were no high-confidence correct trials for modified scenes with item or item and relational manipulations. Furthermore, difference scores (i.e., memory for repetition and detail) were not calculated for the high-confidence analyses because several participants from both groups identified fewer than 3 repeated scenes correctly with high confidence. Therefore, these analyses were based on proportion of total viewing time to the critical region(s) of modified scenes recognized correctly with high-confidence responses. Results from an independent-samples *t*-test indicated that there was not a significant group difference in the proportion of total viewing time directed to the filled region of scenes with an item change, t (34) = 1.15, $p = 0.26$, Cohen's $d = 0.33$, $BF_{01} = 2.32$, but that this difference was marginal for the filled region of

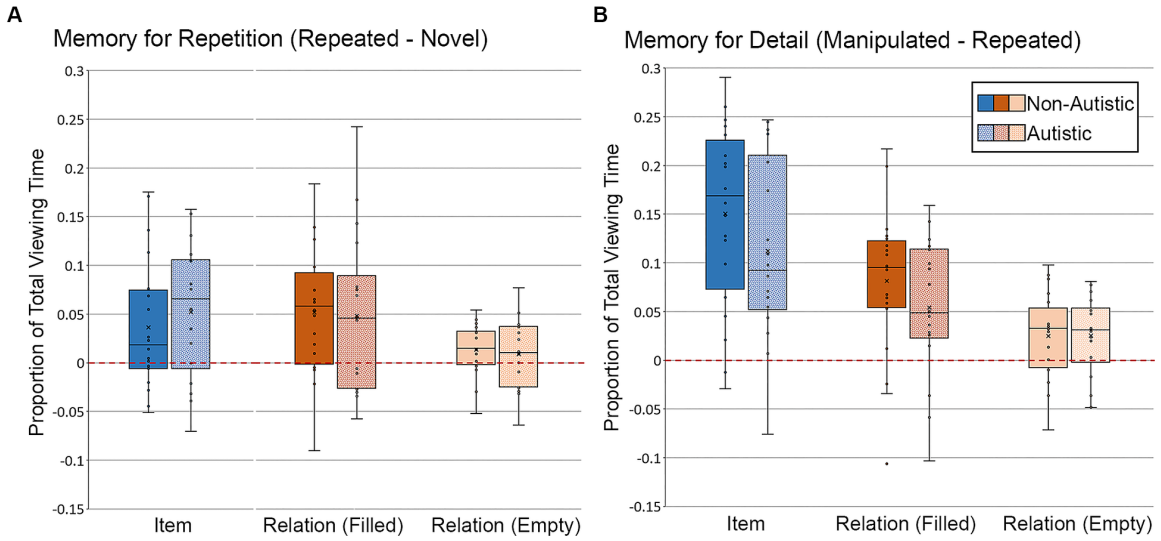


FIGURE 8
Proportion of total viewing time directed to critical regions of scenes for **(A)** Memory for Repetition index (viewing to repeated scenes – viewing to novel scenes) and **(B)** Memory for Detail index (viewing to manipulated scenes – viewing to repeated scenes), subdivided by group, scene type, and critical region for scenes presented during Test Block. Error bars represent standard error of the mean.

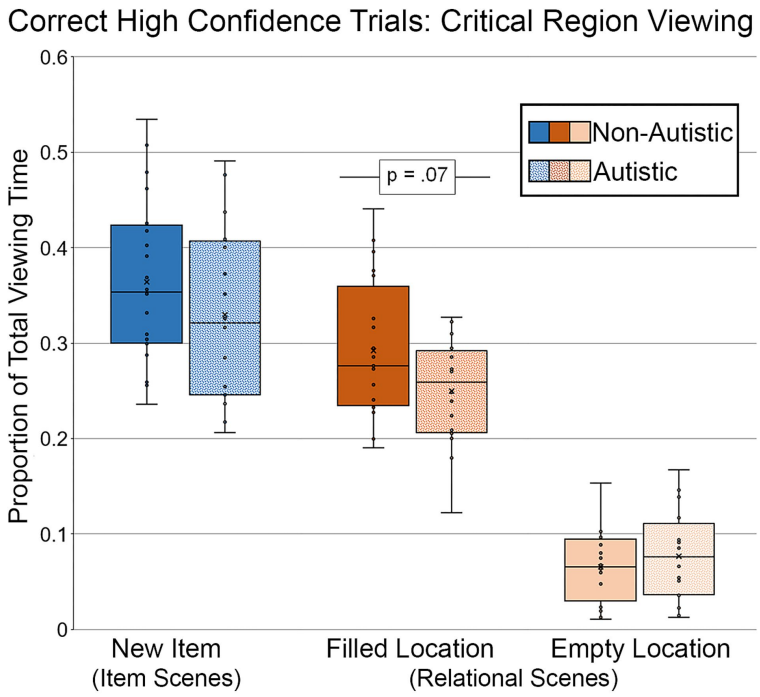


FIGURE 9
Proportion of total viewing time directed to critical regions of scenes, subdivided by group, scene type, and critical region for scenes presented during Test Block, and limited to scenes that were identified correctly with high confidence. Error bars represent standard error of the mean.

scenes with a relational change, t (34) = 1.90, p = 0.066, Cohen's d = 0.61, BF_{01} = 0.91. The proportion of total viewing time was lower for the autistic group than for the non-autistic group. There was no significant group difference in proportion of viewing to the empty critical region, t (34) = 0.77, p = 0.45, Cohen's d = 0.25, BF_{01} = 3.17. The group difference in the relational condition for the filled region became significant after adjusting for age and gender, F (1, 32) = 4.21, p = 0.048, η_p^2 = 0.12.

3.2.2.2. First gaze duration to the filled region of test scenes

We also examined differences in the duration of the first gaze made to the filled critical region (see Figure 10). For scenes in the item condition, there were no significant group differences in the duration of the first gaze directed to the filled critical region for the repetition-based difference score or the detail-based difference score, t's ≤ 0.41, p's ≥ 0.69, Cohen's d's ≤ 0.13, BF_{01}'s ≥ 3.91. For scenes in the relational condition, there was no significant group difference in first gaze for the repetition-based difference score, t (36) = 0.93, $p = 0.72$, Cohen's $d = 0.30$, $BF_{01} = 2.88$, but there was a marginal group difference in duration of first gaze for the detail-based difference score, t (36) = 1.88, $p = 0.068$, Cohen's $d = 0.62$, $BF_{01} = 0.94$, with non-autistic participants spending more time looking at the now-filled regions relative to autistic participants. This group difference for detail-based viewing in the relational condition remained marginally significant after adjusting for age and gender, F (1, 34) = 2.96, $p = 0.095$, $\eta_p^2 = 0.080$.

3.2.2.2.1. High confidence first gaze duration to the filled region

Analyses were performed to determine whether there were differences in first gaze duration toward scenes that were identified correctly with high confidence (see Figure 11). As above, two autistic participants were dropped from this analysis, and difference scores were not calculated because there were so few high-confidence trials for repeated scenes. For scenes with an item change, there was no significant group difference in duration of first gaze, t (34) = 0.92, $p = 0.36$, Cohen's $d = 0.30$, $BF_{01} = 2.84$. However, there remained a marginal group difference in first gaze to the filled region for scenes with relational changes, t (34) = 1.91, $p = 0.065$, Cohen's $d = 0.65$, $BF_{01} = 0.89$. This group difference in the relational condition remained marginal after adjusting for age and gender, F (1, 32) = 3.03, $p = 0.091$, $\eta_p^2 = 0.087$.

3.3. Correlation analyses

Pearson's correlations (r) were calculated to determine whether viewing time to the filled critical region during the study blocks was associated with memory-based (i.e., detail-based) viewing effects and/or recognition performance in the test block. For this set of analyses the average proportion of total viewing time to the filled region of studied scenes was calculated separately for scenes paired with item-specific and relational orienting questions, collapsed across study blocks, for each participant. This grand average (i.e., proportion of total viewing time directed to the filled region during the study phase) was used in all reported analyses. Two test block measures were used to determine whether study phase viewing time was correlated with test block viewing directed to the *filled* critical region for item-specific and relational scenes separately. These two measures were the *memory for detail* difference scores for 1) proportion of viewing time and 2) first gaze duration, which provide us an estimate of viewing time to the critical region due to memory for the original item or the spatial position of the critical item in the test block. Corrected recognition scores for scenes with an item and relational change were also included in the correlation analyses.

3.3.1. Correlations between study and test viewing

First, we compared study and test viewing patterns. For scenes containing an item change, there were no significant correlations between study and test phase viewing patterns for either autistic participants, r's ≤ 0.34, p's ≥ 0.17, or non-autistic participants,

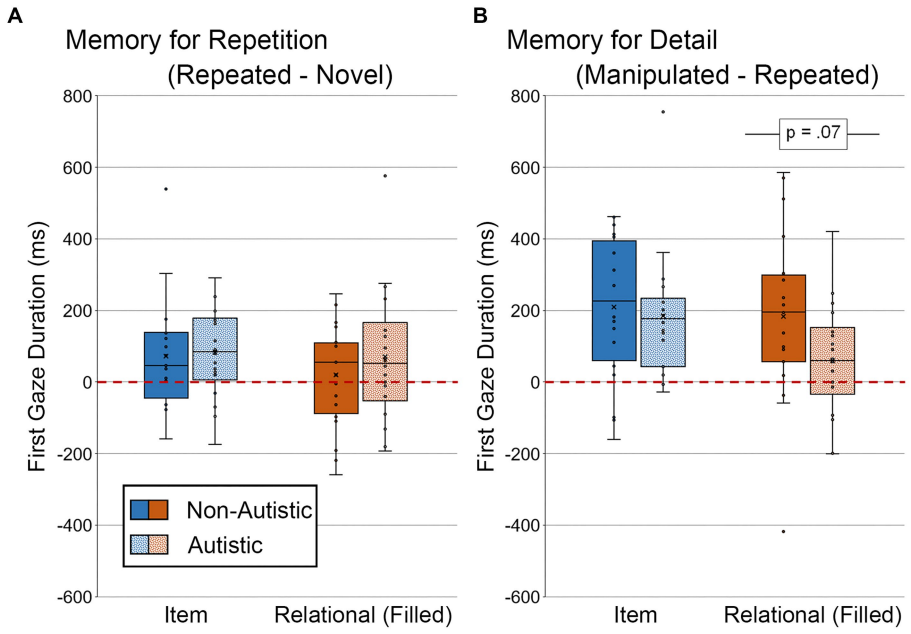


FIGURE 10
First gaze duration (ms) to filled critical region of scenes for **(A)** Memory for Repetition index (viewing to repeated scenes – viewing to novel scenes) and **(B)** Memory for Detail index (viewing to manipulated scenes – viewing to repeated scenes), subdivided by group and scene type for scenes presented during Test Block. Error bars represent standard error of the mean.

