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An Approach to Neuroimaging Interpersonal Interactions in Mental Health Interventions

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ABSTRACT

BACKGROUND: Conventional paradigms in clinical neuroscience tend to be constrained in terms of ecological validity, raising several challenges to studying the mechanisms mediating treatments and outcomes in clinical settings. Addressing these issues requires real-world neuroimaging techniques that are capable of continuously collecting data during free-flowing interpersonal interactions and that allow for experimental designs that are representative of the clinical situations in which they occur.

METHODS: In this work, we developed a paradigm that fractionates the major components of human-to-human verbal interactions occurring in clinical situations and used functional near-infrared spectroscopy to assess the brain systems underlying clinician-client discourse (N = 30).

RESULTS: Cross-brain neural coupling between people was significantly greater during clinical interactions compared with everyday life verbal communication, particularly between the prefrontal cortex (e.g., inferior frontal gyrus) and inferior parietal lobule (e.g., supramarginal gyrus). The clinical tasks revealed extensive increases in activity across the prefrontal cortex, especially in the rostral prefrontal cortex (area 10), during periods in which participants were required to silently reason about the dysfunctional cognitions of the other person.

CONCLUSIONS: This work demonstrates a novel experimental approach to investigating the neural underpinnings of interpersonal interactions that typically occur in clinical settings, and its findings support the idea that particular prefrontal systems might be critical to cultivating mental health.

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A common framework of neuroimaging methods investigating the treatment of psychopathological disorders is to collect neuroimaging data periodically at particular stages of treatment rather than continuously in situ (1). Although this framework is excellent for examining the effects of clinical interventions on behavioral, affective, and physiological responding (2), it creates an important explanatory gap regarding the nature of the neural systems by which these changes are brought about during the clinical interpersonal interactions that are central to a multitude of treatments (Figure 1). In other words, neuroimaging techniques are currently being used to study etiopathogenic mechanisms and cortical dysregulation as well as the effects and efficacy of (non)psychopharmacological treatments on changes in neural activity and behavior, such as functional near-infrared spectroscopy (fNIRS) (2–5). However, observing only the effects of interventions, such as decreases in maladaptive behavior, emotion dysregulation, and functional dysconnectivity (6,7), limits our understanding of the neurocognitive mechanisms by which adaptive changes in mental health are cultivated during treatment (8). For instance, what is it about interpersonal interactions in clinical situations that fosters healthier thinking, feeling, and behaving on the part of patients? Second-person neuroscience approaches to investigating such neuropsychiatric questions might represent a path toward addressing this explanatory gap. Indeed, the neural systems in which clinicians engage to treat patients and those in which patients also probably learn to engage remain largely unclear.

The chief reason why data are not collected in situ is that there are inherent limitations to most neuroimaging methods that constrain the types of experimental designs that can be used in intervention-type settings (1,2). So, to investigate the neurocognitive mechanisms of interest during treatment, the method that should ideally be adopted is one that allows for real-world paradigms and the collection of data relating to interpersonal information processing dynamics. Recent cognitive neuroscientific research has acknowledged this need for a multiperson and, indeed, multimodal framework by using the neuroimaging technique of hyperscanning to explore the intersubject systems underpinning human-to-human interaction (9–23). Hyperscanning measures hemodynamic changes and interpersonal brain synchronization between 2 or more individuals while engaging in interactive tasks in naturalistic or laboratory settings [see (24–27) for reviews]. Neuroimaging methods such as functional magnetic resonance imaging and electroencephalography have used this technique in several studies, with a growing number of publications using fNIRS-based hyperscanning (28). For example, portable, wireless

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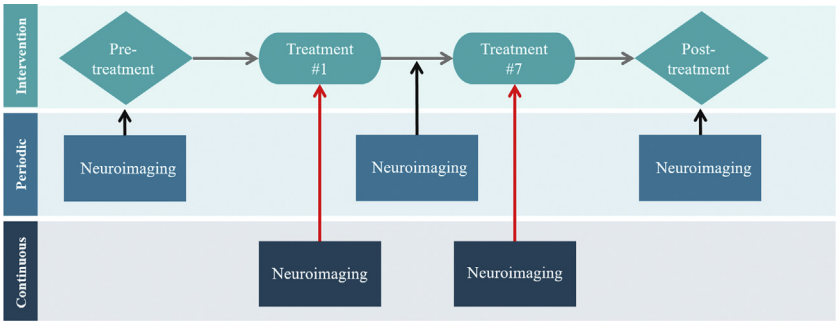

Figure 1. Data collection in psychotherapy. Neuroimaging and psychological methods typically collect physiological, behavioral, cognitive, and affective data periodically, such as pretreatment, between treatment sessions, and after treatment, to examine the effects of an intervention on the dependent variables of interest over time, leaving an explanatory gap regarding the potential neurocognitive mechanisms by which these effects are actuated and cultivated within treatment sessions. Adopting a more in situ approach that collects data within particular treatment sessions should address this issue. Therefore, a hybrid approach of the former and latter stands the best chances of capturing the changes facilitating mental health.

