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Chapter 15
Neurobiological Correlates of the Psychotherapy Relationship and E.M.P.A.T.H.Y.: The Role of Biomarkers in Psychotherapy*

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Keywords Biomarkers • Empathy • Patient–doctor communication • Patient–doctor relationship • Psychotherapy

Introduction

Psychotherapy is associated with measurable changes in central and peripheral neurobiology and is a standard treatment that is as strongly rooted in brain plasticity as are psychopharmacological interventions [1]. Physiological and neurobiological underpinnings of the psychotherapy relationship have been measured by a number of biomarkers, including autonomic nervous system (ANS) arousal manifested by heart rate, respiration rate, muscle tension, the Galvanic Skin Response (GSR), electroencephalography (EEG), and neuroimaging studies of empathy. A key component of empathy in the patient–therapist dyad lies in attunement of the therapist to physiological displays of emotion as well as to patient-reported somatic cues that indicate emotional states with neurobiological correlates. Increased awareness of physiological manifestations and somatic sensations of emotion may assist in deepening the process of psychotherapy. Biomarker research could significantly influence the practice of psychotherapy by providing predictors for the development of specific disorders, aiding diagnoses, predicting and guiding a course of treatment, and tailoring individual treatments for specific disorders. While biomarker research is unfolding, there are neurobiologically based clinical observations organized by using the E.M.P.A.T.H.Y. mnemonic [2] that may guide and enhance psychotherapy. Empathic attunement is vitally necessary for all forms of psychosocial and psychopharmacological interventions with patients.

The theoretical bases for many models of psychotherapy have historically focused on verbal exchanges intended to foster modifications in human feelings, cognitions, attitudes, and behaviors [3]. While common factors such as empathy, trust, respect, support, and openness are considered critical features in most theories of psychotherapy, biological markers for these factors have received relatively little attention despite their crucial role in forming a therapeutic alliance. Empathy is necessary

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but not sufficient for formation of the therapeutic alliance, which has been defined as "the persistent and ultimately predictable and expectable experience on the part of the patient of the steady, reliable, reasonable, fair, kind, tolerant, non-judgmental, but also non-corruptible attitude of the analyst" [4]. According to Havens, "Alliance formation is the first order of clinical business [5]," and the strength of the therapeutic alliance is significantly and consistently related to psychotherapeutic and medical outcomes [6–10].

The theoretical approaches of three widely practiced psychotherapies – psychodynamic therapy (PDT), cognitive behavioral therapy (CBT), and interpersonal therapy (IPT) – suggest that, while attention to emotions and affects is, to varying degrees, an integral part of each of these therapeutic approaches, explicit exploration of somatic manifestations of emotions is not generally considered a necessary means to achieving therapeutic outcomes. Although these conventional therapies are frequently sought in response to somatic sensations signaling anxiety, panic, flashbacks, and other signs of somatic distress, specific training in detection, management, and interpretation of the *physical* manifestations of emotions is not an integral part of most psychotherapy curricula. Modalities that explicitly emphasize attention to the body in order to understand emotional states include biofeedback [11], mindful meditation [12], hypnosis [13], the mind–body relaxation response [14], and internal family systems therapy [15]. These are at times utilized in conjunction with conventional therapies to attend specifically to somatic sensations.

PDT and psychoanalysis encourage patients to use free association and dreams to explore the conscious and unconscious behavioral, cognitive, and emotional patterns that repeat themselves across patients' past and present relationships, and that often manifest themselves in the current relationship between patient and psychotherapist. Through this process, the patterns in the repetition compulsion and their concomitant emotions are examined, and patients are encouraged to identify and express their emotions, resulting in abreaction and the ability to forge more adaptive relationships to one's self and others. Explicit examination of somatic or sensory states accompanying specific affects may occur; however, such exploration is at the discretion of the clinician, as feelings are primarily accessed through words and memories rather than through a direct exploration of somatic experiences or explicit decoding of physical manifestations of emotional states.

CBT, with its roots in Skinner's operant conditioning theory of learning, employs a wide range of written and verbal techniques. These techniques include self-monitoring; identifying and challenging negative or distorted thoughts; and reporting type and intensity of mood, by examining verbal and written accounts of patient experiences. The emphasis in CBT is on changing patient cognitions, leading to change in feeling states and behaviors [16]. Thus, CBT is primarily a cognitive, rather than a somatic exploration.

IPT, based on Harry Stack Sullivan's Interpersonal School, ~~focuses on~~ verbal accounts of current patient relationships ~~focusing~~ on one of four clinical areas (unresolved grief; role transitions; interpersonal and role disputes; and interpersonal deficits) with the aim of exploring thoughts and feelings that lead to dysphoric states. However, IPT does not place emphasis on identifying where these dysphoric states are felt in the body.

Whereas verbal exchange is essential for communication of thoughts and feelings in psychotherapy, the renowned analyst, Elvin Semrad, was well-known for his interest in identifying biological markers that indicated where his patients experienced their emotions. Rako's *Semrad: The Heart of a Therapist* [17] is a compilation of Semrad's therapeutic statements that evince his keen interest in making connections between expressed emotions and where they are felt in the body. These statements include: "This is what makes the difference, the *tissues* of the person involved, not the fancy thought upstairs. He's living a real honest human experience, with every tissue of his being;" "Once he showed his tears, that was enough for me. I respect the autonomic nervous system to show feelings like I respect few other things;" "What does his body tell him?" "Acknowledging the feelings and reality of her body is overwhelming her mind with Guilt" [17]. Semrad was known to explicitly ask his patients, "Where do you feel your pain?" [18]

Emotions are physiologically grounded in the ANS and effect several target organs to enhance individual and species survival via complex neural, hormonal, and physiological processes [19]. Familiar somatic descriptions of negative emotions such as feeling: "heavy hearted," "sick to my stomach," "all choked up," "as if my head were exploding," having "butterflies in my stomach," or "heart-pounding terror," and positive emotions such as feeling "light hearted" and "floating on air" indicate that humans feel their emotions in their bodies.