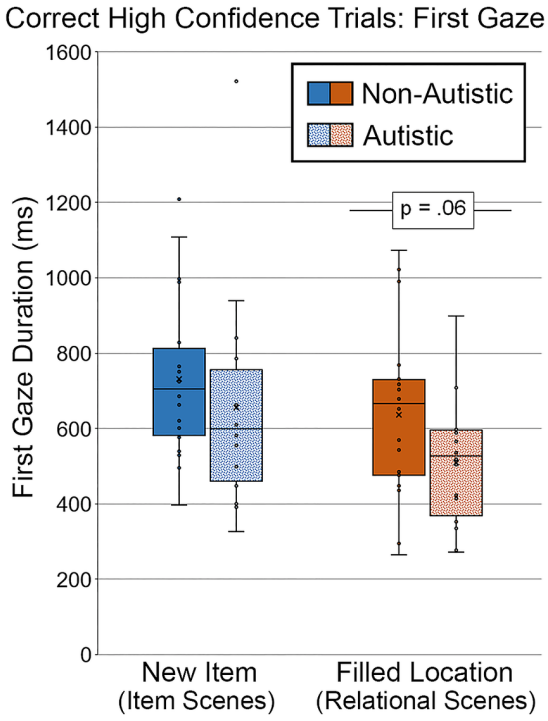


FIGURE 11
First gaze duration (ms) to the filled critical region of scenes, subdivided by group and scene type during Test Block, and limited to scenes identified correctly and with high confidence. Error bars represent standard error of the mean.

r's ≤ 0.16, p's ≥ 0.50. Additionally, there were no significant correlations between study and test phase viewing for scenes containing a relational change for autistic participants, r's ≤ 0.25, p's ≥ 0.32, or non-autistic participants, r's ≤ 0.24, p's ≥ 0.30. Unsurprisingly, there were no significant group differences in correlations between study and testing viewing patterns, z's ≤ 0.54, p's > 0.05.

3.3.2. Correlations between study viewing and recognition performance

Next, we calculated correlations between study viewing patterns and test recognition memory. For scenes that underwent an item change, there was a significant positive correlation between study viewing and item memory for non-autistic participants, $r = 0.51$, $p = 0.022$, but no significant correlation for autistic participants, $r = -0.20$, $p = 0.43$. In contrast, for scenes that underwent a relational change, there was a marginal negative correlation between study viewing and relational memory for autistic participants, $r = -0.45$, $p = 0.059$, but no significant correlation for non-autistic participants, $r = 0.19$, $p = 0.43$. However, only the correlation between study viewing and item recognition memory was significantly different between groups, $z = -2.16$, $p < 0.05$. All other between-group differences in these correlations were not significant, z's ≤ 1.91, p's > 0.05.

3.3.3. Correlations between PSM scores, test viewing, and recognition performance

Finally, we calculated Pearson's correlations to compare Picture Sequence Memory Test (PSM) scores with item-specific and relational corrected recognition memory scores and detail-based (i.e., memory-based) viewing patterns during the Test Block. There was a significant positive correlation between PSM scores and item memory for non-autistic participants, $r = 0.44$, $p = 0.051$, but not for autistic participants, $r = -0.16$, $p = 0.53$. In contrast, there was a significant negative correlation between PSM scores and first gaze duration for scenes in the relational condition for autistic participants, $r = -0.53$, $p = 0.025$, but not for non-autistic participants, $r = -0.11$, $p = 0.64$. None of the between-group differences in these correlations were significant, z's ≤ 1.79, p's > 0.05.

4. Discussion

The current study examined whether memory-specific viewing patterns to realistic, non-social scenes differed between autistic and non-autistic individuals. Here, we employed an eye-tracking paradigm that equated difficulty across item-specific and relational conditions (i.e., Hannula et al., 2010b; Cooper et al., 2015) to control for potential differences in task complexity that may have contributed to past findings. In addition, we used both direct (i.e., explicit responses) and indirect (i.e., eye movements) measures of memory to examine performance. Orienting question accuracy was not significantly different between groups during Study Block 2, suggesting that both groups attended to relevant scene regions when prompted. In Study Block 2, autistic individuals made more scene fixations than non-autistic participants, but there was no evidence for differential viewing of the filled critical region across groups in either study block. Therefore, this difference in total number of scene fixations did not affect time spent viewing the scene region that would be modified in the item and relational conditions during test.

Behaviorally, both autistic and non-autistic participants could distinguish between studied and non-studied scenes. While there was no significant difference in accuracy for scenes that underwent an item change, autistic participants showed a marginal reduction in relational memory accuracy across all trials and a significant reduction in relational memory accuracy for high-confidence trials relative to their non-autistic peers. Additionally, evaluation of the eye-tracking data indicated that both groups showed evidence of memory-based viewing effects (i.e., greater viewing of filled regions of modified scenes relative to analogous regions of yoked novel and repeated scenes) during test. However, autistic individuals spent a marginally smaller proportion of total viewing time on, and demonstrated marginally shorter initial gazes toward, relational changes in scenes relative to their non-autistic counterparts for all trials (for the gaze duration index) and for high-confidence trials (for both the proportion of total viewing time and gaze duration indices). Further, the group difference in proportion of total viewing time for high-confidence trials was significant when adjustments were made for age and gender. Taken together, our recognition and eye-movement measures provide converging evidence for a selective weakness in relational memory in autism.

Correlational analyses revealed no significant between-group differences in associations between performance on a standardized episodic memory task (i.e., Picture Sequence Memory Test) and viewing during test or recognition memory. However, viewing patterns during the study phase were correlated with subsequent recognition accuracy, as has been reported previously (Loth et al., 2011; Ring et al., 2017; Cooper et al., 2017a). Specifically, for scenes assigned to the item condition, there was a positive association

between critical region viewing during the study phase and the successful recognition of scenes with item-specific changes for the non-autistic group, but no similar effect for the autistic group, and this between-groups difference was statistically significant. In contrast, there was a marginal, negative association between study phase viewing and relational memory for the autistic group, though here, there was not a significant between-groups difference. Overall, these outcomes suggest that viewing patterns during encoding may not always predict test phase outcomes in the same way and/or to the same degree in autistic and non-autistic participants, as reported previously by Cooper et al. (2017a).

As outlined above, past work demonstrates that episodic memory processes are atypical in autism. However, the type of representational content impacted by episodic memory difficulties is contested, with some authors reporting weaknesses restricted to item-specific memory (Solomon et al., 2016; Cooper et al., 2017a) and others reporting selective relational memory difficulties (Lind and Bowler, 2009; Bigham et al., 2010; Bowler et al., 2014; Cooper et al., 2017b; Desaunay et al., 2020b), weaknesses in both item and relational memory (Massand and Bowler, 2015; Ring et al., 2016; Semino et al., 2018; Mogensen et al., 2020), or no item-specific or relational memory difficulties (Souchay et al., 2013; Lind et al., 2014; Ring et al., 2015, 2017; Hogeveen et al., 2020). One proposed explanation for contradictory findings is the differential complexity of past item-specific and relational memory tasks (see Cooper and Simons (2019) for review), an issue that Cooper et al. (2015) attempted to address by utilizing a behavioral task that ours is similar to, with materials developed to equate item-specific and relational memory processing demands. Their work showed that autistic individuals identified fewer scenes with item and relational changes than their non-autistic peers, a finding taken as evidence for a potential weakness in both item-specific and relational memory (Cooper et al., 2015).

Because task demands of the current study were closely matched to Cooper et al. (2015), one may question why we only observed group differences in relational recognition performances rather than in both item-specific and relational recognition performances. Importantly, it should be noted that the sample size of the current study was sufficient to detect large effect sizes ($d = 0.9$) but may have been underpowered to detect more subtle effects. However, we did observe significant and marginal group differences in relational memory and memory-based viewing effects for scenes with a relational change. Further, Cooper et al. (2015) reported larger effect sizes for their item memory group differences as compared to their relational memory group differences. Thus, our sample size should have been sufficient to detect a group difference in both item and relational memory. It is possible that the addition of a second study block, which provided participants with a directed viewing task (i.e., via orienting questions) as well as a second opportunity to view scenes, mitigated attentional or executive processing difficulties that would have otherwise impacted explicit recognition memory for items in the autistic group in our study. Indeed, this hypothesis aligns with past work demonstrating improvements in recognition memory performance in autistic participants when explicit encoding instructions are provided (Gaigg et al., 2008; Bowler et al., 2010; Cooper et al., 2017a) and is consistent with the *task support hypothesis,* which proposes that autistic individuals' memory improves when they are provided with "supports" during a memory task (e.g., cues in a recognition memory paradigm; Bowler et al., 2004). However, despite the use of a controlled encoding task here, relational memory could not be rescued in the autistic group relative to the non-autistic group, an outcome consistent with past findings that suggest relational memory is selectively or disproportionately compromised in autistic individuals (Lind and Bowler, 2009; Bigham et al., 2010; Bowler et al., 2014; Cooper et al., 2017b; Desaunay et al., 2020b). The group difference in relational recognition accuracy was marginal when all of the trials were included in our analyses and significant for high-confidence trials, which reinforces prior reports that autistic persons show attenuated memory confidence for correct memories (Wojcik et al., 2013; Grainger et al., 2014; Cooper et al., 2016). Importantly, significant group differences in memory confidence judgments were limited to measures that were sensitive to relational memory in the current study, a finding similar to past work that has documented reduced high-confidence, recollection-related memory in autism (Bowler et al., 2007; Cooper et al., 2015, 2017a).

A strength of the current experiment was the use of eye-tracking methods during both study and test blocks. In contrast to discrete recognition responses, eye-tracking data is recorded continuously, allowing us to examine how scenes are viewed during encoding and retrieval. Of the few previous eye-tracking studies examining encoding-related viewing behavior, none reported differences between autistic and non-autistic groups (Loth et al., 2011; Cooper et al., 2017a). This result was generally replicated here, as there was not a significant group difference in proportion of total viewing time directed to the critical object in either study block. One possibility is that well-matched viewing patterns during the study phase means that the scenes were processed comparably by participants from both groups. However, it is also possible that, while viewing patterns are similar, the depth of processing between groups, in the absence of specific task instructions, is not. The orienting questions in our experiment may have been instrumental in this regard, encouraging participants to pay close attention to the very same details of scenes that might be modified at test. Future studies, with larger sample sizes, should systematically manipulate the use of orienting questions to further examine whether and how they affect recognition performance and eye-movement-based memory effects in autism.