neuroimaging systems are methodological complements to experimental designs that are more naturalistic or ecological (29). But what type of ecological experimental design is then appropriate for investigating clinically representative settings and situations yet retains the degree of scientific control required in contemporary cognitive neuroscience? It is probably one that approaches the conundrum of clinical interpersonal interactions by attempting to fractionate their core modality: verbal communication. The fact that the dialogue between clinicians and clients is typically dialectical in nature represents the most clinically significant use of language in verbal interventions (30–32). For example, clients express thoughts as statements or propositions about goal-incongruent events, reflecting specific dysfunctional cognitive schemas and appraisals (33,34), and, in turn, clinicians use various adaptive strategies to challenge the veracity and utility of these thoughts (35,36).

What is perhaps most demanding of clinicians is their task that immediately precedes this verbal intervention: to critically think about and recogitate clients' beliefs (1,8). A standard position that might be adopted from our knowledge of cognitive neuroscience so far might be that the brain systems taxed by such a process likely depend in part on executive subsystems based in the prefrontal cortex (PFC) that are dedicated to solving ill-structured, linguistically mediated reasoning problems [see (37) for review]. In this case, these subsystems likely modulate a more posterior, semantic network in which maladaptive schema and appraisal processes are represented and stored (38). If this is the case, then the literature in this area of cognitive control (39–47) and emotion regulation [(48–51); see (46,52) for reviews] suggest that the rostral PFC (area 10) and middle frontal gyrus (area 46) might play a marked role in this thinking task that potentially drives not only clinician-led verbal interventions but also eventual client-led ones independent of treatment settings.

A few fNIRS-based hyperscanning studies on verbal communication have recently been conducted to examine the neural underpinnings of dynamic coupling between people during natural dialogue (13,18,19,22,53,54), with common findings in subregions that have long been implicated in speech production and comprehension such as Broca's and Wernicke's areas, respectively, as well as in the PFC subregions mentioned above. Interpersonal synchronization has tended to be significantly greater between people during these verbal interactions as compared with random pairings of participants who nevertheless conversed, but not with each other. However, no study to our knowledge has developed an experimental design that can be adapted to different clinical settings to specifically assess the inter- and intraneural dynamics of verbal exchanges in clinical situations, particularly their epochs (e.g., speaking, listening, and thinking), or have such exchanges been compared with nonclinical verbal communication to assess what is unique about clinical interactions that make the clinician successful or the interaction compelling to the client.

Accordingly, the aim of this work was to use a real-world approach to developing a neuroimaging paradigm that addresses these theoretical and practical lacunae. It was predicted that because clinical situations are inherently more interactive and normative than everyday instances of verbal communication, clinical interpersonal interactions will elicit greater cross-brain coherence in paired participants engaging in the roles of clinician and client compared with a control condition and that within-brain contrasts will show cognitive resource consumption predominately across the PFC. Moreover, because the tasks of clinicians in real-world treatment settings are much less passive than those involved in everyday discourse, it was hypothesized that periods of verbal intervention, in which clinicians are required to dispute dysfunctional cognitions about the self, others, and world, should demonstrate changes in activity above and beyond normal speaking demands, particularly in the rostral PFC (area 10) and more posterior areas related to the semantic network. It was further expected that perhaps to a greater degree, this pattern of activity will also be demonstrated prior to verbal intervention when clinicians covertly reason about dysfunctional cognitions, namely in the rostral PFC and right middle frontal gyrus (area 46).

METHODS AND MATERIALS

Participants

A total of 30 healthy adults (15 pairs; 80% female; mean age = 30.17 ± 12.68 years; 97% right-handed) participated in the study (55). All participants provided written informed consent in accordance with guidelines provided by the Yale Human Investigation Committee (HIC #1501015178) and were reimbursed for participation. Dyads were assigned in order of recruitment, and no individual participated in more than one dyad. Eligibility of participation was determined using two

screening tasks, namely a right-handed finger-thumb tapping task and passive viewing of a reversing checkboard while fNIRS signals were acquired. A participant was selected for the hyperscanning experiment if countercorrelated oxyhemoglobin (HbO_2) and deoxyhemoglobin (HbR) signals were observed in the left motor hand area for the finger-tapping task ($p < .05$) and in the bilateral occipital lobe for the passive viewing task ($p < .05$). This screening procedure attempted to ensure that the fNIRS signals of the sample were reliable and not confounded by irregularities in skull thickness, fat deposits, bone density, and blood chemistry (56–58).

Experimental Paradigm

Participants were seated approximately 140 cm across a table and with a full field of vision of each other in a normal room (Figure S1). A computer screen was also positioned approximately 45° to the side of this face-to-face orientation and 70 cm from each participant's face; so, the participants in each dyad had their own computer screens from which to view stimuli that only they could see and at which they needed not to turn their heads to look. Participants engaged in four conditions (counterbalanced). The two factors classifying them were situation and role. In the clinical situation, each participant was able to act as both the clinician and client; in the control condition, each participant was able to act as the speaker and responder (Figure S2). No participant was used more than once, and each partner in a dyad was always different. The experimental design was therefore blocked and adopted a repeated-measures approach.