Porges' polyvagal theory states that, in mammals, the neurological basis of social engagement is evolutionarily linked to the ANS and how it relays emotional experiences [20]. Porges describes three parts of the ANS, including (a) vagal visceral unmyelinated afferents which decrease metabolism in response to environmental threats and contribute to somatic feelings associated with emotional distress, including behavioral immobilization (also called the "freeze" response) seen in certain animals feigning death; (b) the sympathetic nervous system, which increases heart rate and motor activity for the "fight or flight" response; and (c) the para-sympathetic nervous system involving the myelinated vagus nerve regulating cardiac activity with discriminating responsiveness to social approach or avoidance by down-regulating cardiovagal tone. The myelinated vagus nerve is also linked to adaptive social behavior by relay mechanisms to the cranial nerves that regulate facial expression, vocalizations, and listening, all critical components of interpersonal engagement.

The interface of psychological and physiological variables during psychotherapy has been the subject of investigation for decades. Reports on physiological changes measuring ANS activity occurring in patients during psychotherapy date back as early as the 1930s, when affective changes during psychoanalysis were correlated with GSR and heart rate [21]. Since then, numerous investigators have reported physiological changes in patients during psychotherapy, including changes in finger temperature [22], muscle tension [23], respiration rate [24], heart rate, blood pressure, body temperature, gastric motility, EEG, and GSR [25, 26]. GSR, also known as the electrodermal response, is a method of measuring the electrical resistance of the skin. GSR measures sympathetic nervous system activity (but not para-sympathetic) because the skin is innervated primarily by the sympathetic nervous system. The human eccrine gland secretes sweat in direct proportion to sympathetic arousal. Thus, GSR is highly sensitive to emotional states, including anger, fear, and the startle response, occurring between two people. In addition, reductions in GSR have been correlated with patient mastery and control over threatening material, and, conversely, increases in GSR have been correlated with decreased sense of mastery [25]. These studies support the hypothesis that affective intensity during psychotherapy (especially negative affect) is associated with greater autonomic arousal than calm affect states representing greater mastery or sense of control [25].

Physiology Between Patient and Clinician

Another group of physiological studies examined physiological states *between* patient and therapist during psychotherapy where the autonomic arousal of both members of the dyad was simultaneously measured. Early studies using measures of skin conductance (SC) and heart rate suggested that patients and therapists were highly reactive to each other [27].[1] These studies showed that physiologic responses in patients and therapists sometimes varied together in "concordance" and at other

[1] SC provides a satisfactory overall measure of GSR. There are two distinct processes of measurement occurring at high and low levels of Galvanic skin resistance that overlap in the mid-range. The resistance measurement of these two widely different levels spans the range of reactivity from the low to the higher levels of autonomic arousal. The differing magnitudes of the measures of these two reactive phenomena can be meaningfully combined in, and quantitatively represented on a single scale of measurement when using units of conductance.) [115].

times varied oppositely in "discordance" during a psychotherapy session [28]. This research showed a relationship between concurrent SC fluctuations (as a representation of autonomic activity) and perceived empathy in dyadic interactions [25], a finding that was recently replicated at Massachusetts General Hospital (MGH) [29, 30].

The evidence for the significance of perceived therapist empathy by patients during psychotherapeutic treatments [31, 32] has led to investigations into the biological correlates of empathy. The rationale for using biological markers during psychotherapy is that greater awareness of simultaneous autonomic responses may assist in deepening the process of psychotherapy. Neuroimaging and psychophysiology research have revealed significant insights into underlying mechanisms of empathy and interpersonal processes that may affect the patient–doctor relationship [33]. Humans have sophisticated perceptions of others' behavior that either elicit feelings of social comfort or potential danger, which may be particularly acute in the patient–psychotherapist relationship. The ANS is linked to the affective experiences of self and other that motivate approach and avoidance behaviors based on systems of social engagement. Therefore, exquisite sensitivity to ANS activation may enhance therapist and patient awareness of real or perceived interpersonal threats, fantasies, thoughts, conflicts, impulses, or emotions [25].

According to Ax, psychotherapist empathy could be thought of as "an autonomic nervous system state which tends to simulate that of another person" [34] and his research revealed linkages between the physiological responses of psychotherapist and patient. DiMascio found that patient and therapist heart rate varied together "in concordance" during some moments in psychotherapy and oppositely in "discordance" during other moments in psychotherapy [35]. These early studies provided indirect support for a physiological component to "empathic relatedness" during psychotherapy [28, 36].