In contrast to results from encoding, subtle differences in retrieval-related eye movements were observed for autistic participants in the present study, in a manner that was consistent with the relational memory weakness observed in recognition memory accuracy. Past eye-tracking studies documented differences in memory-based eye-movement behaviors (Ring et al., 2017; Cooper et al., 2017a). Specifically, in a relational memory paradigm, it was reported that autistic participants spent less time viewing critical scene regions as compared to their non-autistic counterparts (Ring et al., 2017). While memory-based viewing results in our experiment trended in the same general direction, with autistic participants showing reduced viewing to critical regions associated with a relational change, our group differences were relatively small and were sometimes only observed when we analyzed high-confidence responses separately. Several factors may account for the difference in the strength of this effect between our current work and previous findings. One possibility is that our results did not reach statistical significance due to low statistical power (e.g., Bayes factors that indicated evidence for group differences was inconclusive). However, another possibility is that differences in the demands of the retrieval tasks in previously published studies and our current study affected the outcomes. For instance, participants were required to switch between two different retrieval tasks in Ring et al.'s (2017) study. Sometimes, they had to

place a presented object in the location where it had been studied in the scene previously (on "explicit" trials), and sometimes they had to avoid that location, placing the object in a new spot (on "implicit" trials). This kind of task-switching may have placed greater demands on other cognitive functions, such as cognitive flexibility (i.e., set shifting), which seems to be a weakness for autistic individuals (e.g., Van Eylen et al., 2011; Andreou et al., 2022; although see Geurts et al., 2009). Importantly, results from our study suggest that eye-movement-based relational memory effects are modestly impaired even in the absence of task-switching demands and even when the encoding task encourages processing of the very same relationships that are changed during the test phase. Collectively then, these results provide converging evidence for a selective reduction in viewing effects that are sensitive to relational memory in autism.

Consistent with previous results showing differences in high confidence responding or recollection (Bowler et al., 2007; Cooper et al., 2015, 2017a) as well as with explicit recognition results reported here, when high confidence recognition trials were examined separately, marginal group differences remained and/or emerged in relational, memory-based viewing at test. These viewing time differences suggest that even when relational scenes are identified correctly with high confidence at test, there may be differences in how relationships amongst scene elements are processed by autistic individuals. Specifically, autistic individuals demonstrated a reduction in proportion of total viewing time directed to the filled region of scenes that contained a relational change and also showed shorter initial gaze durations toward critical regions of those scenes. Together with significant reductions in recognition performance for this same set of relational scenes, our results support the hypothesis that there is a disruption in recollection-related retrieval processes in autism, which appear to be selective to relational memory (Cooper et al., 2017a). Therefore, subtle differences in retrieval-related relational memory processes and/or the quality of relational memory representations (e.g., subjective quality) may exist, consistent with findings reported in past work (Lind and Bowler, 2009; Bigham et al., 2010; Bowler et al., 2014; Cooper et al., 2017b; Desaunay et al., 2020b). Of note, other processing differences, such as group differences in criteria for confidence judgments or group differences in mnemonic cues used to make confidence judgments, could partially explain the marginal effects that emerged during analysis of high-confidence trials. However, these explanations are unable to fully account for intact effects in the item-specific condition and results from the relational condition based on the full set of trials, which also provided evidence for a relational memory weakness for autistic participants.

Importantly, the absence of group differences in item-specific memory in our work should not be taken as evidence for equivalent memory processes in autistic and non-autistic individuals. For example, despite explicit memory performances that appear comparable between autistic and non-autistic individuals, electrophysiological studies report differences in magnitude and/or spatial location of event-related potentials (ERPs) associated with memory retrieval (Massand et al., 2013; Massand and Bowler, 2015; Desaunay et al., 2020b) and imaging studies document hyper-recruitment and connectivity differences between autistic and non-autistic individuals (Hogeveen et al., 2020), suggesting that compensatory neural processes may contribute to seemingly intact behavioral memory performances. Indeed, the results of correlation analyses in the present study were suggestive of processing differences between groups. Consistent with prior work (e.g., Cooper et al., 2017a), we observed a relationship between viewing during study and subsequent recognition performances. However, these relationships were different between the autistic and non-autistic groups. For example, the correlation between viewing during study and item recognition in non-autistic individuals was absent for the autistic group. Further, though the association was not significantly different between groups, the direction of a marginally significant association between viewing during study and relational memory for the autistic group was opposite that which we might expect, with a smaller proportion of viewing toward the critical region during study being associated with better relational memory in the autistic group. Altogether, these findings suggest that correlations between indirect and direct measures of memory may be sensitive to subtle differences between groups that are not observed when these types of measures are examined separately.

Several limitations of the current study should be considered. First, specific characteristics of the sample included here may have impacted our findings. For example, the autistic individuals who participated in this study were without co-morbid intellectual disability diagnoses (IQ $\geq$ 70); thus, results may not be generalizable to an autistic population with intellectual disability. Further, the age range of participants, spanning from adolescence to young adulthood in both groups, may have obscured or attenuated episodic memory differences between groups. Notably, the neural circuits associated with memory continue to develop from early childhood and adolescence to adulthood (Naveh-Benjamin, 2000; Grady et al., 2003; DeMaster et al., 2014). Therefore, it is possible that item memory weaknesses, for example, may only emerge later in adulthood for autistic individuals, when development of these networks is more fully matured. With these caveats in mind, the current study contributes to the growing body of evidence that documents disproportionate relational memory difficulties in autism, even when structured encoding conditions are provided and the complexity of memory tasks is equated. In future work, indirect measures of memory (i.e., eye movements) and judgments of mnemonic accuracy should be simultaneously collected because more subtle group differences may emerge when limiting analyses to high-confidence responses.

In conclusion, relational memory differences between autistic and non-autistic individuals persist, even with a controlled encoding task, and direct and indirect memory indices are useful in fully characterizing these nuanced memory effects. Reductions in recognition accuracy and memory-based viewing in the autistic group, for high confidence and correctly identified relational scenes in particular, suggest that previously reported relational memory weaknesses may have been accurately identified in past work, consistent with the *relational binding account* of episodic memory in autism (Bowler et al., 2011). Further, differences in the association between study phase viewing and recognition accuracy between groups suggest dissimilarities in underlying processes that contribute to learning and/or retrieval of learned information for autistic and non-autistic individuals. Taken together, our findings suggest differences in the integrity of relational memory representations and/or the relationships between memory subcomponents in autism.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by UC Davis Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

GM: methodology, software, formal analysis, visualization, writing – original draft, and writing – review and editing. DH: methodology, software, formal analysis, visualization, writing – original draft, writing – review and editing, and supervision. AG: investigation and writing – review and editing. A-MI: formal analysis and writing – review and editing. JR: writing – review and editing. MS: funding acquisition (NIMH #1R01MH106518), project administration, writing – review and editing, and supervision. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Akshoomoff, N., Beaumont, J. L., Bauer, P. J., Dikmen, S. S., Gershon, R. C., Mungas, D., et al. (2013). NIH Toolbox Cognition battery (CB): Composite scores of crystallized, fluid, and overall cognition. *Monogr. Soc. Res. Child. Dev.* 78, 119–132. doi: 10.1111/mono.12038

Althoff, R. R., and Cohen, N. J. (1999). Eye-movement based memory effect: A reprocessing effect in face perception. *J. Exp. Psychol.* 25, 997–1010. doi: 10.1037//0278-7393.25.4.997

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (*5th*). American Psychiatric Publishing. Washington, DC

Andreou, M., Konstantopoulos, K., and Peristeri, E. (2022). Cognitive flexibility in autism: Evidence from young autistic children. *Autism Res.* 15, 2296–2309. doi: 10.1002/aur.2828

Banker, S. M., Gu, X., Schiller, D., and Foss-Feig, J. H. (2021). Hippocampal contributions to social and cognitive deficits in autism spectrum disorder. *Trends Neurosci.* 44, 793–807. doi: 10.1016/j.tins.2021.08.005

Barnea-Goraly, N., Frazier, T. W., Piacenza, L., Minshew, N. J., Keshavan, M. S., Reiss, A. L., et al. (2014). A preliminary longitudinal volumetric MRI study of amygdala and hippocampal volumes in autism. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 48, 124–128. doi: 10.1016/j.pnpbp.2013.09.010

Bauman, M., and Kemper, T. (2005). Neuroanatomic observations of the brain in autism: A review and future directions. *Int. J. Dev. Neurosci.* 23, 183–187. doi: 10.1016/j.ijdevneu.2004.09.006

Belmonte, M. K., and Yurgelun-Todd, D. A. (2003). Functional anatomy of impaired selective attention and compensatory processing in autism. *Cogn. Brain Res.* 17, 651–664. doi: 10.1016/S0926-6410(03)00189-7

Ben Shalom, D. (2003). Memory in autism: Review and synthesis. *Cortex* 39, 1129–1138. doi: 10.1016/S0010-9452(08)70881-5

Bigham, S., Boucher, J., Mayes, A., and Anns, S. (2010). Assessing recollection and familiarity in autistic spectrum disorders: Methods and findings. *J. Autism Dev. Disord.* 40, 878–889. doi: 10.1007/s10803-010-0937-7

Blumenfeld, R. S., and Ranganath, C. (2007). Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. *Neuroscientist* 13, 280–291. doi: 10.1177/1073858407299290

Boucher, J. (1981). Immediate free recall in early childhood autism: Another point of behavioural similarity with the amnesic syndrome. *Br. J. Psychol.* 72, 211–215. doi: 10.1111/j.2044-8295.1981.tb02177.x

Boucher, J., Mayes, A., and Bigham, S. (2012). Memory in autistic spectrum disorder. *Psychol. Bull.* 138, 458–496. doi: 10.1037/a0026869

Boucher, J., and Warrington, E. K. (1976). Memory deficits in early infantile autism: Some similarities to the amnesic syndrome. *Br. J. Psychol.* 67, 73–87. doi: 10.1111/j.2044-8295.1976.tb01499.x

Bowler, D. M., Gaigg, S. B., and Gardiner, J. M. (2010). Multiple list learning in adults with autism spectrum disorder: Parallels with frontal lobe damage or further evidence of diminished relational processing? *J. Autism Dev. Disord.* 40, 179–187. doi: 10.1007/s10803-009-0845-x

Bowler, D. M., Gaigg, S. B., and Gardiner, J. M. (2014). Binding of multiple features in memory by high-functioning adults with autism spectrum disorder. *J. Autism Dev. Disord.* 44, 2355–2362. doi: 10.1007/s10803-014-2105-y

Bowler, D., Gaigg, S., and Lind, S. (2011). "Memory in autism: Binding, self and brain" in *Research the Autism Spectrum: Contemporary Perspectives*. eds. I. Roth and P. Rezaie (Cambridge: Cambridge University Press), 316–346.