The subtasks across these conditions and within dyads included speaking, listening, and thinking epochs (Figure 2). These subtasks, together with the stimuli, varied in nature depending on whether the interpersonal interaction was clinical. Namely, all stimuli shown on the computer screens were linguistic propositions, but in clinical blocks they were affective, or hot, conceptual valuations (59) [i.e., cognitive appraisals (34)] and, more specifically, were dysfunctional in that they were irrational and unrealistic in terms of being ungrounded in logic, empiricism, and pragmatism (33), representing a conjunction of the major types of irrational thinking (e.g., catastrophizing, self-downing, demandingness), for example, "My friends must always treat me fairly," whereas the propositions in control blocks were purely descriptive facts about the world, containing no evaluative or normative component: "It is cheaper to buy produce from a farmers market."

Signal Acquisition and Optode Localization

fNIRS signal acquisition of hemodynamics was acquired using a 80-fiber (108-channel) continuous-wave fNIRS system (LABNIRS; Shimadzu Corp.) configured for hyperscanning (54 channels per person) and sampled at a rate of 27 Hz at three wavelengths of light (780, 805, and 830 nm). A light-emitting diode probe (Daiso Corp.) was used to achieve an orthogonal connection between the fNIRS optodes and scalp (i.e., to displace hair in the cap). Anatomical locations of optodes in relation to standard head landmarks, including inion and top center (Cz) and left and right tragi, were determined using a Patriot 3D Digitizer (Polhemus) and linear transform techniques (60–64). Montreal Neurological Institute (MNI) coordinates (65) for each channel were obtained using NIRS-SPM software (66) with MATLAB (The MathWorks, Inc.).

Regions of Interest

The anatomical coverage of the channel configuration corresponded with 11 bilateral regions of interest (ROIs) (Table 1 and Figure S3): rostral PFC (Brodmann area [BA] 10), middle frontal gyrus (BA 46/9), inferior frontal gyrus (BA 44/45/47), angular gyrus (BA 39), supramarginal gyrus (BA 40), middle temporal gyrus (BA 21), superior temporal gyrus (BA 22),

Clinical	Speak 1/Listen 1	Think	Speak 2/Listen 2
Patient (A)	Utter affective proposition	~ (Wait for reply)	Listen to reasoning
Clinician (B)	Listen to utterance	Solve ill-structured reasoning problem	Verbal intervention

≈10s ≈10s ≈10s

1 Trial

Control	Speak 1/Listen 1	Think	Speak 2/Listen 2
Speaker (A)	Utter descriptive proposition	~ (Wait for reply)	Listen to repeating
Repeater (B)	Listen to utterance	Solve well-structured linguistic problem	Repeat proposition

≈10s ≈10s ≈10s

1 Trial

Figure 2. Epochs. In a single trial of a clinical block, the patient read a statement representing an affective valuation while the clinician listened. The clinician was required to first silently reason (recogitate) about how the statement was dysfunctional and then explain this reasoning while the patient listened. In a single trial of a control block, the speaker read a statement representing a descriptive proposition while the repeater listened. The repeater was required to first silently solve a problem relating to the language of the statement and then repeat the statement multiple times.

Table 1. Group Median Coordinates, Anatomical Regions, and Atlas Probabilities of Channels