Patient–Clinician Skin Conductance Concordance

Historically, investigation of perceived empathy and simultaneous SC fluctuations was first conducted in non-clinical student–counselor dyads [37]. The frequency of SC peaks between clients and counselors was positively correlated with student ratings of counselors' empathy. Subsequent studies have demonstrated support for a physiological basis of empathy. Wiesenfeld measured SC responses of women watching video clips of infants expressing a range of emotions where high empathy females had larger SC responses and matched facial expressions of the infants more often than low empathy females [38]; Levenson and Reuf found that subjects' ratings of negative emotion when watching a video clip of a distressed married couple were highest when the subject and the couple had high levels of physiologic concordance [33]; Marci and Orr found low levels of perceived empathy and low SC ~~concordance~~ in patients interviewed with high emotional distance expressed by the interviewer [39]. These studies suggest that empathy and physiological concordance occurs in dyadic settings that do not necessarily have a therapy focus but may represent critical factors in caring human relationships.

Studies of dyadic and group interactions during psychotherapy have also demonstrated that both the behavior of the patient and the therapist influence one another physiologically in a powerful way. When there is psychological rapport, autonomic activity in both is reduced; however, when there is conflict and negative interaction, autonomic activity is heightened for both patient and therapist [40, 41]. The most important conclusion from these studies is that physiological synchrony between patient and therapist occurs when the therapist is accurately perceiving and empathizing with the patient. Thus, physiological changes during therapy do not occur in isolation, but instead reflect moment-to-moment interactions within the therapy pair. This may be interpreted as an exquisitely tuned index of therapeutic alliance [25].

Recent research at MGH of 20 patient–therapist dyads specifically investigated the relationship between SC and perception of therapist empathy during psychotherapy in videotaped sessions where simultaneous measures of patient and therapist SC were obtained. The results demonstrated a significant correlation between the number of epochs of physiological SC concordance and patient-perceived empathy as measured by the Empathic Understanding Scale ($r=0.47$, $p=0.03$) [42]. These results support a biological model of physiological concordance and perceived patient empathy during psychotherapy. The moment-to-moment physiological concordance suggests there is an unconscious central nervous system mapping of one person's experience on the other that is mediating a physiological response; neuroimaging research supports this claim [43].

Clinical Case Example: Using Skin Conductance Monitoring in Psychotherapy

A middle-aged woman presented for psychotherapy with a psychodynamically oriented psychiatrist for help with understanding and responding to her mother's obsession with the patient's weight, which was manifested by verbal and emotional abuse. The patient had learned to conceal her emotional needs from her mother since childhood, for fear of overwhelming her overburdened mother. The patient was 70 lb overweight, had never lost weight, and her weight was steadily increasing, despite her primary care physician's repeated concerns about her health. Although she made significant progress in setting limits on her mother's verbal abuse and was able to increasingly tolerate the "silent treatment" issued by her mother about her eating habits, she stated explicitly that weight loss was not her therapy goal, nor would she want to discuss her weight with her therapist.

Subsequently, her therapist was asked to participate in a research investigation where therapists and patients would receive SC monitoring during a videotaped psychotherapy session. The therapist asked the patient if she would be interested in enrolling, and the patient said she would be happy to enroll in the study, especially if it could help others or herself. The SC tracings demonstrated a high degree of physiological concordance, which matched the patient's assessment of the therapist as empathic on the questionnaire for the monitored session [42]. However, measurements of SC also revealed a hidden state of autonomic arousal in this patient who had learned to mask her anxious feelings since childhood as a way of maintaining a connection with her overburdened mother [29]. In sharp contrast to the rest of the session, there were a few moments in which the patient's SC spiked to three times that of the therapist's, despite the fact that the patient showed no overt signs of anxiety or autonomic activation. The patient had repeated her early pattern of concealing her anxiety from her mother now, with her psychiatrist.

It is important to consider whether sharing biomarker data is therapeutically indicated. For example, paranoid or obsessive patients may find this type of information threatening, negative, or critical in nature [25]. The decision to introduce this question was based on the formulation of the patient in addition to the patient's expressed interest in how the findings of the study could help others and herself. The episodes of discrepancy between ~~the~~ SC in the therapy pair led the therapist to ask the patient if she were interested in seeing the results and to discuss the possible meanings of the findings. When the patient examined the tracings, she murmured, "It's as if I'm seeing an 'x-ray' of my psyche."

The patient had been the most agreeable child in a large family, with siblings who had physical disabilities. She had learned to conceal her own anxious states in the service of acting as her mother's emotional caretaker and confidant. The patient used food to soothe herself, became obese, and subsequently became the object of her mother's ridicule, which ultimately led her to seek psychotherapy to resolve this painful double-bind. This case (present author was the therapist) demonstrates that

some patients may benefit both emotionally and clinically from direct observation of their own SC tracings. The therapy dyad together examined their simultaneous autonomic arousal levels gathered from time-series analysis. (For examples of SC tracings, see [29, 42]).

The physiological data allowed the therapist to gain deeper empathy for her patient because it illuminated the patient's emotional experience in a way that had never been expressed. Importantly, the data also led the therapist to examine the videotape of the monitored session for indications of subtle clues of somatic markers that revealed signs of her patient's anxiety. The high peaks of autonomic arousal corresponded to physical changes in facial expression and skin tone (slight flushing), averted eye contact, fingers raised to hair, and a throaty chortle. These physical signs served as markers for detecting subtle signs of anxiety that were not verbally expressed, but matched the spikes on the SC data. These observations of the patient's unique physical manifestations of her anxiety led to a deeper level of therapist insight into how this patient revealed her anxiety and fostered greater empathy for this patient's suffering.