Bowler, D. M., Gardiner, J. M., and Berthollier, N. (2004). Source memory in adolescents and adults with Asperger's syndrome. *J. Autism Dev. Disord.* 34, 533–542. doi: 10.1007/s10803-004-2548-7

Bowler, D. M., Gardiner, J. M., and Gaigg, S. B. (2007). Factors affecting conscious awareness in the recollective experience of adults with Asperger's syndrome. *Conscious. Cogn.* 16, 124–143. doi: 10.1016/j.concog.2005.12.001

Bowler, D. M., Matthew, N. J., and Gardiner, J. M. (1997). Asperger's syndrome and memory: Similarity to autism but not amnesia. *Neuropsychologia* 35, 65–70. doi: 10.1016/S0028-3932(96)00054-1

Burack, J. A. (1994). Selective attention deficits in persons with autism: Preliminary evidence of an inefficient attentional loss. *J. Abnorm. Psychol.* 103, 535–543. doi: 10.1037/0021-843X.103.3.535

Cabeza, R., Ciaramelli, E., Olson, I. R., and Moscovitch, M. (2008). The parietal cortex and episodic memory: An attentional account. *Nat. Rev. Neurosci.* 9, 613–625. doi: 10.1038/nrn2459

Chita-Tegmark, M. (2016). Attention allocation in ASD: A review and meta-analysis of eye-tracking studies. *Res. Dev. Disabil.* 3, 209–223. doi: 10.1007/s40489-016-0077-x

Ciaramelli, E., Faggi, G., Scarpazza, C., Mattioli, F., Spaniol, J., Ghetta, S., et al. (2017). Subjective recollection independent from multifeatural context retrieval following damage to the posterior parietal cortex. *Cortex* 91, 114–125. doi: 10.1016/j.cortex.2017.03.015

Cooper, R. A., Plaisted-Grant, K. C., Baron-Cohen, S., and Simons, J. S. (2016). Reality monitoring and metamemory in adults with autism spectrum conditions. *J. Autism Dev. Disord.* 46, 2186–2198. doi: 10.1007/s10803-016-2749-x

Cooper, R. A., Plaisted-Grant, K. C., Baron-Cohen, S., and Simons, J. S. (2017a). Eye movements reveal a dissociation between memory encoding and retrieval in adults with autism. *Cognition* 159, 127–138. doi: 10.1016/j.cognition.2016.11.013

Cooper, R. A., Plaisted-Grant, K. C., Hannula, D. E., Ranganath, C., Baron-Cohen, S., and Simons, J. S. (2015). Impaired recollection of visual scene details in adults with autism spectrum conditions. *J. Abnorm. Psychol.* 124, 565–575. doi: 10.1037/abn0000070

Cooper, R. A., Richter, F. R., Bays, P. M., Plaisted-Grant, K. C., Baron-Cohen, S., and Simons, J. S. (2017b). Reduced hippocampal functional connectivity during episodic memory retrieval in autism. *Cereb. Cortex* 27, 888–902. doi: 10.1093/cercor/bhw417

Cooper, R. A., and Simons, J. S. (2019). Exploring the neurocognitive basis of episodic recollection in autism. *Psychon. Bull. Rev.* 26, 163–181. doi: 10.3758/s13423-018-1504-z

Davachi, L. (2006). Item, context and relational episodic encoding in humans. *Curr. Opin. Neurobiol.* 16, 693–700. doi: 10.1016/j.conb.2006.10.012

Davachi, L., Mitchell, J. P., and Wagner, A. D. (2003). Multiple routes to memory: Distinct medial temporal lobe processes build item and source memories. *Proc. Natl. Acad. Sci. U. S. A.* 100, 2157–2162. doi: 10.1073/pnas.0337195100

DeMaster, D., Pathman, T., Lee, J. K., and Ghetti, S. (2014). Structural development of the hippocampus and episodic memory: Developmental differences along the anterior/posterior axis. *Cereb. Cortex* 24, 3036–3045. doi: 10.1093/cercor/bht160

Demetriou, E. A., Lampit, A., Quintana, D. S., Naismith, S. L., Song, Y. J. C., Pye, J. E., et al. (2018). Autism spectrum disorders: A meta-analysis of executive function. *Mol. Psychiatry* 23, 1198–1204. doi: 10.1038/mp.2017.75

Desaunay, P., Briant, A. R., Bowler, D. M., Ring, M., Gérardin, P., Baleyte, J., et al. (2020a). Memory in autism spectrum disorder: A meta-analysis of experimental studies. *Psychol. Bull.* 146, 377–410. doi: 10.1037/bul0000225

Desaunay, P., Clochon, P., Doidy, F., Lambrechts, A., Wantzen, P., Wallois, F., et al. (2020b). Exploring the event-related potentials' time course of associative recognition in autism. *Autism Res.* 11, 1998–2016. doi: 10.1002/aur.2384

Dobbins, I. G., and Wagner, A. D. (2005). Domain-general and domain-sensitive prefrontal mechanisms for recollecting events and detecting novelty. *Cereb. Cortex* 15, 1768–1778. doi: 10.1093/cercor/bhi054

Ecker, C., Marquand, A., Mourão-Miranda, J., Johnston, P., Daly, E. M., Brammer, M. J., et al. (2010). Describing the brain in autism in five dimensions – Magnetic Resonance Imaging-assisted diagnosis of Autism Spectrum Disorder using a multiparameter classification approach. *J. Neurosci.* 30, 10612–10623. doi: 10.1523/JNEUROSCI.5413-09.2010

Eichenbaum, H., Yonelinas, A. R., and Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* 30, 123–152. doi: 10.1146/annurev.neuro.30.051606.094328

Fetit, R., Hillary, R. F., Price, D. J., and Lawrie, S. M. (2021). The neuropathology of autism: A systematic review of post-mortem studies of autism and related disorders. *Neurosci. Biobehav. Rev.* 129, 35–62. doi: 10.1016/j.neubiorev.2021.07.014

Fletcher, P. C., and Henson, R. N. A. (2001). Frontal lobes and human memory: Insights from functional neuroimaging. *Brain* 124, 849–881. doi: 10.1093/brain/124.5.849

Gaigg, S. B., Bowler, D. M., Ecker, C., Calvo-Merino, B., and Murphy, D. G. (2015). Episodic recollection difficulties in ASD result from atypical relational encoding: Behavioral and neural evidence. *Autism Res.* 8, 317–327. doi: 10.1002/aur.1448

Gaigg, S. B., Gardiner, J. M., and Bowler, D. M. (2008). Free recall in autism spectrum disorder: The role of relational and item-specific encoding. *Neuropsychologia* 46, 938–992. doi: 10.1016/j.neuropsychologia.2007.11.011

Geurts, H. M., Corbett, B., and Solomon, M. (2009). The paradox of cognitive flexibility in autism. *Trends Cogn. Sci.* 13, 74–82. doi: 10.1016/j.tics.2008.11.006

Grady, C. L., McIntosh, A. R., and Craik, F. I. (2003). Age-related differences in the functional connectivity of the hippocampus during memory encoding. *Hippocampus* 13, 572–586. doi: 10.1002/hipo.10114

Grainger, C., Williams, D. M., and Lind, S. E. (2014). Metacognition, metamemory, and mindreading in high-functioning adults with autism spectrum disorder. *J. Abnorm. Psychol.* 123, 650–659. doi: 10.1037/a0036531

Griffin, J. W., Bauer, R., and Gavett, B. E. (2021). The episodic memory profile in autism spectrum disorder: A Bayesian meta-analysis. *Neuropsychol. Rev.* 32, 316–351. doi: 10.1007/s11065-021-09493-5

Hannula, D. E., Althoff, R. R., Warren, D. E., Riggs, L., Cohen, N. J., and Ryan, J. D. (2010a). Worth a glance: Using eye movements to investigate the cognitive neuroscience of memory. *Front. Hum. Neurosci.* 4:166. doi: 10.3389/fnhum.2010.00166

Hannula, D. E., Ranganath, C., Ramsay, I. S., Solomon, M., Yoon, J., Niendam, T. A., et al. (2010b). Use of eye movement monitoring to examine item and relational memory in schizophrenia. *Biol. Psychiatry* 68, 610–616. doi: 10.1016/j.biopsych.2010.06.001

Hannula, D. E., Tranel, D., Allen, J. S., Kirchhoff, B. A., Nickel, A. E., and Cohen, N. J. (2015). Memory for items and relationships among items embedded in realistic scenes: Disproportionate relational memory impairments in amnesia. *Neuropsychology* 29, 126–138. doi: 10.1037/neu0000119

Hannula, D. E., Tranel, D., and Cohen, N. J. (2006). The long and short of it: Relational memory impairments in amnesia, even at short lags. *J. Neurosci.* 26, 8352–8359. doi: 10.1523/JNEUROSCI.5222-05.2006

Heisz, J. J., and Shore, D. I. (2008). More efficient scanning for familiar faces. *J. Vis.* 8, 1–10. doi: 10.1167/8.1.9

Hogeveen, J., Krug, M. K., Geddert, R. M., Ragland, J. D., and Solomon, M. (2020). Compensatory hippocampal recruitment supports preserved episodic memory in autism spectrum disorder. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 5, 97–109. doi: 10.1016/j.bpsc.2019.08.009

Jacoby, L. L. (1991). A process dissociation framework: Separating automatic from intentional uses of memory. *J. Mem. Lang.* 30, 513–541. doi: 10.1016/0749-596X(91)90025-F

Keehn, B., Müller, R., and Townsend, J. (2013). Atypical attentional networks and the emergence of autism. *Neurosci. Biobehav. Rev.* 37, 164–183. doi: 10.1016/j.neubiorev.2012.11.014

Keehn, B., Westerfield, M., and Townsend, J. (2019). Brief report: Cross-modal capture: Preliminary evidence of inefficient filtering in children with autism spectrum disorder. *J. Autism Dev. Disord.* 49, 385–390. doi: 10.1007/s10803-018-3674-y

Kim, H. (2010). Dissociating the roles of the default-mode, dorsal, and ventral networks in episodic memory retrieval. *NeuroImage* 50, 1648–1657. doi: 10.1016/j.neuroimage.2010.01.051

Konkel, A., Warren, D. E., Duff, M. C., Tranel, D. N., and Cohen, N. J. (2008). Hippocampal amnesia impairs all manner of relational memory. *Front. Hum. Neurosci.* 2:15. doi: 10.3389/neuro.09.015.2008

Lai, C. L. E., Lau, Z., Lui, S. S. Y., Lok, E., Tam, V., Chan, Q., et al. (2017). Meta-analysis of neuropsychological measures of executive functioning in children and adolescents with high-functioning autism spectrum disorder. *Autism Res.* 10, 911–939. doi: 10.1002/aur.1723

Landry, R., and Bryson, S. E. (2004). Impaired disengagement of attention in young children with autism. *J. Child Psychol. Psychiatry* 45, 1115–1122. doi: 10.1111/j.1469-7610.2004.00304.x

Li, G., Chen, M., Li, G., Wu, D., Lian, C., Sun, Q., et al. (2022). Volumetric analysis of amygdala and hippocampal subfields for infants with autism. *J. Autism Dev. Disord.* 53, 2475–2489. doi: 10.1007/s10803-022-05535-w