Left Hemisphere					Right Hemisphere				
Channel No.	Coordinates	Anatomical Region	BA	Probability	Channel No.	Coordinates	Anatomical Region	BA	Probability
1	−49, −44, 57	Supramarginal gyrus	40	0.97	28	53, −48, 55	Supramarginal gyrus	40	1
2	−45, 38, 32	Middle frontal gyrus	46	0.68	29	62, −38, 48	Supramarginal gyrus	40	0.9
3	−54, 14, 38	Middle frontal gyrus	9	0.78	30	63, −15, 45	Premotor cortex	6	0.53
4	−58, −11, 47	Premotor cortex	6	0.70	31	60, 8, 38	Premotor cortex	6	0.46
5	−58, −36, 51	Supramarginal gyrus	40	0.82	32	50, 33, 31	Middle frontal gyrus	46	0.7
6	−16, 60, 34	Middle frontal gyrus	9	0.54	33	61, −53, 38	Supramarginal gyrus	40	0.96
7	−44, 48, 22	Middle frontal gyrus	46	0.52	34	67, −27, 40	Supramarginal gyrus	40	0.46
8	−57, 24, 21	Inferior frontal gyrus	45	0.54	35	66, −4, 37	Premotor cortex	6	0.99
9	−62, −2, 35	Premotor cortex	6	0.92	36	60, 20, 25	Inferior frontal gyrus	45	0.42
10	−64, −25, 41	Supramarginal gyrus	40	0.26	37	50, 43, 22	Middle frontal gyrus	46	0.8
11	−61, −51, 40	Supramarginal gyrus	40	0.99	38	29, 56, 33	Middle frontal gyrus	9	0.6
12	−55, 32, 12	Inferior frontal gyrus	45	0.57	39	68, −41, 29	Supramarginal gyrus	40	0.94
13	−63, 6, 19	Premotor cortex	6	0.50	40	70, −18, 30	Primary somatosensory cortex	2	0.21
14	−68, −16, 27	Subcentral area	43	0.27	41	66, 5, 23	Premotor cortex	6	0.55
15	−67, −41, 30	Supramarginal gyrus	40	0.96	42	59, 30, 16	Inferior frontal gyrus	45	0.56
16	−19, 71, 13	Rostral prefrontal cortex	10	1.00	43	65, −56, 17	Superior temporal gyrus	22	0.6
17	−53, 42, 1	Inferior frontal gyrus	47	0.53	44	71, −32, 20	Supramarginal gyrus	40	0.42
18	−58, 17, 2	Superior temporal gyrus	22	0.29	45	70, −9, 18	Subcentral area	43	0.44
19	−67, −9, 13	Subcentral area	42	0.35	46	63, 13, 10	Inferior frontal gyrus	44	0.51
20	−69, −32, 18	Superior temporal gyrus	22	0.40	47	56, 40, 7	Middle frontal gyrus	46	0.52
21	−66, −55, 17	Superior temporal gyrus	22	0.67	48	31, 67, 12	Rostral prefrontal cortex	10	1
22	−32, 66, −1	Rostral prefrontal cortex	10	0.97	49	70, −47, 6	Superior temporal gyrus	22	0.63
23	−48, 49, −6	Inferior frontal gyrus	47	0.54	50	73, −24, 4	Superior temporal gyrus	22	0.45
24	−54, 27, −8	Inferior frontal gyrus	47	0.87	51	68, −4, −2	Middle temporal gyrus	21	0.62
25	−66, −4, −11	Middle temporal gyrus	21	1.00	52	59, 27, 1	Inferior frontal gyrus	47	0.62
26	−70, −24, 0	Middle temporal gyrus	21	0.49	53	53, 47, 0	Inferior frontal gyrus	47	0.48
27	−69, −46, 4	Superior temporal gyrus	22	0.52	54	40, 63, 1	Rostral prefrontal cortex	10	1

BA, Brodmann area.

somatosensory cortex (BA 1/2/3), premotor and supplementary motor cortex (BA 6), subcentral area (BA 43), and primary auditory cortex (BA 42). These ROIs were specified a priori based on recent hyperscanning research on human-to-human verbal communication (13,18,19,22,53,54), neuroimaging and cortical brain stimulation meta-analyses in emotion regulation [e.g., reappraisal (48–51)], and neuroimaging and neuropsychological research on frontal lobe functions (37,46,47), particularly on the activation biasing of stimulus-independent attention (67) in favor of generating novel strategies (39–43,45,68,69). That is, the channel configuration was designed to achieve coverage only over these theoretically constrained ROIs (70).

Signal Processing

Preprocessing of raw fNIRS signals consisted of removing global systemic effects such as respiration, heart rate, and blood pressure (71), using a principal component analysis spatial filter (72,73), a technique that uses the distributed optode coverage to distinguish signal components originating from local and distal (i.e., extracerebral) sources. Onsets and durations of the epochs of each trial of each block were extracted to generate the stimulus design, with which the canonical hemodynamic response function was then convolved using NIRS-SPM. A general linear model analysis then fitted these predicted signals to the data, yielding beta estimates for each parameter in the single-subject design matrices. The contrast effects of these data were then reshaped into three-dimensional volume images using SPM12 and normalized to standard MNI space using linear interpolation. The results of second-level, random-effects analyses via summary statistics (74) based on these estimates and effects were rendered on a standard MNI brain template. Anatomical locations of peak voxel activity were identified using NIRS-SPM. Because this study collected data only from the ROIs and there were no whole-brain contrasts, corrections were not applied to the results; the false discovery rate, for example, would have been too conservative for the nature of the study.

Interbrain synchronization (cross-brain coherence) was evaluated across dyads (n = 30) for comparison of the clinical and control interpersonal interactions using the wavelet analysis approach described in (75). Wavelet analysis assesses the extent to which two or more brains (i.e., hemodynamic signals) are correlated over time (58,76), an indirect measure of nonsymmetrical coupled dynamic systems (77). The wavelet function was the Complex Gaussian 2 from the MATLAB wavelet toolbox because of its proximity to the hemodynamic response function. The number of octaves was 4 and the range of frequencies was 0.4 to 0.025 Hz. Therefore, there were 16