During the next year of psychotherapy, the patient–therapist relationship deepened to a new level of compassion. For the first time, the patient was able to talk about her shame regarding her weight and lack of exercise. Insight into her habitual sedentary lifestyle and use of food to soothe herself led to more adaptive behaviors to manage her anxiety. She hired an exercise trainer and became more comfortable revealing her anxiety and vulnerability to her therapist. And, most remarkably, the patient lost 40 lb in the next year, the first time this patient had ever lost weight. The therapist's attunement to physical signals of emotional pain and anxiety increased her empathy, and ultimately helped her patient achieve not only her initial, stated therapy goals, but an unexpressed goal to lose weight, that had been too threatening to state when she had initiated the psychotherapeutic process.

This case illustrates a session where, even with a high overall degree of physiological concordance and high ratings of perceived therapist empathy, the areas of discrepancy illuminated areas of concealed anxiety. One could mistakenly conclude that an optimal session would depict full physiological concordance. In this case, the discrepant SC tracing provided a window to explore less obvious, but ultimately very important, causes of her anxiety and led to dramatic weight loss. Examination of the patient's defenses of masking her anxiety and vulnerability ultimately led to greater empathy and more relational solutions to manage her anxiety. The patient hired a trainer to help her exercise and began to express her anxiety to her therapist more directly. This case provides an example of the potential of a biological marker of physiological activity to enhance attention to clinical manifestations of emotions and to improve outcomes in psychotherapy. It also provides evidence that subtle physical signs or mannerisms manifested during psychotherapy may be markers for internal, but undisclosed, affects, such as anxiety. Careful therapist attunement to these signs may enhance and deepen psychotherapy if explored.

This case supports the notion that therapist observation of patient signals (such as playing with hair, fidgeting, or other voluntary signals) may enhance appreciation for emotional signals, even if the facial expression of the patient does not reveal emotions. Empathy is an emotional, social, and cognitive process that allows an observer to understand and feel another's emotions. Empathic individuals appear to show a non-conscious motor mimicry of facial expressions, postures, and mannerisms of others to a greater extent than less empathic individuals [44–47]. Action representations of others' facial and bodily movements that are mapped onto the brain of the observer appear to involve the ACC and the insula, which together form a "salience network" that functions to segregate the most relevant internal and extrapersonal stimuli in order to guide behavior. The anterior and posterior insula appear to interact as a hub, to integrate salient stimuli and events with visceral and autonomic activity. Together, they help to generate a heightened physiological awareness of salient stimuli and to generate appropriate behavioral responses [48].

The Neurobiology of Empathy

The neurobiology of empathy has its roots in early mirror neuron research. A specialized class of neurons in the premotor cortex and inferior parietal cortex, called "mirror neurons," provided the first neurobiological basis for translating motor actions that individuals observe in others into internal representations in the observers brain, facilitating understanding of ~~other~~ person's actions [49]. Initial claims that mirror neurons were responsible for a wide range of abilities including speech acquisition, perception, altruism, emotion, empathy, theory of mind, autism spectrum disorders (deficiency of mirror neurons) have recently been challenged by some investigators [50, 51]. However, early mirror neuron research led to prolific fMRI investigations of "self" versus "other" brain mechanisms that facilitate empathic understanding of one person's experiences by another. Current research is identifying similar hemodynamic changes in neuroanatomical structures ~~in~~ "self" and "other" that facilitate understanding of other persons' experience that are activated both when a subject experiences and observes touch, somatic sensations [52], pain [53, 54], and emotions, such as disgust [55]. Much of the information needed to empathize with patients can be accomplished by perception of facial expressions, posture, tone of voice, affect, and awareness of the observer's own physiological response to the patient [33].

There is significant overlap between central neuroanatomical structures implicated in neuroimaging studies of empathy and brain structures that control SC fluctuations. Converging clinical and neuroimaging findings suggest that the anterior cingulated cortex (ACC) (specifically the subgenual ACC, which connects with neighboring ventral striatal, orbitofrontal cortex (OFC), and medial temporal regions) mediates modulation of emotion, cognition, sensation, and movement. Important functions of the cingulate also include the mobilization of appropriate responses to internal and external stimuli, emotional-cognitive integration, motor preparation, and conflict monitoring. The ACC carries out these functions by activating somatic states that focus attention on internal and external demands and motivate appropriate action [43]. The ACC generates emotional motivation through its projections to autonomic, visceromotor, and endocrine systems.

A principal function of the ACC is the regulation of bodily states of arousal to meet concurrent behavioral demands. The ACC, the OFC, and the amygdala are involved in decoding facial expression, direction of gaze, and other non-verbal behaviors. Together, these provide information about the social context that directly affects the emotional appraisal process and autonomic response for threatening or benign stimuli with projections to the amygdala to extract threatening stimuli [56]. The orbitofrontal circuit modulates the pursuit of reward by evaluating context, consequences, and risk associated with behavior. The ACC plays a major role in coordinating these emotional appraisals and autonomic arousal processes with cognitive and social perceptions, such as observing others experiencing pain and experiencing self pain, which relate directly to neural structures implicated in empathy. These structures include activity in the insula, ACC, the midcingulate cortex (MCC), and supplementary and pre-supplementary motor areas which are involved in the processing of acute pain and the selection and organization of movements involved in participant *and observer* movements of avoidance during pain observation. One neuroimaging study demonstrated a link between observing others' pain and the response of the observer's motor system, suggesting that part of the empathic response (like that of a response to pain itself) consists of overt motor actions such as motor preparedness for approach or avoidance, such as flinching when seeing another person cut his finger [57]. Other reports implicate the anterior insula, which is activated both for experiencing pain and in observing others in pain, suggesting a shared neural circuitry for empathy for pain [53, 58, 59].