Lind, S. E., and Bowler, D. M. (2009). Recognition memory, self-other source memory, and theory-of-mind in children with autism spectrum disorder. *J. Autism Dev. Disord.* 39, 1231–1239. doi: 10.1007/s10803-009-0735-2

Lind, S. E., and Bowler, D. M. (2010). Episodic memory and episodic future thinking in adults with autism. *J. Abnorm. Psychol.* 119, 896–905. doi: 10.1037/a0020631

Lind, S. E., Bowler, D. M., and Raber, J. (2014). Spatial navigation, episodic memory, episodic future thinking, and theory of mind in children with autism spectrum disorder: Evidence for impairments in mental simulation? *Front. Psychol.* 5:1411. doi: 10.3389/fpsyg.2014.01411

Lord, C., Risi, S., Lambrecht, L., Cook, E. H. Jr., Leventhal, B. L., DiLavore, P. C., et al. (2000). The Autism Diagnostic Observation Schedule-Generic: A standard measure of social and communication deficits associated with the spectrum of autism. *J. Autism Dev. Disord.* 30, 205–223. doi: 10.1023/A:1005592401947

Loth, E., Gómez, J. C., and Happé, F. (2011). Do high-functioning people with autism spectrum disorder spontaneously use event knowledge to selectively attend to and remember context-relevant aspects in scenes? *J. Autism Dev. Disord.* 41, 945–961. doi: 10.1007/s10803-010-1124-6

Luck, S. J., and Gold, J. M. (2008). The translation of cognitive paradigms for patient research. *Schizophr. Bull.* 34, 629–644. doi: 10.1093/schbul/sbn036

Massand, E., and Bowler, D. M. (2015). Atypical neurophysiology underlying episodic and semantic memory in adults with autism spectrum disorder. *J. Autism Dev. Disord.* 45:s10803-013-1869-9. doi: 10.1007/s10803-013-1869-9

Massand, E., Bowler, D. M., Mottron, L., Hosein, A., and Jemel, B. (2013). ERP correlates of recognition memory in autism spectrum disorder. *J. Autism Dev. Disord.* 43, 2038–2047. doi: 10.1007/s10803-012-1755-x

Minshew, N. J., and Goldstein, G. (1998). Autism as a disorder of complex information processing. *Ment. Retard. Dev. Disabil. Res. Rev.* 4, 129–136. doi: 10.1002/(SICI)1098-2779(1998)4:2<129::AID-MRDD10>3.0.CO;2-X

Minshew, N. J., and Goldstein, G. (2001). The pattern of intact and impaired memory functions in autism. *J. Child Psychol. Psychiatry Allied Discip.* 42, 1095–1101. doi: 10.1111/1469-7610.00808

Mogensen, R. L. H., Hedegaard, M. B., Olsen, L. R., and Gebauer, L. (2020). Linking the puzzle pieces of the past: A study of relational memory in children with autism spectrum disorder. *Autism Res.* 13, 1959–1969. doi: 10.1002/aur.2379

Molitor, R. J., Ko, P. C., Hussey, E. P., and Ally, B. A. (2014). Memory-related eye movements challenge behavioral measures of pattern completion and pattern separation. *Hippocampus* 24, 666–672. doi: 10.1002/hipo.22256

Moscovitch, M., Cabeza, R., Winocur, G., and Nadel, L. (2016). Episodic memory and beyond: The hippocampus and neocortex in transformation. *Annu. Rev. Psychol.* 67, 105–134. doi: 10.1146/annurev-psych-113011-143733

Mostert-Kerckhoffs, M. A. L., Staal, W. G., Houben, R. H., and de Jonge, M. V. (2015). Stop and change: Inhibition and flexibility skills are related to repetitive behavior in children and young adults with autism spectrum disorders. *J. Autism Dev. Disord.* 45, 3148–3158. doi: 10.1007/s10803-015-2473-y

Murphy, J. W., Foxe, J. J., Peters, J. B., and Molholm, S. (2014). Susceptibility to distraction in autism spectrum disorder: Probing the integrity of oscillatory alpha-band suppression mechanisms. *Autism Res.* 7, 442–458. doi: 10.1002/aur.1374

Naveh-Benjamin, M. (2000). Adults age differences in memory performance; Test of an associative deficit hypothesis. *J. Exp. Psychol. Learn. Mem. Cogn.* 26, 1170–1187. doi: 10.1037//0278-7393.26.5.1170

Olsen, R. K., Chiew, M., Buchsbaum, B. R., and Ryan, J. D. (2014). The relationship between delay period eye movements and visuospatial memory. *Journal of Vision* 14(1), 1–11. doi: 10.1167/14.1.8

Papagiannopoulou, E. A., Chitty, K. M., Hermens, D. F., Hickle, I. B., and Lagopoulos, J. (2014). A systematic review and meta-analysis of eye-tracking studies in children with autism spectrum disorders. *Soc. Neurosci.* 9, 610–632. doi: 10.1080/17470919.2014.934966

Pertzov, Y., Avidan, G., and Zohart, E. (2009). Accumulation of visual information across multiple fixations. *J. Vis.* 9, 1–12. doi: 10.1167/9.10.2

Ranganath, C. (2010). Binding items and contexts. *Curr. Dir. Psychol. Sci.* 19, 131–137. doi: 10.1177/0963721410368805

Reinhardt, V. P., Iosif, A., Libero, L., Heath, B., Rogers, S. J., Ferrer, E., et al. (2020). Understanding hippocampal development in young children with autism spectrum disorder. *J. Am. Acad. Child. Adolesc. Psychiatry* 59, 1069–1079. doi: 10.1016/j.jaac.2019.08.008

Ring, M., Bowler, D. M., and Gaigg, S. B. (2017). An eye-movement study of relational memory in adults with autism spectrum disorder. *J. Autism Dev. Disord.* 47, 2981–2991. doi: 10.1007/s10803-017-3212-3

Ring, M., Gaigg, S. B., and Bowler, D. M. (2015). Object-location memory in adults with autism spectrum disorder. *Autism Res.* 8, 609–619. doi: 10.1002/aur.1478

Ring, M., Gaigg, S. B., and Bowler, D. M. (2016). Relational memory processes in adults with autism spectrum disorder. *Autism Res.* 9, 97–106. doi: 10.1002/aur.1493

Rugg, M. D., and Vilberg, K. L. (2013). Brain networks underlying episodic memory retrieval. *Curr. Opin. Neurobiol.* 23, 255–260. doi: 10.1016/j.conb.2012.11.005

Rutter, M., Bailey, A., and Lord, C. (2003). *Social Communication Questionnaire*. Los Angeles, CA: Western Psychological Services.

Ryan, J. D., Althoff, R. R., Whitlow, S., and Cohen, N. J. (2000). Amnesia is a deficit in relational memory. *Psychol. Sci.* 11, 454–461. doi: 10.1111/1467-9280.00288

Ryan, J. D., Hannula, D. E., and Cohen, N. J. (2007). The obligatory effects of memory on eye movements. *Memory* 15, 508–525. doi: 10.1080/09658210701391022

Schlichting, M. L., and Preston, A. R. (2015). Memory integration: Neural mechanisms and implications for behavior. *Curr. Opin. Behav. Sci.* 1, 1–8. doi: 10.1016/j.cobeha.2014.07.005

Schmitt, L. M., White, S. P., Cook, E. H., Sweeney, J. A., and Mosconi, M. W. (2018). Cognitive mechanisms of inhibitory control deficits in autism spectrum disorder. *J. Child Psychol. Psychiatry* 59, 586–595. doi: 10.1111/jcpp.12837

Semino, S., Ring, M., Bowler, D. M., and Gaigg, S. B. (2018). The influence of task demands, verbal ability, and executive functions on item and source memory in autism spectrum disorder. *J. Autism Dev. Disord.* 48, 184–197. doi: 10.1007/s10803-017-3299-6

Solomon, M., McCauley, J. B., Iosif, A. M., Carter, C. S., and Ragland, J. D. (2016). Cognitive control and episodic memory in adolescents with autism spectrum disorders. *Neuropsychologia* 89, 31–41. doi: 10.1016/j.neuropsychologia.2016.05.013

Solomon, M. S., Ozonoff, S. J., Cummings, N., and Carter, C. S. (2008). Cognitive control in autism spectrum disorders. *Int. J. Dev. Neurosci.* 26, 239–247. doi: 10.1016/j.ijdevneu.2007.11.001

Solomon, M., Ozonoff, S. J., Ursu, S., Ravizza, S., Cummings, N., Ly, S., et al. (2009). The neural substrates of cognitive control deficits in autism spectrum disorders. *Neuropsychologia* 47, 2515–2526. doi: 10.1016/j.neuropsychologia.2009.04.019

Souchay, C., Wojcik, D. Z., Williams, H. L., Crathern, S., and Clarke, P. (2013). Recollection in adolescents with autism spectrum disorder. *Cortex* 49, 1598–1609. doi: 10.1016/j.cortex.2012.07.011

Spaniol, J., Davidson, P. S. R., Kim, A. S. N., Han, H., Moscovitch, M., and Grady, C. L. (2009). Event-related fMRI studies of episodic encoding and retrieval: Meta-analyzes using activation likelihood estimation. *Neuropsychologia* 47, 1765–1779. doi: 10.1016/j.neuropsychologia.2009.02.028

Staresina, B. P., and Davachi, L. (2008). Selective and shared contributions of the hippocampus and perirhinal cortex to episodic item and associative encoding. *J. Cogn. Neurosci.* 20, 1478–1489. doi: 10.1162/jocn.2008.20104

Tonizzi, I., Giofrè, D., and Usai, M. C. (2021). Inhibitory control in autism spectrum disorders: Meta-analyses on indirect and direct measures. *J. Autism Dev. Disord.* 52, 4949–4965. doi: 10.1007/s10803-021-05353-6

Trontel, H. G., Duffield, T. C., Bigler, E. D., Abildskov, T. J., Froehlich, A., Prigge, M. B. D., et al. (2015). Mesial temporal lobe and memory function in autism spectrum disorder: An exploration of volumetric findings. *J. Clin. Exp. Neuropsychol.* 37, 178–192. doi: 10.1080/13803395.2014.997677

Van Eylen, L., Boets, B., Steyaert, J., Evers, K., Wagemans, J., and Noens, I. (2011). Cognitive flexibility in autism spectrum disorder: Explaining the inconsistencies? *Res. Autism Spectr. Disord.* 5, 1390–1401. doi: 10.1016/j.rasd.2011.01.025

Wainwright-Sharp, J. A., and Bryson, S. E. (1993). Visual orienting deficits in high-functioning people with autism. *J. Autism Dev. Disord.* 23, 1–13. doi: 10.1007/BF01066415

Wechsler, D. (2011). *Weschler Abbreviated Scale of Intelligence – II (WASI-II)* [Database record]. APA PsycTests. Washington, DC

Wojcik, D. Z., Moulin, C. J. A., and Souchay, C. (2013). Metamemory in children with autism: Exploring 'feeling of knowing' in episodic and semantic memory. *Neuropsychology* 27, 19–27. doi: 10.1037/a0030526