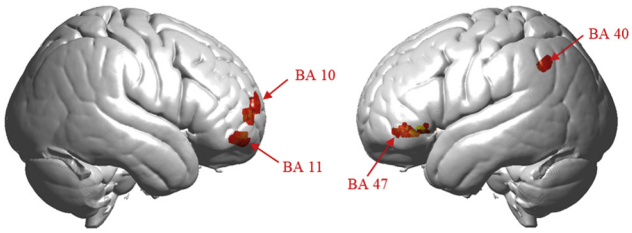

Figure 3. Clinical topic interaction. Contrast comparison of situation type (clinical > control) collapsed across role type and all subtasks for the regions of interest (N = 30). Greater activation during the clinical blocks is represented in red. The clinical situation uniquely elicited the right orbitofrontal cortex (Brodmann area [BA] 11) and rostral prefrontal cortex (BA 10) and the left inferior frontal gyrus (BA 47) and supramarginal gyrus (BA 40). See Table 2.

scales for which the wavelength difference was 2.5 seconds. Task regressors were also removed according to psychophysiological analysis convention (78) to examine coherence that was not related to task-specific processes, but rather to dynamic coupling processes. Neural synchrony of the wavelet components of these residuals was explored also for scrambled dyads (randomly matched pairs) to control for potential effects of shared component processes that were not unique to paired participants. As with the within-brain analyses, channels were grouped into anatomical regions (i.e., 11 ROIs) based on shared anatomy for wavelet analysis. Finally, all analyses were conducted on both HbO_2 and HbR, but the interpretation of results was based on research suggesting that HbR signals are less affected by systemic confounds (79). For example, fNIRS paradigms involving overt as well as covert speech tasks produce changes in arterial CO_2 that, likely due to changes in respiration, alter the HbO_2 signal to a greater degree than HbR (80,81).

RESULTS

Contrast Effects: ROIs

Within-brain statistical comparisons of ROIs that were determined a priori for situation and role types and the relative subtasks of these conditions were conducted at the threshold of α = 0.01. Examining the effects of clinical discourse interactions compared with nonclinical interpersonal interactions (clinical > control), collapsed across all subtasks and roles, revealed significant differences in the orbitofrontal cortex (BA 11) ($p < .001$, $t_{28} = 2.93$), inferior frontal gyrus (BA 47) ($p < .001$, $t_{28} = 3.08$), rostral PFC (BA 10) ($p < .001$, $t_{28} = 3.05$), and supramarginal gyrus (BA 40) ($p < .001$, $t_{28} = 2.64$) (Figure 3 and Table 2).

Subtracting the activation in the thinking substask of repeaters in the control condition from that of the thinking substask of clinicians in the clinical condition (clinical thinking > control thinking) demonstrated a significant increase in the recruitment of the left rostral PFC ($p < .001$, $t_{28} = 3.13$), as well as in a cluster covering the right middle frontal gyrus and inferior frontal gyrus, particularly pars orbitalis ($p < .001$, $t_{28} = 3.21$) and in a cluster over the subcentral area (BA 43) and primary auditory cortex ($p < .001$, $t_{28} = 3.18$) (Figure 4 and Table 3).

Comparing the verbal intervention subtask of clinicians in the clinical condition against the repeating substask of repeaters in the control condition (intervention > repeating) that occurred subsequent to the thinking epochs showed significant—albeit less—activation in the rostral PFC ($p < .001$, $t_{28} = 2.91$), angular and supramarginal gyri (BA 39) ($p < .001$, $t_{28} = 2.58$), and premotor and supplementary motor cortices ($p < .001$, $t_{28} = 3.02$) (Figure 5 and Table 4). Results including cluster sizes, MNI coordinates, probability estimates, and hemispheric localizations of these contrasts are presented in Tables 2–4.

Dynamic Neural Coupling

Cross-brain coherence between dyads during clinical discourse interactions (clinical situation > control situation) significantly increased between the inferior frontal gyrus (BA 44) and supramarginal gyrus ($p = .002$, $t_{29} = 3.35$) (uncorrected) (see Figure 6). Changes in coherence (y-axis) are plotted over 30-second periods (x-axis). This coherence was not observed when the partners were computationally shuffled (right panel), that is, randomly paired with every participant except the

Table 2. Voxelwise GLM Contrast Comparisons (deOxyHb Signals) of Situation Type

Contrast	Coordinates[a]	t Value	p	Anatomical Regions in Cluster	BA	Probability	Voxels
Situation, Clinical > Control	38, 50, −8	2.93	.003	Orbitofrontal area	11	0.63	28
				Rostral prefrontal cortex	10	0.27	
				Inferior frontal gyrus	47	0.10	
	−54, 38, −4	3.08	.002	Inferior frontal gyrus	47	0.71	24
				Inferior frontal gyrus	45	0.15	
	34, 53, 4	3.05	.002	Rostral prefrontal cortex	10	0.99	29
	−60, −52, 38	2.64	.005	Supramarginal gyrus	40	0.87	10
				Angular gyrus	39	0.13	
Situation, Control > Clinical	66, −22, 16	−2.63	.007	Primary auditory association cortex	42	0.39	18
				Supramarginal gyrus	40	0.18	
				Subcentral area	43	0.18	
				Superior temporal gyrus	22	0.15	

Threshold p = .01; df = 28.
BA, Brodmann area; deOxyHb, deoxyhemoglobin; GLM, general linear model; MNI, Montreal Neurological Institute.
[a]Coordinates are based on the MNI system, and negative values indicate the left hemisphere.