The human ability to empathize requires cognitive information or direct observation of others experiencing painful or other emotions. Neuroimaging studies have identified neural correlates of empathy by identifying brain activity associated with the imitation and observation of different facial expressions of emotion [44]. Another novel MRI study demonstrated that empathic responses can be

elicited automatically without emotional cues such as a facial expression, but merely by presenting an arbitrary cue such as a colored light that signals the feeling state of another person. In a groundbreaking study of 16 couples, the female partners received a neutral signal that indicated that their spouses were receiving painful electric shocks to their hands. Simply observing a cue that their partners were experiencing pain resulted in the activation of a well-defined pain matrix in the female partners' brains [53].

This was the first neuroimaging study to demonstrate that when people say, "I feel your pain," it is not just a figure of speech. They feel the pain in an attenuated form because most (but not all) of their own neural pain matrix is activated when they know that someone else is experiencing pain. The neural systems that are activated in experiences of both "self" and "other" pain include the rostral ACC, bilateral anterior insula (extending into inferior prefrontal cortex), cerebellum, and brainstem. Areas specific to *receiving* pain in subjects include activity in the posterior insula/secondary somatosensory cortex, the sensorimotor cortex, and the caudal ACC. The authors reported a direct correlation between activity in the observers' ACC and scores on empathy scales [53].

Detection of Physical and Physiological Signs of Emotion with the E.M.P.A.T.H.Y. Mnemonic

There is a critical need to improve empathy in all areas of medicine that could be addressed with specific training protocols [60]. Enhanced detection of physical markers of emotion can assist clinicians in becoming more attuned to patients' needs. Biomarkers have been defined as "a specific physical trait used to measure or indicate the effects or progress of a disease, illness, or condition" [61]. Many physical signals and signs of emotion are frequently overlooked in the practice of psychiatry, including psychotherapy. Not only can these physical manifestations be important indicators of what is happening with the patient, but they may also provide a window into underlying neurobiology and, hence, may play a similar role to conventional biomarkers. These signals and signs can be organized using a novel mnemonic device, E.M.P.A.T.H.Y. [2].

The E.M.P.A.T.H.Y. Training Model (ETM) recently demonstrated statistically significant increases on scales of self-reported empathy, scores on an assessment of knowledge of the neurobiology of empathy in resident physicians, and statistical trends on scales of patient perception of physician empathy and communication skills in a pilot study [62]. The E.M.P.A.T.H.Y. approach may enhance therapeutic practices common to all models of psychotherapy and to the patient–doctor relationship in general. At the pedagogical level, this novel review of physical manifestations of emotion could be included in the traditional "review of systems" in that it is part of a comprehensive patient interview. This may encourage up-regulation of empathy in the patient–doctor relationship at the critical time of forming an alliance with a new or prospective patient. This practice could be applied to all specialties, as it is a critical component of humanism in medicine [60]. Use of this mnemonic to review physical manifestations of emotions could easily be incorporated into psychotherapy process and outcomes research to determine if enhanced awareness to biological markers facilitates ~~not only~~ empathy~~, but also discussions of possible undisclosed emotions.~~ There are biological correlates to empathy.

The E.M.P.A.T.H.Y. Mnemonic

In order to empathize with the patient's anxiety in the clinical case example, it was critical to have enhanced awareness of her physical clues. By scrutinizing the video tapes for physical signs of anxiety that matched the indicators on the SC tracings, the author was led to develop a new tool for

enhancing empathy in patient–doctor relations [2]. Such training includes an approach emphasizing attention to physical signals. The mnemonic **E.M.P.A.T.H.Y.** focuses attention on specific neural correlates of empathy that are grounded in the neuroscience and attachment literature. They include **(E)** for making meaningful **eye contact**; **(M)** for decoding **muscles of facial expression; (P)** for **posture decoding**; **(A)** for **affect perception**; **(T)** for **tone of voice; (H) hearing** and **healing** the patient**;** and **(Y)** for **"Your Response,"** which asks clinicians to take notice of their own emotional response to the patient. Attention to these behaviors and responses, like measuring skin conductivity or GSR, can serve as phenotypes of a sort, in that they can reflect meaningful neurobiological activity and can also be considered as a gateway to exploring critical but less obvious manifestations of patients' symptoms. Use of this mnemonic as a device to review physical manifestations of emotions could easily be incorporated into psychotherapy process and outcomes research to determine if enhanced awareness to biological markers facilitates not only empathy, but also discussions of possible undisclosed emotions.

Neural Correlates of E.M.P.A.T.H.Y.

E = Eye contact

Philosophers and child psychiatrists have long understood the importance of gaze. "The look of the other is necessary to know I exist," observed philosopher Jean-Paul Sartre [63], and O'Donohue echoes, "One of the deepest longings of the human soul is the longing to be seen" [64]. The necessity of eye contact for secure maternal–infant attachment is well described by Bowlby. The initial focal point of an infant's gaze is 17 cm, the approximate distance between the infant's eye and the mother's face, when held in her arms while feeding. Research shows that infants are negatively affected by a lack of eye contact. In addition, the lack of engagement by a depressed mother's "still face" predicts insecure attachment as early as 6 months [65–67]. Research by Ainsworth [67] and Bowlby [68] provide a study of affective engagement as a motivated human behavior for human connection.