Yarbus, A. L. (1967). *Eye Movements and Vision*. New York: Plenum Press.

frontiers | Frontiers in Neuroanatomy

TYPE Brief Research Report
PUBLISHED 24 October 2023
DOI 10.3389/fnana.2023.1214629

OPEN ACCESS

EDITED BY
Dorit Ben Shalom,
Ben-Gurion University of the Negev, Israel

REVIEWED BY
Hiroaki Ishida,
Tokyo Metropolitan Institute of Medical Science, Japan
Antonio Di Ieva,
Macquarie University, Australia

*CORRESPONDENCE
Michael Kogan
✉ mikogan@salud.unm.edu

RECEIVED 30 April 2023
ACCEPTED 11 October 2023
PUBLISHED 24 October 2023

CITATION
Skandalakis GP, Barrios-Martinez J, Kazim SF, Rumalla K, Courville EN, Mahto N, Kalyvas A, Yeh F-C, Hadjipanayis CG, Schmidt MH and Kogan M (2023) The anatomy of the four streams of the prefrontal cortex. Preliminary evidence from a population based high definition tractography study. *Front. Neuroanat.* 17:1214629. doi: 10.3389/fnana.2023.1214629

The anatomy of the four streams of the prefrontal cortex. Preliminary evidence from a population based high definition tractography study

Georgios P. Skandalakis[1], Jessica Barrios-Martinez[2], Syed Faraz Kazim[1], Kavelin Rumalla[1], Evan N. Courville[1], Neil Mahto[1], Aristotelis Kalyvas[3], Fang-Cheng Yeh[2], Constantinos G. Hadjipanayis[2], Meic H. Schmidt[1] and Michael Kogan[1]*

[1]Department of Neurosurgery, University of New Mexico Hospital, Albuquerque, NM, United States, [2]Department of Neurosurgery, University of Pittsburgh, Pittsburgh, PA, United States, [3]Division of Neurosurgery, Toronto Western Hospital, University Health Network, Toronto, ON, Canada

The model of the four streams of the prefrontal cortex proposes 4 streams of information: motor through Brodmann area (BA) 8, emotion through BA 9, memory through BA 10, and emotional-related sensory through BA 11. Although there is a surge of functional data supporting these 4 streams within the PFC, the structural connectivity underlying these neural networks has not been fully clarified. Here we perform population-based high-definition tractography using an averaged template generated from data of 1,065 human healthy subjects acquired from the Human Connectome Project to further elucidate the structural organization of these regions. We report the structural connectivity of BA 8 with BA 6, BA 9 with the insula, BA 10 with the hippocampus, BA 11 with the temporal pole, and BA 11 with the amygdala. The 4 streams of the prefrontal cortex are subserved by a structural neural network encompassing fibers of the anterior part of the superior longitudinal fasciculus-I and II, corona radiata, cingulum, frontal aslant tract, and uncinate fasciculus. The identified neural network of the four streams of the PFC will allow the comprehensive analysis of these networks in normal and pathological brain function.

KEYWORDS

cingulum, frontal slant tract, dorsal superior longitudinal fasciculus, SLF-I, uncinate fasciculus

Introduction

The pre-frontal cortex (PFC) has been suggested to serve as the central executive system of the human brain by controlling refined motor movements, goal-directed behavior, reasoning, planning, language, emotion, and memory (Wood and Grafman, 2003; Seeley et al., 2007). The medial PFC is a key component of our default mode network whereas the lateral PFC is fundamental in orchestrating high order functions (Jobson et al., 2021; Friedman and Robbins, 2022). Recently, Ben Shalom and Bonneh proposed a functional parcellation of the PFC in 4

streams, suggesting the BA8 is implicated in motor functions, BA9 for emotional processing, BA10 for memory, and BA11 for processing emotionally related sensory information (Ben Shalom and Bonneh, 2019). This model is based on data demonstrating strong functional connectivity of BA8 with BA6, BA 9 with the insula, BA10 with the hippocampus, and BA11 with the anterior temporal lobe (Shalom, 2009). Based on the functional network proposed, we hypothesize that the four streams of the PFC are subserved by connections between BA8 and BA6, BA 9 and insula, BA10 and hippocampus, and BA11 and temporal pole. To further elucidate the organization of these regions we investigated their structural connectivity using population based high definition tractography.

Methods

We performed fiber tracking using DSI Studio software developed by FCY on a population-averaged diffusion MRI template (HP-ADMRIT) generated from diffusion MRI (dMRI) data of 1,065 human healthy subjects acquired from the Human Connectome Project (HCP) of the WashU consortium (Glasser et al., 2016; Yeh, 2022). The age range was 22–37 years, and the average age was 28.75 years. The multi-diffusion scheme included three *b*-values at 1,000, 2,000, and 3,000 s/mm^2 and each shell had 90 sampling directions with isotropic spatial resolution at 1.25 mm, and slice thickness at 1.25 (Van Essen et al., 2013). The number of diffusion sampling directions were 90, 90, and 90, respectively. The b-table was checked by an automatic quality control routine to ensure its accuracy (Schilling et al., 2019). The diffusion data were reconstructed in the MNI space using q-space diffeomorphic reconstruction (Yeh and Tseng, 2011) to obtain the spin distribution function (Yeh et al., 2010). A diffusion sampling length ratio of 1.7 was used. The restricted diffusion was quantified using restricted diffusion imaging (Yeh et al., 2017).

Regions of interest (ROI) were assigned according to Brodmann atlas (Pijnenburg et al., 2021). ROIs of the precentral cortex included the supplementary motor area (BA6), superior frontal gyrus (BA8), medial prefrontal cortex (BA9), anterior prefrontal cortex (BA10), lateral and medial orbitofrontal cortex (BA11), insula, hippocampus, and temporal pole. We performed fiber tractography analyses to identify anatomical connections between two regions of interest following our proposed hypothesis of connection on the PFC as follows, BA 8 with BA6, BA 9 with insula, BA10 with hippocampus, BA11 with temporal pole, and BA11 with amygdala. Each region of interest was placed on the MNI space and were based on the Brodmann atlas included in the DSI Studio package. Once regions of interest were placed and anatomically verified by an anatomist. Cortical regions were assigned as "regions of interest" to allow whole brain seeding and to allow tracts to be filtered during the analyses. White matter regions were assigned as "seed" to refine fiber tractography results as this specifies the algorithm to start at this "seed" point. Tracking parameters included tracking threshold at 0, angular threshold at 0, and step size at 0 (based on default parameters). Length of fibers were based on default parameters as well (minimum length at 30 mm and maximum length at 200 mm), and these particular parameters allows to exclude tracts that are either too short (to exclude excessive u-fibers) or too long (to exclude long false continuations). In addition, we allow fiber tractography to end at 1,000,000 seeds to allow us to obtain as many results as possible. Finally, topology informed pruning was applied at 4 iterations to eliminate false continuations, a patented method described in recent publications (Yeh et al., 2019). To check for result accuracy, we followed a single-ROI approach to evaluate if fibers generated by this method will result in the same trajectories when compared to fibers obtained by pairwise tractography, and results are discussed in the results section.

Results

Fibers running within the anterior part of the dorsal component of the superior longitudinal fasciculus (SLF-Ia) were observed interconnecting BA8 of the superior frontal gyrus (SFG) with BA6 of the pre-SMA and SMA proper. These fibers reside within the paracingulate gyrus dorsal to the body of corpus callosum. BA6 and BA8 are also interconnected with U-fibers residing within the SFG and middle frontal gyrus (MFG) as well as fibers of the superior longitudinal fasciculus II (SLF-II) (Figure 1). In addition, fibers from the frontal aslant tract (FAT) were observed connecting BA6 and BA8. Fibers interconnecting BA9 of the SFG and MFG with the insula, more specifically the posterior insular cortex, were tracked. These fibers run within the corona radiata at a rostrocaudal direction parallel to fibers of the external capsule (Figure 2). The connectivity of BA10 and hippocampus was tracked through two different fiber bundles (Figure 3). Cingulum fibers were recorded arching dorsal to the corpus callosum between BA10 and hippocampus (Figure 3). Fibers of the uncinate were tracked interconnecting BA11 with amygdala and temporal pole. Fibers implicating the amygdala were observed running medial and posterior to the fibers implicating the temporal pole. To test result accuracy, we used a single-ROI tractography approach and compared results with our original method. For example, we placed the hippocampus as a single ROI assigned as a seed to evaluate if obtained trajectories were similar to fibers obtained by pairwise tractography. Results show that fibers generated by single-ROI and two-ROI approach are the same trajectories that project from the hippocampus to BA10, which proves the pairwise tractography to be a valid method to evaluate connections of the PFC (Figure 4).

Discussion

In this population-based tractography study, we identified direct connections of BA 8 with BA6, BA 9 with the posterior insular cortex, BA10 with the hippocampus, and BA11 with the temporal pole and amygdala through the SLF-Ia, FAT, U-Fibers, SLFII, corona radiata, and cingulum. To the best of our knowledge this is the first study demonstrating the structural connectivity of the proposed four streams of the prefrontal cortex using an HP-ADMRIT generated from dMRI data of 1,065 human healthy subjects acquired from HCP.

The connectivity between BA6 and BA8 has been demonstrated in non-human primates through tracer injections (Arikuni et al., 1988). We have recently characterized the connectivity between BA8

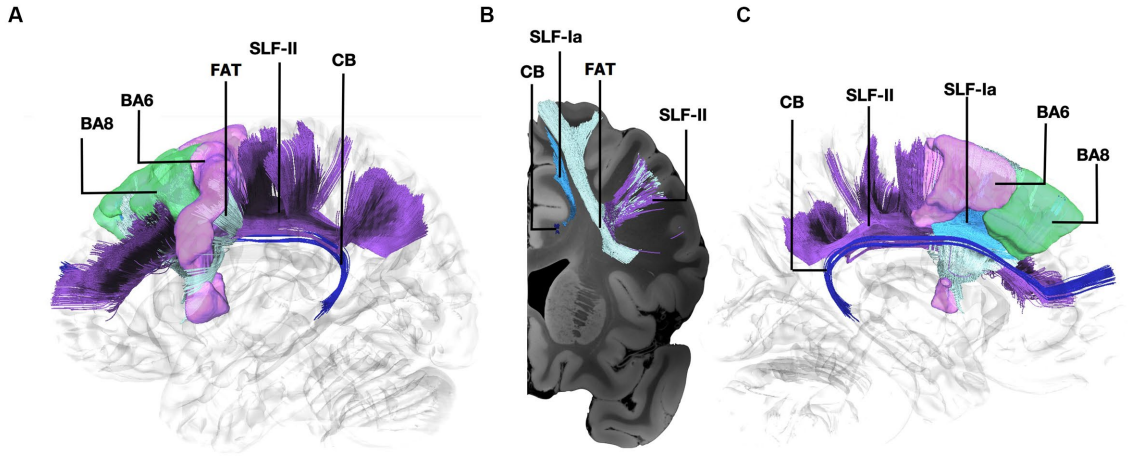


FIGURE 1
Fiber tract connectivity between BA8 and BA6 through the Frontal Aslant Tract, U-fibers, and the anterior part of the dorsal component of the Superior Longitudinal Fasciculus and Superior Longitudinal Fasciculus-II. **(A)** Lateral view demonstrating the anterior part of the left dorsal component of the superior longitudinal fasciculus in light blue, FAT in silver, and the anterior part of the superior longitudinal fasciculus II in purple interconnecting BA6 (purple) and BA8 (green) superimposed on a left hemisphere isosurface. Fibers of the cingulum are shown in dark blue. **(B)** Coronal section at the level of BA8 demonstrating the spatial relationship of the different pathways interconnecting BA6 and BA8. **(C)** Medial view demonstrating the relationship between SLF-Ia and cingulum. SLF-Ia, anterior part of the left dorsal component of the superior longitudinal fasciculus; SLF-II, Superior Longitudinal Fasciculus-II; CB, cingulum bundle; BA8, Brodmann area 8; BA6, Brodmann area 6.