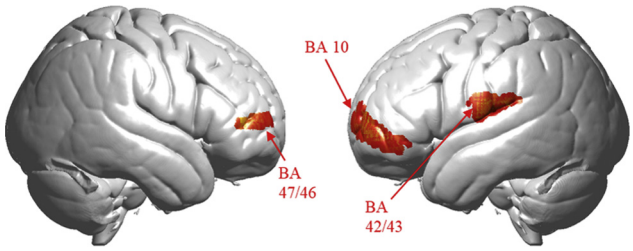

Figure 4. Recogitation. Contrast comparison of the thinking subtask of the clinical condition (i.e., internal reasoning about dysfunctional appraisals) (clinical thinking > control thinking) for the regions of interest (N = 30). Greater activation during the thinking subtask of the clinical condition is represented in red. The cognitive resource demands of this type of recogitation (1) significantly recruited the left rostral prefrontal cortex (Brodmann area [BA] 10), subcentral area (BA 43), and primary and auditory association cortices (BA 42) and the right pars orbitalis (BA 47) and middle frontal gyrus (BA 46). See Table 3.

original partner, which is consistent with the idea that neural coupling is dyad specific.

DISCUSSION

This study adapted the recent approaches of multiperson neuroscience paradigms investigating aspects of verbal communication (13,18,19,22,53,54) to capture human-to-human interactions that might be clinically significant. The development and application of this novel paradigm constitute a proof of principle, but the results were surprisingly consistent with the prediction that interpersonal interactions in the context of psychotherapy place unique demands on neural systems that normal verbal communication does not. More specifically, the within- and cross-brain coherence evidence found in the clinical condition exhibited a pattern of mutual engagement of subregions along the anterior-posterior axis of the lateral surface of the cerebral cortex, particularly in the PFC and inferior parietal lobule. The fact that the clinical condition showed greater dynamic neural coupling between pairs of participants is consistent with other observations of physiological synchronization (heart and breathing rates) between clinicians and clients (82–85), which stresses the need for a more multimodal approach. Indeed, additional neuroimaging techniques could complement temporal and spatial resolutions, and other dependent measures such as eye gaze and facial cues could enhance researchers' ability to index coupling between systems during clinical interactions (20,86). One explanation for these findings is that they might derive from normative nature of the commutation; it was largely dialectical, and discourse in everyday life is typically not. An additional element worth considering is the prosocial efforts on the part of the clinician to positively influence the dysfunctional information processing of the client, which could be a more specific source of influence on the strength of interactivity between individuals in these situations.

Table 3. Voxelwise GLM Contrast Comparisons (deOxyHb Signals) of Reasoning Task

Contrast	Coordinates[a]	*t* Value	*p*	Anatomical Regions in Cluster	BA	Probability	Voxels
Thinking, Clinical > Control	−32, 52, 0	3.13	.002	Rostral prefrontal cortex	10	0.97	305
	46, 38, 6	3.21	.002	Middle frontal gyrus	46	0.49	58
				Inferior frontal gyrus	47	0.24	
				Inferior frontal gyrus	45	0.17	
				Rostral prefrontal cortex	10	0.11	
	−66, −14, 18	3.18	.002	Primary and auditory association cortex	42	0.25	188
				Subcentral area	43	0.22	
				Superior temporal gyrus	22	0.14	
				Pre- and supplementary motor cortex	6	0.11	
Thinking, Control > Clinical	−52, 34, 20	−3.17	.002	Middle frontal gyrus	46	0.71	17
				Inferior frontal gyrus	45	0.28	
	50, 38, 20	−2.85	.004	Middle frontal gyrus	46	0.72	13
				Middle frontal gyrus	9	0.17	
	−34, 26, 34	−3.45	.0009	Middle frontal gyrus	9	0.76	57
				Frontal eye fields	8	0.24	
	−64, −26, 42	−2.80	.005	Supramarginal gyrus	40	0.41	10
				Primary somatosensory cortex	2	0.23	
				Pre- and supplementary motor cortex	6	0.12	
				Primary somatosensory cortex	1	0.11	
	−58, −12, 44	−2.70	.006	Pre- and supplementary motor cortex	6	0.59	10
				Primary somatosensory cortex	3	0.18	
				Primary somatosensory cortex	1	0.10	

Threshold p = .01; df = 28.
BA, Brodmann area; deOxyHb, deoxyhemoglobin; GLM, general linear model; MNI, Montreal Neurological Institute.
Threshold p = .01; df = 28.
BA, Brodmann area; deOxyHb, deoxyhemoglobin; GLM, general linear model; MNI, Montreal Neurological Institute.
[a]Coordinates are based on the MNI system and negative values indicate the left hemisphere.