The human face provides a wealth of information about expressed emotion and is a primary instrument for social communication. For example, eye contact is usually the first signal that one person has been noticed by another person [69]. Neural correlates of eye gaze processing have been found to be abnormal in children with autism. Neuroimaging and electrophysiological studies have shown that in normal controls, eye contact is processed in the superior temporal sulcus and the amygdala [70], and brain activation patterns in these areas are affected by whether changes in gaze are congruent or incongruent with neurological responses to visual emotional targets (such as facial expression). While individuals with autism show neural activity in similar regions as normal individuals (amygdala and superior temporal sulcus), modulation of eye contact to respond to new targets in different contexts is reduced [71].

A functional magnetic resonance imaging (fMRI) study on the effects of eye contact on amygdala sensitivity to anger and fear faces found that gaze direction differentially modulates the perception of anger and fear facial displays. Anger faces with direct gaze (unambiguous threat) and fear faces with averted gaze (indicating where in the environment the threat is located) are recognized more quickly and accurately. Whereas anger faces with averted gaze (ambiguous threat) and fear with direct eye contact (also an ambiguous threat) elicited stronger responses in the left amygdala [72]. The importance of eye contact in the patient–therapist relationship underscores the necessity of making eye contact perceived as safe to the patient. Clinicians who avert their gaze while entering data on their computers or taking extensive notes with averted gaze risk alienating their patients. Patients may experience signs of disengagement conveyed by poor eye contact and an averted face as a lack of interest, disapproval, or dislike.

M = Muscles of Facial Expression

The capacity to understand another person's actions, intentions, and emotions is critical to human survival. The cranial nerves that regulate social engagement through facial expression, vocal and verbal communication, and affective experiences are connected neuroanatomically to the portion of the vagus nerve that regulates cardiac contractions. When a person sees a safe or trustworthy facial expression, a neural circuit that projects from the temporal cortex to the amygdala inhibits limbic defensive fight, flight, or freeze behaviors [73]. In patient–therapist encounters, subtle micro-expressions of the face [74] may be particularly threatening to the patient due to the unequal status of the relationship, and the patient's internal regulatory processes may promote withholding of particular affects and information. Members of the same species who are in unequal positions of power are especially sensitive to perceived facial threats, and when communication is inhibited, all parties are at risk for interpersonal misperceptions. Clinicians should be aware of the negative effects that blank expressions can have on patients. Cohn's research demonstrates that the same still-face paradigms that are emotionally disorganizing and predict insecure attachment as early as 6 months of life can also be elicited by the unresponsive face of a caregiver [66]. Because of the vital importance of good communication, understanding the neural correlates of interpersonal communication may help physicians become better attuned to accurate perception of patients' implicit communications.

Humans and their primate relatives use muscles of facial expression to communicate. According to Darwin, who cataloged the importance of facial expression in *The Origin of Emotions in Man and Animals* [75], the primary function of emotions is to ensure survival of the individual and species by awareness and reflection. Paul Ekman, a pioneer in the field of facial expression, concluded that humans have seven basic emotions that are common across all cultures. The seven universal emotions are sadness, anger, fear, surprise, happiness, disgust, and contempt. Micro-expressions of emotions are generally displayed for 0.25 s and the untrained eye can easily miss important information conveyed by a patient's fleeting facial expression [76]. Mirror neurons facilitate translation of observed actions into internal representations that may be felt, to some degree, by the observer.

Neuroimaging studies have explored the neural correlates of empathic experience by comparing brain activity associated with the observation versus imitation of pictures showing different emotional facial expressions [44]. For example, one study measured neural responses elicited by watching videos of faces with disgusted versus pleased expressions and compared those results to responses induced by smelling aversive versus pleasant odors. Activity in the insular cortex was elicited by a disgusting smell and also by the sight of the facial expression for disgust [55]. These results support the observation that regions associated with feeling an emotion can be activated by seeing the facial expression of the same emotion. Therefore, by looking closely at an emotional face, the same neural networks associated with the specific emotion displayed are activated in the observer's brain. Moreover, if the facial expression is imitated by the observer, the neural circuits are stronger than by observation alone. This phenomenon gives doctors a useful tool to understand the emotions of their patients. By imitating the facial expression (e.g., a sad face), the observer elicits the emotional experience of sadness [44].

Additionally, investigators have also found that automatic mimicry reactions to observing emotional facial expressions of happiness or anger in observers occurs to a higher degree in high-empathy observers than low-empathy subjects, as measured by electromyographic (EMG) activity. The differences between the groups in emotional empathy were reported to be related to differences in automatic somatic reactions to facial stimuli rather than to differences in their conscious interpretation of the emotional situation [77, 78]. Saarela et al. demonstrated that humans can detect intensity of pain from another's face. When subjects observed painful expressions, increased activation was observed in the observers' bilateral anterior insula, left ACC, and left inferior parietal lobe, which correlated with the intensity of observed pain, and also with subjects' self-rated empathy.

Thus, the intersubjective representation of pain in the human brain may be more detailed than previously thought [79]. Theoretically, this empathic experiencing of another's suffering often motivates the observer to act to relieve that person's suffering [74].