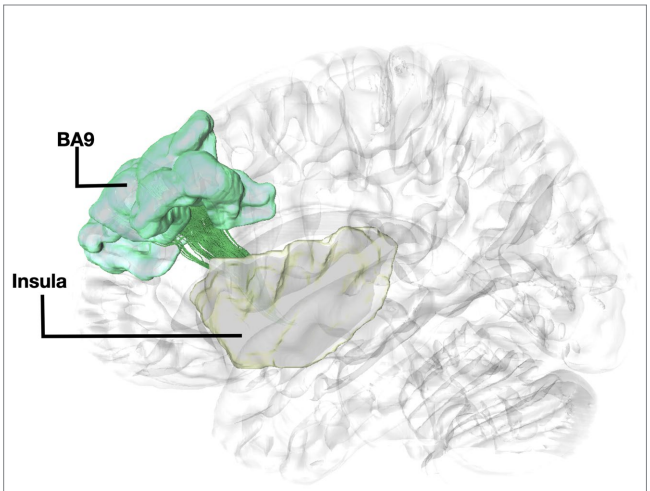


FIGURE 2
Fiber tract connectivity between BA9 and insula. Lateral view demonstrating fibers within the left corona radiata in green interconnecting the BA9 (green) with insula (posterior insular cortex) (yellow) superimposed on a left hemisphere isosurface. BA9, Brodmann area 9.

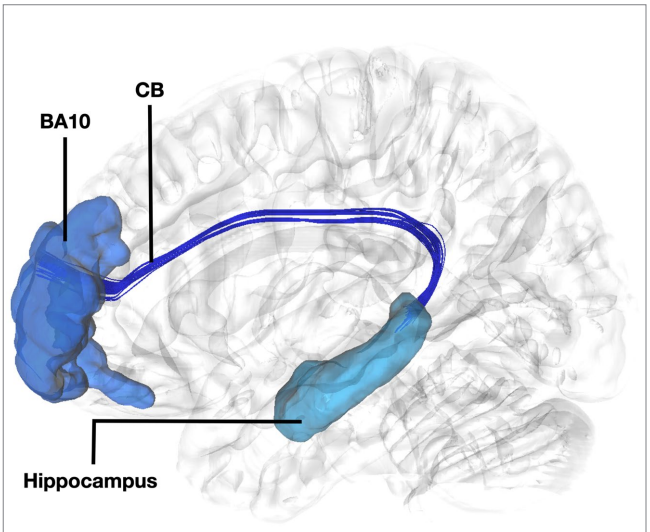


FIGURE 3
Fiber tract connectivity between BA10 and hippocampus. Lateral view demonstrating fibers of the left cingulum in dark interconnecting BA10 (dark blue) with the dorsal hippocampus (light blue) superimposed on a left hemisphere isosurface. BA10, Brodmann area 10; CB, Cingulum Bundle.

and BA6 through the SLF-Ia in the human brain using blunt fiber microdissections in normal human hemispheres (Komaitis et al., 2019). Our dissection results suggested that the dorsal part of the superior longitudinal fasciculus is segmented at the level of the anterior paracentral lobule in an anterior and posterior part (Komaitis et al., 2019). In line with previous anatomical studies in humans, we found the connectivity of the more lateral parts of BA8 and BA6 through the FAT, U-fibers, and the anterior segment of the SLF-II (Wang et al., 2016; Bozkurt et al., 2017).

The structural connectivity of the insula with BA9 has been previously demonstrated through a dataset of $n = 199$ subjects (Nomi et al., 2018). In addition, studies have shown connections between BA9 and BA10 and several association pathways, including cingulum and fibers from BA9 connecting to the ventral part of the insula (Petrides and Pandya, 2007). Histological studies have identified von Economo neurons both within the insula and BA9 (Fajardo et al., 2008; Allman et al., 2011). To the best of our knowledge, this is the first study reporting the trajectory, and directionality of the fibers interconnecting these regions. A tracer injection study identified major connection to BA10 including projections from parahippocampal areas, which supports our findings of fibers connecting BA10 and hippocampus (Burman

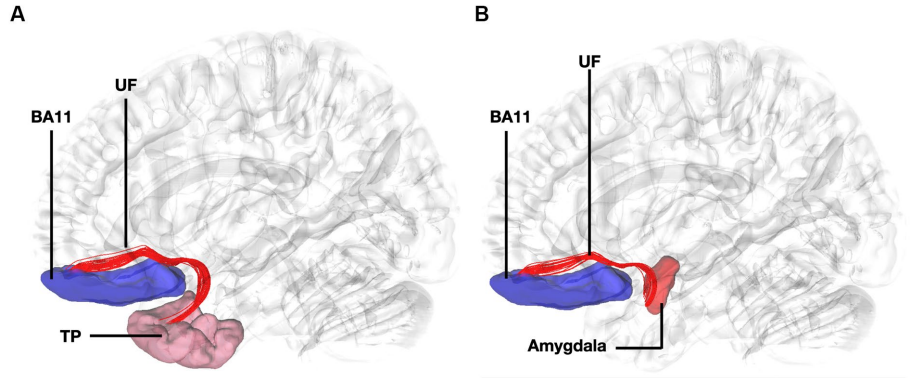


FIGURE 4
Fiber tract connectivity between BA11 and temporal pole through the uncinate fasciculus. **(A)** Lateral view demonstrating fibers of the left uncinate fasciculus in red interconnecting BA11 with temporal pole superimposed on a left hemisphere isosurface. BA11, Brodmann area 11. **(B)** Lateral view demonstrating fibers of the uncinate fasciculus interconnecting BA11 and region of amygdala superimposed on a left hemisphere isosurface. BA11, Brodmann area 11; UF, uncinate fasciculus.

et al., 2011). Furthermore, research in monkeys has demonstrated that distant regions also exhibit significant laminar similarities resulting in true anatomical connections, which has been observed in the case of projections between the BA9 and BA10 cortical areas through association fibers (Barbas, 2015). Our results show that fibers interconnecting the insula with BA9 travel within the centrum semiovale exhibiting a parallel directionality with the cortico-striatal pathways. Fibers traveling within the centrum semiovale exhibit a very complex fiber orientation pattern. Imaging results in such areas with kissing and crossing fibers are more prone to false positives (Fernandez-Miranda et al., 2012). Therefore, these results should be taken into consideration with caution. Nevertheless, results obtained by single-ROI and two-ROI approach result in the same trajectories entering the prefrontal cortex, which allows to validate our method for accuracy, and the presence of histological and imaging evidence of the connectivity of the insula with BA9, in the absence of any other fiber tracts connecting these regions support our current results.

The connectivity of BA10 and hippocampus was tracked through the cingulum. Connectivity of the BA10 and hippocampus has been reported by means of the cingulum bundle through an abundance of studies (Bubb et al., 2018; Skandalakis et al., 2020; Komaitis et al., 2022). A recent study applying diffusion tensor imaging (DTI) in children demonstrated a correlation between emotional dysregulation and increased radial diffusivity (RD), as well as decreased fractional anisotropy (FA) of the cingulum-callosal fibers, supporting the hypothesis that connecting fibers of the cingulum between BA10 and hippocampus are part of the four streams and subserving an important functional aspect of emotional regulation (Hung et al., 2020). In line with numerous fiber dissection and imaging studies in humans we showed the fibers of the uncinate interconnecting BA11 with the amygdala and temporal pole (Liakos et al., 2021). Fibers interconnecting these areas exhibit same trajectory and connectivity between humans and non-human primates (Thiebaut de Schotten et al., 2012). Furthermore, several areas of the prefrontal cortex have been shown to have similarities between human and non-human primates. However, other areas in the anterior prefrontal cortex, particularly the frontopolar region in humans, appears to be unique and not easily matched to macaque prefrontal regions, suggesting distinct cognitive capabilities in human anterior prefrontal cortex (Neubert et al., 2014). This highlights the intriguing interaction between evolutionary consistency and uniqueness within the prefrontal cortex.

DMRI provides exceptional means to study fiber tracts *in vivo*, in a fast detailed manner, allowing analysis between large populations (Yeh, 2022). Still, fiber tractography provides indirect measurements according to the diffusion of water molecules (Dyrby et al., 2018). Thus, results should be interpreted judiciously if they are not validated by cadaveric data (Yendiki et al., 2022).