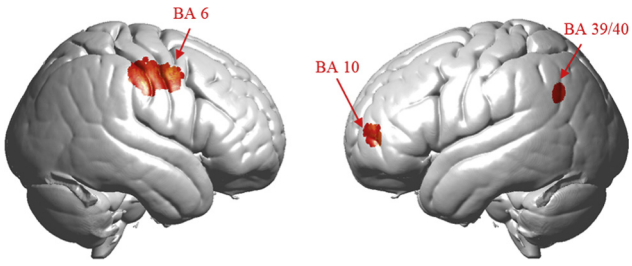

Figure 5. Verbal intervention. Contrast comparison of verbal intervention (intervention > repeating) for the regions of interest (N = 30). Greater activation during verbal intervention in the clinical condition is represented in red. The cognitive resource requirements of verbal reasoning about dysfunctional appraisals significantly recruited the left rostral prefrontal cortex (Brodmann area [BA] 10), angular gyrus (BA 39), and supramarginal gyrus (BA 40), and the right premotor and supplementary motor cortices (BA 6). See Table 4.

The within-brain findings support the role of specific PFC subregions in carrying out the task of clinicians to verbally intervene and restructure clients' dysfunctional thinking. Significant activation was observed in the left rostral PFC (BA 10) and right middle frontal gyrus (BA 46) during the clinical thinking task, with the largest cluster being recruited in BA 10 (coordinates: −32, 52, 0). These results are in line with the postulation that this task largely depends on a cognitive ability (i.e., recogitation) that reasons about propositional attitudes in open-ended situations to produce changes that are conducive to well-being (1). Such an ability should place marked demands on stimulus-independent operations that support self-initiated procedures for generating and testing novel hypotheses about linguistic propositions [(40–45,68,69); see (37,46)]. If this is the case, then it makes sense that such a manipulation of self-generated information would rely on sustained activation biasing in the rostral attentional gateway (67). The actual testing and rejecting of thought hypotheses are potentially mediated by the dorsolateral PFC (right BA 46) in checking whether semantic criteria—stored in more posterior areas such as BA 39 and BA 40—are satisfied; it is also possible that the dorsal anterior cingulate cortex might be involved in this procedure (87). Future research might explore these possibilities.

The findings relating to periods of verbal intervention support not only the importance of the PFC but also that of more posterior subregions of the inferior parietal lobule, namely the angular gyrus (BA 39) and supramarginal gyrus (BA 40). These two subregions comprise what is often termed Geschwind's territory in the literature, which is an area associated with multisensory integration of information such as sight, sound, and body sensation, and it is thicker in humans than in other primates and one of the last areas of the brain to mature, other than the rostral PFC (88); it also mediates bidirectional information processing between Broca's and Wernicke's areas via the arcuate fasciculus (89). What is unique about these regions having been recruited is that the clinicians' pattern of activation strongly reflects that which is typically found in the participants of emotion regulation paradigms, particularly ones involving cognitive reappraisal [see (90–92) for reviews]. It appears that while restructuring the dysfunctional cognitive processes of others', clinicians engaged the same brain regions associated with the semantic network in modifying conceptual valuations during cognitive change strategies. In other words, clinicians are experts at using potentially the same systems at which they aim for clients to become adept. This possibility raises two interesting questions. First, would it be possible, then, to distinguish between experienced and inexperienced clinicians? Indeed, recent research has shown interesting differences between novice and expert surgeons (93). Such an investigation in the context of psychotherapy might have implications for developing training programs. Second, could examining discrepancies in patterns of activation between healthy populations (e.g., clinicians) and clinical ones lead to insights that would inform efforts to reduce these differences (e.g., cognitive training paradigms to help clients recogitate their dysfunctional thoughts)? Changes in such functional variations might serve as reliable biomarkers for how clients respond to treatment at the level of the brain and be predictive of treatment outcome measures. These possibilities are in line with recent literature on the potential applications of multiperson neuroscience to neuropsychiatry (94,95). In addition, within the framework of the Interactive Brain Hypothesis (96), interbrain

Table 4. Voxelwise GLM Contrast Comparisons (deOxyHb Signals) of Verbal Task

Contrast	Coordinates[a]	t Value	p	Anatomical Regions in Cluster	BA	Probability	Voxels
Intervention, Verbal Intervention > Verbal Repeating	−44, 52, 6	2.91	.003	Rostral prefrontal cortex	10	0.36	31
				Middle frontal gyrus	46	0.20	
				Inferior frontal gyrus	47	0.17	
	−52, −56, 30	2.58	.008	Angular gyrus	39	0.49	10
				Supramarginal gyrus	40	0.49	
	50, 0, 42	3.02	.003	Pre- and supplementary motor cortex	6	0.80	326
Intervention, Verbal Repeating > Verbal Intervention	−66, −4, 18	−2.92	.003	Pre- and supplementary motor cortex	6	0.36	12
				Subcentral area	43	0.20	
				Superior temporal gyrus	22	0.17	

Threshold p = .01; df = 28.
BA, Brodmann area; deOxyHb, deoxyhemoglobin; GLM, general linear model; MNI, Montreal Neurological Institute.
Threshold p = .01; df = 28.
BA, Brodmann area; deOxyHb, deoxyhemoglobin; GLM, general linear model; MNI, Montreal Neurological Institute.
[a]Coordinates are based on the MNI system and negative values indicate the left hemisphere.

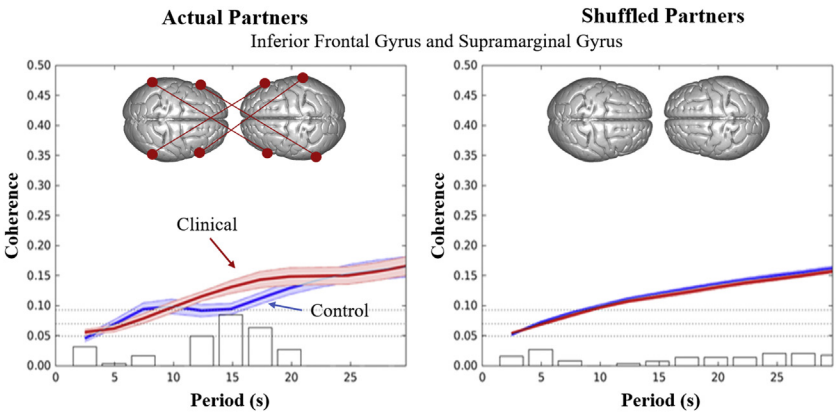

Figure 6. Neural synchronization. Coherence of brain-to-brain signals between clinical and control blocks collapsed across all roles and subtasks (N = 30). Signal coherence between dyads (y-axis) is plotted against the period (x-axis) for the clinical (red) and control (blue) conditions. Bar graphs indicate significance levels for the separations between the two conditions for each of the period values on the x-axis. The upper horizontal dashed line indicates $p \leq .01$, and the lower line indicates $p \leq .05$. The left panel shows coherence between actual partners and the right panel shows coherence between shuffled partners. Cross-brain coherence is greatest in the clinical condition between the inferior frontal gyrus and supramarginal gyrus.

synchronization—or lack thereof—in clinical situations might be interpreted as a dialectical misattunement of coupled, dynamic systems (97,98). Clearly, these possibilities warrant further research, and there is yet much to learn from the brains of clinicians (1).

The fact that this sample did not consist of licensed clinicians suggests something more general about the findings, namely that the evidenced neural systems represent aspects of the normal human functions that work toward modifying propositional attitudes; clinicians are simply a population of experts at engaging these systems. Some of these functions are individually well understood in the areas of language, social interaction, emotion regulation, and executive function but less well understood in their confluence toward achieving the recogitation of not only dysfunctional cognitions but also everyday thoughts people have about the world, others, and self. This study has shown that aspects of the rostral PFC, inferior and middle frontal gyri, and supramarginal and angular gyri are potentially key to this general network. The sample also did not consist of clients with real diagnoses, and therefore it will be important when working with a clinical sample to assess the ways in which activation trends might differentiate from healthy participants during verbal intervention (99). However, it is worth noting that clinicians and clients should be able to interact naturally while neuroimaging data are collected, without computer mediation. To achieve this, interpersonal interactions could be fractionated in similar ways to the epochs of this design but with brain-first approaches to extracting the stimulus design whereby significant functional events in particular brain regions are estimated from observed HbO_2 and HbR signals (100). Portable and wireless neuroimaging devices (28) seem also to be a prerequisite to collecting data in authentic clinical settings (1). Moreover, it will be important to include additional measures of people's phenomenological experience of clinical settings in which neuroimaging data are collected to account for factors that might influence the information processing systems of interest, such as nervousness, novelty, attitudes toward the therapeutic alliance, and so forth.

In sum, the practical applications of using ecological designs, tasks, and methods to investigate clinically relevant phenomena are numerous, and the findings of this study demonstrate a precedent for the real-world neuroimaging of inter- and intrabrain systems supporting the interpersonal interactions that have long been integral to psychotherapeutic treatment. If it is the case that understanding the intervention tasks of clinicians at the levels of the brain and information processing is crucial to explaining treatment outcomes, such as improvements in emotion regulation, adaptive behavior, and functional connectivity, and also the case that these are the same or markedly similar tasks that clinicians aim to cultivate in clients, then recruitment of the neural subsystems supporting these tasks on the part of clients might relate to their ability to identify, dispute, and modify their own affective valuations about goal-incongruent events and, therefore, to the success of downregulating negative emotion. Future research would benefit from using a hybrid experimental design that takes advantage of the periodic measurement framework of existing designs and the continuous, in situ approach of this study to investigate the neurocognitive mechanisms by which psychiatric change is achieved as a consequence of evidence-based treatments for the pathogenesis of psychopathological symptoms.

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