P = Posture

Darwin suggested that the evolutionary purpose of emotions is to predispose humans to act adaptively, and that characteristic body movements and postures are associated with emotional states that have evolved to promote survival [80]. Although most investigations of emotion perception have focused on neural activity generated by images of facial expressions for decoding emotions, body movements may be just as important for understanding the neurobiology and meaning of emotional behaviors [58]. In the clinical case described earlier, the patient's motor movements while playing with her hair coincided with spikes in her SC tracings, indicating a motor and postural sign of her anxiety that the therapist began to recognize after examining the SC data. While perception of facial expressions involve the amygdala, fusiform cortex, prefrontal cortex, OFC, medial frontal cortex, superior temporal sulcus, and somatosensory cortex [81, 82], some of these same areas also play a role in processing body movements. An important finding is that observing bodily postures activates two well-known areas that are predominantly associated with processing facial expression (the inferior occipital gyrus and middle fusiform gyrus). The activation in facial-expression-related areas may result from context-specific perceptual mechanisms that fill in the missing face information. There appears to be a striking similarity in visual encoding between faces and body postures [83].

A 2004 fMRI study found that viewing fearful whole-body expressions, as contrasted with emotionally neutral postures, produces high activity in areas that are known to specifically process emotional information (amygdala, OFC, posterior cingulate, anterior insula, retrosplenial cortex, and nucleus accumbens). Conversely, comparisons of happy bodily expressions with neutral ones only yielded increased activity in visual areas. These finding may suggest that potentially threatening or dominant body postures, such as standing over patients, asserts undue authority and may intimidate patients and prevent them from expressing their intimate concerns. Likewise, physical barriers between patients and clinicians may also create emotional boundaries. A computer screen positioned between the doctor and patient and an averted gaze may express emotional distance whether or not intended. When doctors are seated at eye level, a collaborative message is conveyed, and studies show that patients perceive the doctor as having spent more time with them and as having been more empathic than when standing [84, 85].

Recent neurobiological models of empathy suggest that motor, perceptual, or emotional states of one individual activate corresponding representations in another individual who is observing that state [86–89]. In primate studies, single-cell recordings show that premotor ("mirror") neurons become activated both during execution of a given action and during observation of the same action performed by another primate. This may account for the unconscious "mirroring" that takes place when two individuals seated opposite one another find themselves assuming the identical posture. Shared motor responses are also seen when one person is injured (such as getting a hand slammed in a car door) and both the participant and the observer react by flinching. Similar indications of motor activity signaling pain or anxiety, such as the touching of hair in the case example, can be understood as a motor manifestation (external marker) of internal pain and may even be unconsciously shared or mirrored by the observer [53, 57, 58]. Similar to facial expressions, manipulating posture has been used to produce feelings of anger, sadness, disgust, and fear in the observer [90–92]. Interestingly, prideful [illegible] be experimentally manipulated [93], and arrogance and pride [94] are qualities in physicians that are linked to malpractice claims, suggesting that prideful postures portrayed by clinicians evoke negative emotions.

A = Affect

Affect refers to the emotion conveyed by the patient that is consciously observed by the clinician. Emotional appraisal of patient affects allows therapists to orient themselves to the particular emotion of the session. Neural correlates of affect include perceptions routed through the thalamus, ACC, amygdala and OFC, all of which project to the insula, which in turn relays emotional contents to limbic areas [44, 53, 58, 59]. Attunement to patient affects, and mirroring changes in affect by verbal and facial expression, may facilitate empathic responsiveness on the part of the physician and affect regulation on the part of the patient. Ainsworth's [67] and Bowlby's [68] research provides support for a human motivation of affective engagement. Physicians must also be aware of the effect of no affective expression on patients.

T = Tone of Voice

Human beings are exquisitely sensitive to variations in tone of voice. Hearing helps humans to understand actions and motivations of others via neural mechanisms for shared experiences for sounds [95]. Research by Ambady, using content-filtered slices of conversations between surgeons and patients, preserving only intonation, pitch, and rhythm but erasing the content, showed that judges could accurately predict which surgeons had been sued and which ones had not [94]. The affective tone of a therapy session may be set more by tone of voice than the words spoken. Changes in patient tone of voice and how a clinician responds may determine that patient's perception of the therapist's empathy and attunement. Aggressive tones of anger and rage versus gentle, soothing sounds have been shown to induce the identical range of emotional feelings in the listener when passages were read using the pace, rhythm, and pitch of these emotions [96–98].

H = Hearing/Healing

"What am I hearing and what would be healing for this patient today?" This item in the mnemonic asks the clinician to be mindful of what is coming across in the patient's narrative to which it is most salient for the clinician to respond. This requires as assessment of the overall state of the patient. It may be noticing an especially intense affect, a situation in the patient's life, or something that has happened to a loved one that calls for stated compassion and empathy. It could also be a rupture in the patient–therapist relationship that needs attending to and healing. The neural correlates for hearing have been discussed [96–98], and the shared neurobiology of pain and painful facial expressions [44, 53] should prompt an empathic response to the patient that would hopefully be experienced as healing. A compassionate nod, a gentle tone of voice, can make the emotional difference in an office visit.

Y = Your Response

Dimascio [99] was the first to demonstrate the importance of the shared autonomic physiological response between patient and therapist in psychotherapy. Many studies support the notion that empathy has a physiological substrate that provides an internal experience that is shared between people.

The psychoanalytic concept of "projective identification" [100] is a process whereby patients' unexpressed emotions are experienced by the clinician as the first signal of what the patient is feeling. "Projective identification" may occur by a process in which patients' feelings are projected onto clinicians through a summation of therapist perceptions of patients' explicit and implicit physical and physiological cues that are both consciously and unconsciously perceived by the therapist. This results in an internal representation of patient affect that is introjected and experienced by the clinician.

Projective identification has recently been validated by mirror neuron and physiological research [29, 49, 99], which supports the theory that observers have an internal representation of another's experience. Neuroimaging studies indicate that these projections are decoded by the action of mirror neurons that identify subtle cues and micro-expressions [74] that do not meet threshold consciousness but are experienced by the observer. Many clinicians are aware of dreading certain patient encounters because of the negative affects they associate with those patients. By developing a critical curiosity [101] about their own feelings, physicians may be able to identify the affect that the patient generally engenders within themselves. Negative effects such as guilt, anger, entitlement, or disrespect elicited in the physician may be the precise feelings that the patient is experiencing but not disclosing. When clinicians are able to reflect on their own feelings with curiosity and not simply react to what is being projected on to them, a space for new possibilities is created. The capacity to respond with what would be helpful to the patient, rather than react emotionally, is what distinguishes a clinician who can detect the vulnerability behind even the most intense projections and focus on the patient's needs rather than focus on him or herself.

Psychotherapy and Brain Biomarkers

Psychotherapy: Associated with Biomarkers of Physiological Changes in the Brain

[AU1]

Neuroimaging, EEG, ~~genetic~~ and physiological responses, measured by GSR and SC research, are revolutionizing biological psychiatry. In addition to clinical biomarkers of emotion, research advances are demonstrating physiological changes in the brain associated with psychotherapy. Whereas psychopharmacological interventions have been a primary focus for biomarker research, a comprehensive review indicated a great potential for neuroscientific tools to be used in psychosocial treatments [102].

Studies using fMRI and positron emission tomography (PET) have found psychotherapy has measurable effects on the brain [103, 104], and the following are some examples: PET studies have shown similar changes in brain activity by both pharmacotherapy and psychotherapy. For example, in obsessive–compulsive disorder, both cognitive behavioral therapy (CBT) and pharmacotherapy were associated with a reduction in metabolic activity in the caudate nucleus [105]. In depressed patients, decreases in dorsal and ventral prefrontal cortical metabolism were found both with IPT and pharmacotherapy [106]; and short-term PDT and pharmacotherapy demonstrated increased brain serotonin 5-HT_{1A} [107]. In phobic disorders, CBT and pharmacotherapy demonstrated significant reduction of activity in limbic and paralimbic regions [108]. Further psychotherapy biomarker research is needed to continue to elucidate patterns for treatment selection and to tailor individual treatments for specific disorders.

[AU2]

Biomarkers: Also Associated with Treatment Response to Psychotherapy

EEG and neuroimaging studies have revealed effects of psychotherapy on brain function across a range of psychiatric disorders [109]. Several studies have suggested that EEG may help to identify persistent versus episodic biological characteristics of major depressive and anxiety disorders [109–111]. Specifically, the EEG gamma band was useful for identifying anxiety states from baseline and relaxation in patients with generalized anxiety disorders compared to controls [109]. Thase and colleagues examined depressed patients and the relationship between EEG sleep profiles and response to IPT and found that subjects with abnormal sleep profiles had poorer clinical outcomes than subjects with more normal sleep profiles [112]. In an earlier study, they found that CBT and tricyclic antidepressants may share several common EEG sleep correlates of treatment responsivity [113].

Neuroimaging, EEG, GSR, SC, and genetic research are revolutionizing biological psychiatry. Whereas psychopharmacological interventions have been a primary focus for biomarker research, the aforementioned studies indicate a great potential for neuroscientific tools, including the untapped field of genetics, to be used in psychosocial treatments as well. Prospective studies are needed to provide algorithms for tailored individualized treatment plans for psychotherapeutic interventions, allowing clinicians and patients to avoid lengthy costly "trial and error" approaches [102]. A major shortcoming of psychotherapy is that it is currently very difficult to predict which treatment is best for which patient, and treatment failure may not become apparent until weeks or months or even years have been invested. There is an urgent need for continued biomarker research in psychotherapy, which promises individualized, biologically based data to improve selection, effectiveness, and efficiency of psychosocial treatments.

In parallel with ongoing biomarker research, emphasis must be placed on detecting physiological signs of emotion that are grounded in neuroanatomy and physiology that will enhance clinical effectiveness.

Clinicians must be trained to detect subtle signs of emotions [60, 114], and the E.M.P.A.T.H.Y. approach may enhance therapeutic practices common to all models of psychotherapy. In the future, psychotherapy will be increasingly guided by advances in neuroscience research that will help to provide a strong scientific foundation. Together with scientific research, the clinician's mandate will always include forming a working alliance with patients guided by astute clinical observation of all aspects of the patient's presentation. There is no substitute for looking at, hearing, experiencing, identifying, and empathizing with our patients. The therapeutic relationship is the substance and substrate of empathy for all forms of psychotherapy, and the necessary foundation for all psychiatric interventions.

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Author Queries

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Queries	Details Required	Author's Response
AU1	Please check if edits to the section heading "Psychotherapy: Associated with Biomarkers of Physiological Changes in the Brain" and the next one are okay.	
AU2	Please check the edit made in the sentence starting with "In depressed patients…" and correct if necessary.	
AU3	Refs. [29, 44] and [54, 59] were identical, hence, the latter reference has been deleted and the subsequent references have been renumbered sequentially. Please check.	
AU4	Please update Refs. [2, 93].	
AU5	Please check the inserted volume number for Ref. [23] and correct if necessary.	