Conclusion

The 4 streams of the prefrontal cortex are subserved by a structural neural network involving fibers of the anterior part of the superior longitudinal fasciculus-I, superior longitudinal fasciculus-II, corona radiata, uncinate fasciculus, frontal aslant tract, and U-fibers. The identified neural network of the four streams of the PFC will allow a more comprehensive analysis of these networks in normal and pathological brain function.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the studies involving humans because the patients/participants provided their written

informed consent to participate in this study. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

GS, F-CY, KR, SK, CH, AK, and MK: concept and design. GS, F-CY, KR, SK, NM, AK, EC, CH, MS, and MK: data acquisition and analysis. GS, AK, F-CY, CH, MS, and MK: supervision. GS, KR, SK, EC, and NM: drafting. GS, F-CY, KR, SK, AK, CH, MS, and MK: critical review and editing. All authors reviewed and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Allman, J. M., Tetreault, N. A., Hakeem, A. Y., Manaye, K. F., Semendeferi, K., Erwin, J. M., et al. (2011). The von Economo neurons in the frontoinsular and anterior cingulate cortex. *Ann. N. Y. Acad. Sci.* 1225, 59–71. doi: 10.1111/j.1749-6632.2011.06011.x

Arikuni, T., Watanabe, K., and Kubota, K. (1988). Connections of area 8 with area 6 in the brain of the macaque monkey. *J. Comp. Neurol.* 277, 21–40. doi: 10.1002/cne.902770103

Barbas, H. (2015). General cortical and special prefrontal connections: principles from structure to function. *Annu. Rev. Neurosci.* 38, 269–289. doi: 10.1146/annurev-neuro-071714-033936

Ben Shalom, D., and Bonneh, Y. S. (2019). Editorial: the medial prefrontal cortex and integration in ASD and typical cognition. *Front. Hum. Neurosci.* 13:74. doi: 10.3389/fnhum.2019.00074

Bozkurt, B., Yagmurlu, K., Middlebrooks, E. H., Cayci, Z., Cevik, O. M., Karadag, A., et al. (2017). Fiber connections of the supplementary motor area revisited: methodology of Fiber dissection, DTI, and three dimensional documentation. *J. Vis. Exp* 123:55681. doi: 10.3791/55681

Bubb, E. J., Metzler-Baddeley, C., and Aggleton, J. P. (2018). The cingulum bundle: anatomy, function, and dysfunction. *Neurosci. Biobehav. Rev.* 92, 104–127. doi: 10.1016/j.neubiorev.2018.05.008

Burman, K. J., Reser, D. H., Yu, H.-H., and Rosa, M. G. (2011). Cortical input to the frontal pole of the marmoset monkey. *Cereb. Cortex* 21, 1712–1737. doi: 10.1093/cercor/bhq239

Dyrby, T. B., Innocenti, G. M., Bech, M., and Lundell, H. (2018). Validation strategies for the interpretation of microstructure imaging using diffusion MRI. *Neuroimage* 182, 62–79. doi: 10.1016/j.neuroimage.2018.06.049

Fajardo, C., Escobar, M. I., Buriticá, E., Arteaga, G., Umbarila, J., Casanova, M. F., et al. (2008). Von Economo neurons are present in the dorsolateral (dysgranular) prefrontal cortex of humans. *Neurosci. Lett.* 435, 215–218. doi: 10.1016/j.neulet.2008.02.048

Yeh, F.-C., Wedeen, V. J., and Tseng, W.-Y. I. (2010). Generalized q-sampling imaging. *IEEE Trans. Med. Imaging* 29, 1626–1635. doi: 10.1109/TMI.2010.2045126

Fernandez-Miranda, J. C., Pathak, S., Engh, J., Jarbo, K., Verstynen, T., Yeh, F. C., et al. (2012). High-definition fiber tractography of the human brain: neuroanatomical validation and neurosurgical applications. *Neurosurgery* 71, 430–453. doi: 10.1227/NEU.0b013e3182592faa

Friedman, N. P., and Robbins, T. W. (2022). The role of prefrontal cortex in cognitive control and executive function. *Neuropsychopharmacology* 47, 72–89. doi: 10.1038/s41386-021-01132-0

Glasser, M. F., Smith, S. M., Marcus, D. S., Andersson, J. L. R., Auerbach, E. J., Behrens, T. E. J., et al. (2016). The human connectome Project's neuroimaging approach. *Nat. Neurosci.* 19, 1175–1187. doi: 10.1038/nn.4361

Hung, Y., Uchida, M., Gaillard, S. L., Woodworth, H., Kelberman, C., Capella, J., et al. (2020). Cingulum-Callosal white-matter microstructure associated with emotional dysregulation in children: a diffusion tensor imaging study. *Neuroimage* 27:102266. doi: 10.1016/j.nicl.2020.102266

Jobson, D. D., Hase, Y., Clarkson, A. N., and Kalaria, R. N. (2021). The role of the medial prefrontal cortex in cognition, ageing and dementia. *Brain Commun.* 3:125. doi: 10.1093/braincomms/fcab125

Komaitis, S., Skandalakis, G. P., Kalyvas, A. V., Drosos, E., Lani, E., Emelifeonwu, J., et al. (2019). Dorsal component of the superior longitudinal fasciculus revisited: novel insights from a focused fiber dissection study. *J. Neurosurg.* 132, 1265–1278. doi: 10.3171/2018.11.JNS182908

Komaitis, S., Stranjalis, G., Kalamatianos, T., Drosos, E., Kalyvas, A. V., Skandalakis, G. P., et al. (2022). A stepwise laboratory manual for the dissection and illustration of limbic and paralimbic structures: lessons learned from the Klingler's technique. *Surg. Radiol. Anat.* 44, 1045–1061. doi: 10.1007/s00276-022-02981-0

Liakos, F., Komaitis, S., Drosos, E., Neromyliotis, E., Skandalakis, G. P., Gerogiannis, A. I., et al. (2021). The topography of the frontal terminations of the Uncinate fasciculus revisited through focused Fiber dissections: shedding light on a current controversy and introducing the insular apex as a key anatomoclinical area. *World Neurosurg.* 152, e625–e634. doi: 10.1016/j.wneu.2021.06.012

Neubert, F.-X., Mars, R. B., Thomas, A. G., Sallet, J., and Rushworth, M. F. (2014). Comparison of human ventral frontal cortex areas for cognitive control and language with areas in monkey frontal cortex. *Neuron* 81, 700–713. doi: 10.1016/j.neuron.2013.11.012

Nomi, J. S., Schettini, E., Broce, I., Dick, A. S., and Uddin, L. Q. (2018). Structural connections of functionally defined human insular subdivisions. *Cereb Cortex* 28, 3445–3456. doi: 10.1093/cercor/bhx211

Petrides, M., and Pandya, D. N. (2007). Efferent association pathways from the rostral prefrontal cortex in the macaque monkey. *J. Neurosci.* 27, 11573–11586. doi: 10.1523/JNEUROSCI.2419-07.2007

Pijnenburg, R., Scholtens, L. H., Ardesch, D. J., De Lange, S. C., Wei, Y., and Van Den Heuvel, M. P. (2021). Myelo- and cytoarchitectonic microstructural and functional human cortical atlases reconstructed in common MRI space. *Neuroimage* 239:118274. doi: 10.1016/j.neuroimage.2021.118274

Schilling, K. G., Yeh, F. C., Nath, V., Hansen, C., Williams, O., Resnick, S., et al. (2019). A fiber coherence index for quality control of B-table orientation in diffusion MRI scans. *Magn. Reson. Imaging* 58, 82–89. doi: 10.1016/j.mri.2019.01.018

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., et al. (2007, 2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci.* 27, 2349–2356. doi: 10.1523/JNEUROSCI.5587-06.2007

Shalom, D. B. (2009). The medial prefrontal cortex and integration in autism. *Neuroscientist* 15, 589–598. doi: 10.1177/1073858409336371

Skandalakis, G. P., Komaitis, S., Kalyvas, A., Lani, E., Kontrafouri, C., Drosos, E., et al. (2020). Dissecting the default mode network: direct structural evidence on the morphology and axonal connectivity of the fifth component of the cingulum bundle. *J. Neurosurg.* 134, 1–12. doi: 10.3171/2020.2.JNS193177

Thiebaut de Schotten, M., Dell'Acqua, F., Valabregue, R., and Catani, M. (2012). Monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex* 48, 82–96. doi: 10.1016/j.cortex.2011.10.001

Van Essen, D. C., Smith, S. M., Barch, D. M., Behrens, T. E., Yacoub, E., Ugurbil, K., et al. (2013). The WU-Minn human connectome project: an overview. *Neuroimage* 80, 62–79. doi: 10.1016/j.neuroimage.2013.05.041

Wang, X., Pathak, S., Stefaneanu, L., Yeh, F. C., Li, S., and Fernandez-Miranda, J. C. (2016). Subcomponents and connectivity of the superior longitudinal fasciculus in the human brain. *Brain Struct. Funct.* 221, 2075–2092. doi: 10.1007/s00429-015-1028-5

Wood, J. N., and Grafman, J. (2003). Human prefrontal cortex: processing and representational perspectives. *Nat. Rev. Neurosci.* 4, 139–147. doi: 10.1038/nrn1033

Yeh, F.-C. (2022). Population-based tract-to-region connectome of the human brain and its hierarchical topology. *Nat Commun* 13:4933. doi: 10.1038/s41467-022-32595-4

Yeh, F.-C., Liu, L., Hitchens, T. K., and Wu, Y. L. (2017). Mapping immune cell infiltration using restricted diffusion MRI. *Magn. Reson. Med.* 77, 603–612. doi: 10.1002/mrm.26143

Yeh, F.-C., Panesar, S., Barrios, J., Fernandes, D., Abhinav, K., Meola, A., et al. (2019). Automatic removal of false connections in diffusion MRI tractography using topology-informed pruning (TIP). *Neurotherapeutics* 16, 52–58. doi: 10.1007/s13311-018-0663-y

Yeh, F.-C., and Tseng, W.-Y. I. (2011). NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. *Neuroimage* 58, 91–99. doi: 10.1016/j.neuroimage.2011.06.021

Yendiki, A., Aggarwal, M., Axer, M., Howard, A. F. D., van Walsum, A. M. C., and Haber, S. N. (2022). Post mortem mapping of connectional anatomy for the validation of diffusion MRI. *Neuroimage* 256:119146. doi: 10.1016/j.neuroimage.2022.119146

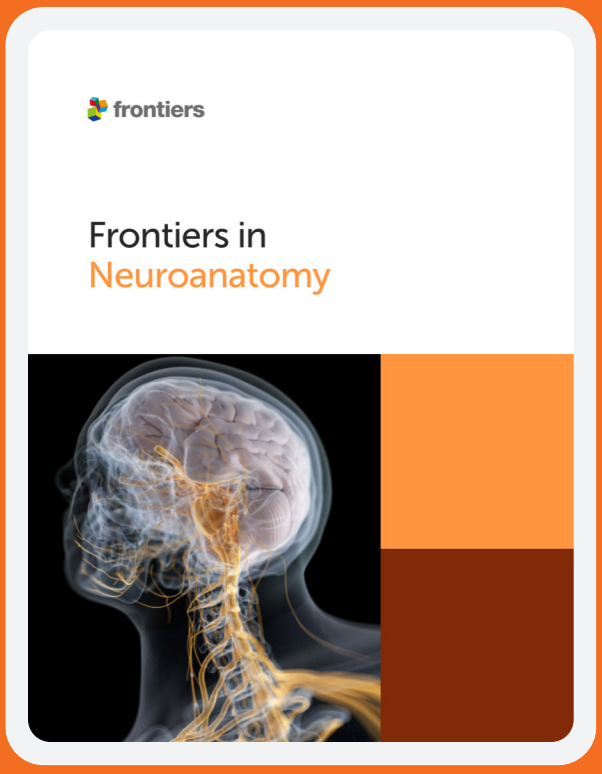
Frontiers in Neuroanatomy

Explores the anatomical organization of nervous systems across all species

Advances our understanding of neuroanatomy - from sub-cellular and connectivity anatomy to immunocytochemistry mapping protein expression patterns.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact