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49 Psychoneuroimmunology Assessment

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It is widely accepted that psychosocial factors contribute to the onset and progression of many diseases, and that the immune system plays a critical role in these relationships. Conversely, immune signals communicate with the brain and impact mood, cognitive function and behavior. These bidirectional pathways are the focus of the field of psychoneuroimmunology (PNI; Chapter 35). Psychoneuroimmunology researchers have employed a variety of measures with the aim of understanding the impact of psychosocial factors on immune system functioning, and the potential clinical relevance of these effects. In this chapter, we review the most commonly used measures in the field, with a focus on describing the measure, how it is assessed and used and whether results are reliable.

Overview of Immune System

The immune system is a complex network of cells and soluble mediators that protects the body from foreign matter (antigens). For descriptive purposes, immune processes are classified as innate or adaptive. Innate immunity includes non-specific responses to any

Table 49.1 Cells of the immune system

Cell type	Percentage of PBMCs (peripheral blood mononuclear cells)	Cluster of differentiation (CD) markers	Associated cytokines
Monocytes/macrophages	10–30	CD14+, CD33+	IL-1, IL-6, TNF-α
Dendritic cells	1–2	CD11c+, CD123+	IL-1, IL-12, TNF-α
NK cells	15	CD16+, CD56+, CD3–	IFN-γ, IL-4
T-cells	45–70	CD3+	–
Cytotoxic T-cells	5–30	CD3+, CD8+	IFN-γ, TNF-α/β
T-helper cells	25–60	CD3+, CD4+	–
Th1	–	CXCR3+, CCR5+	IFN-γ, IL-4, TNF-α/β, IL-2, GM-CSF
Th2	–	CRTH2+, CCR4+, CCR3+	IL-5, IL-6, IL-4, IL-10, IL-5, IL-13
Treg	–	Foxp3+, CD25+	TGF-β, IL-10
B-cells	15	CD19+, CD20+	IL-10, TGF-β, TNF-α

compounds not recognized as self. These responses are functional at birth and activate quickly (minutes to hours). Adaptive immunity is slower (days) and provides a more targeted response against specific antigens.

The innate immune system includes physical barriers (e.g. skin) and cells that recognize common foreign pathogens (e.g. natural killer (NK) cells and granulocytes, including neutrophils, dendritic cells and macrophages). NK cells recognize and destroy altered self-cells (e.g. tumor or virally infected cells). Granulocytes are phagocytic cells that engulf and destroy foreign material present in extracellular fluids. When activated, macrophages play a key role in coordinating inflammatory responses, producing soluble factors called cytokines. Pro-inflammatory cytokines act locally to attract immune cells to the site of infection and systemically to activate an acute phase response that helps to contain the pathogen. Cytokines also communicate with the central nervous system and initiate sickness symptoms, including fever, lethargy and anorexia. In addition to producing cytokines, activated macrophages and dendritic cells process antigens and present them to cells of the adaptive immune system, initiating a targeted immune response.

The adaptive immune response is divided into cellular and humoral components, named for primary defense against intracellular and extracellular pathogens, respectively. The primary cells of the cellular immune response are T-cells (designated as T- because these cells develop in the thymus). Cytotoxic T-cells can recognize altered self-cells (e.g. virally infected or tumor cells), while T-helper cells process extracellular antigens and present them to the primary cells of the humoral system, the B-cells (designated as B- because these cells mature in the bone marrow). All cells of the cellular and humoral pathways release cytokines that direct the actions of other immune cells (e.g. macrophages, B-cells, other T-cells). Cytokine signaling finetunes the immune response in order to combat a specific pathogen. In addition to producing cytokines, B-cells release antibodies that coat extracellular pathogens, identifying them for destruction by phagocytic cells of the innate immune system. Antibodies recognize specific patterns (epitopes) on invading antigens. It is this property of recognition specificity that makes antibodies useful tools for immunology assessment: antibodies can be manufactured to detect specific targets and tagged with indicators used for detection and quantification. Finally, some B- and T-cells activated during the primary immune response become memory cells. Memory cells can quickly recognize pathogens upon repeated infection and stimulate a rapid secondary immune response, which is the basis of vaccination.

Enumerative Assays

Given that efficacy of the immune response depends upon adequate numbers of immune cells in appropriate ratios, many PNI studies focus on quantifying the number of immune cells in peripheral circulation. Although there are established normal ranges for immune cell subtypes in peripheral circulation, these values vary by age, sex, ethnicity and country of origin (Mandala *et al.*, 2014). White blood cell (WBC) counts can be determined from a complete blood count (CBC, a standard clinical laboratory test; also called full blood count (FBC)); however, further quantification of immune cell subtypes requires flow cytometry, a laser-based technology that detects fluorescently tagged cells flowing in a single-cell stream. Here, cell subtypes are determined using fluorescently labeled monoclonal antibodies that bind to characteristic markers on the surface of cells (cluster of differentiation (CD) markers; Table 49.1) and fluoresce when exposed to the laser, permitting them to be quantified as an absolute concentration (cells/uL) or a percentage of overall cells (e.g. percentage of all lymphocytes). In addition, other cell surface molecules can indicate the activation state of these cells.

There are limitations to measuring cell subtype numbers/concentrations as an index of immune competence. First, the number of circulating cell subtypes varies as a function of hemoconcentration and hydration status, and with changes in plasma volume related to blood pressure (Marsland *et al.*, 1997). Second, immune cells migrate between lymphoid organs, the margins of blood vessels and lymphatic and peripheral circulation; thus, assessment at any single time-point may not accurately depict systemic immune status. Additionally, the clinical value of enumerative measures remains uncertain: while declining numbers of T-helper cells may be clinically relevant in human immunodeficiency virus (HIV)-infected patients, the clinical significance of transient alterations in subsets of immune cells within normal values is unknown. Use of cell ratios and markers of immune cell activation, in conjunction with functional measures, may improve overall validity of enumerative measures.

In Vivo Assessments of Immune Function

Viral Challenge

Viral challenge studies are important for investigating causal links between stable psychosocial factors (e.g. social support, stressful life experiences) and susceptibility to infectious disease (Cohen *et al.*, 1993,

1997). In these experimental studies, researchers obtain psychosocial measures before exposing participants to a rhinovirus (a virus associated with the common cold). Researchers then follow participants for the development of cold symptoms and for evidence of virus-specific antibodies, a marker of viral infection. Antibody levels are determined using an enzyme-linked immunosorbent assay (ELISA). Briefly, ELISAs employ monoclonal antibodies to quantify an analyte of interest. The detection antibody is tagged with an enzyme that produces a color change when a substrate is added. The amount of analyte in a sample is determined using light spectroscopy by comparing the color of the sample with standards of known analyte concentration. Because not all individuals who are infected develop symptoms of illness, objective measures of cold-related symptoms are assessed separately, using measures of mucociliary clearance and mucus secretion. Mucociliary clearance is a measure of nasal congestion quantified by the time it takes for dye administered intranasally to reach the nasopharynx. Mucus secretion is evaluated by collecting all facial tissues used by the participant and calculating the weight of the mucus. Although costly and time-consuming to conduct, viral challenge studies provide some of the best evidence that psychosocial factors contribute to individual differences in susceptibility to viral infection.

Wound Healing

Experimental examinations of wound healing have also established a clear association between psychological stress and an observable immune-related health outcome. In these studies, wounds are experimentally induced by barrier disruption, punch biopsy or blistering. Barrier disruption involves stripping the skin (e.g. with cellophane tape) on the forearm or cheek area and measuring the amount of transepidermal water loss (TEWL). Transepidermal water loss is a measure of the integrity of the epidermal skin barrier, with lower values indicating greater wound healing. Punch biopsy wounds are standard biopsies of skin taken from the forearm or the hard palate inside the mouth. Wound healing is assessed as decreases in area of the wound over time. Finally, blister wounds are created using a suction device plus heat applied to the inner surface of the forearm. Blister wounds permit the direct examination of fluids, and thus immune processes that contribute to wound healing.

Wound healing studies show an association of psychological stress (e.g. caregiving, examination periods, marital conflict) with longer wound healing time (Christian *et al.*, 2007), which is consistent with clinical evidence that stress prolongs the healing of surgical wounds (Broadbent *et al.*, 2003). Many additional factors contribute to longer wound healing time, including poor wound care, presence of bacteria, older age, poor nutritional status and poor health behaviors (Christian *et al.*, 2007). The extent to which these factors contribute to slower wound healing during periods of psychosocial stress remains unclear.

Vaccine Response

Vaccination is a prophylactic procedure used to stimulate formation of memory B-cells, which in turn produce antibodies that prevent infection. Vaccine response can be quantified as the level of antigen-specific antibody (using ELISA), offering an *in-vivo* measure of immunocompetence. Individuals vary substantially in magnitude of antibody response to vaccination, with individuals who mount lower responses at increased risk of clinical disease when exposed to the pathogen. The magnitude of a vaccination response is influenced by biological, behavioral and psychosocial factors. For example, lower levels of antibody response are associated with male sex, older age, smoking and obesity (Van Loveren *et al.*, 2001), as well as chronic stress, high trait negative affectivity and low trait positive affectivity (Burns *et al.*, 2003). Unfortunately, many studies fail to consider prior exposure to the pathogen by immunization or infection, which is known to influence magnitude of antibody response to vaccination.

Delayed-Type Hypersensitivity (DTH)

Delayed-type hypersensitivity is a low-cost, functional measure of cellular immune response. This paradigm involves intra-dermal injection of an antigen to which an individual has been previously exposed, resulting in activation of adaptive immune memory and a local inflammatory response. Typical antigens used in this paradigm include tetanus toxoid and tuberculin. In some protocols, participants are injected with a novel non-pathogenic antigen (e.g. keyhole limpet hemocyanin) to establish immune memory; DTH response is then assessed upon re-exposure 6–14 days later. The magnitude of DTH response is typically measured as the area (mm^2) of swelling, hardness (induration) and redness that develops at the site of injection. Smaller areas are interpreted as evidence of *in-vivo* cellular immune suppression, although the clinical significance of the magnitude of this local response is unclear.

A strength of the DTH paradigm is its examination of the coordinated cellular immune response; however, it does not permit an evaluation of specific immune mechanisms, and its stability over time is unknown. Nevertheless, research has shown that higher levels of anxiety and perceived stress correlate with smaller responses (e.g. Smith *et al.*, 2004), suggesting that negative psychological states may be associated with decreased cellular immune competence.

Antibodies to Latent Virus

The majority of the population is infected with latent viruses, such as Epstein–Barr virus, herpes simplex virus, varicella zoster (chicken pox) and cytomegalovirus, which are held in check by the immune system. Elevated circulating levels of antibodies to these latent viruses may reflect a weakened ability of the immune system to prevent such viruses from replicating. Thus, higher antibody levels to latent viruses are interpreted as indicating poorer immunocompetence. Consistent evidence shows that stress (e.g. caregiving, stressful life events) is positively correlated with higher antibody levels to latent viruses (Segerstrom & Miller, 2004).

Circulating Biomarkers

Recently, PNI studies have focused on the assessment of cytokines and other immune mediators, such as acute phase proteins, in peripheral blood, CSF, fluids drained from tumors, sputum and saliva; although the latter may only reflect immune processes taking place in the mouth. Blood plasma and serum samples are typically collected using venipuncture, but it is also possible to obtain blood samples using finger pricks and dried blood spots. Dried blood spots provide a cost-effective and practical method of collecting samples in the field.

Regardless of sample type or mode of collection, immune mediators can be quantified using ELISAs, which afford high specificity and reliable measurement of cytokine levels. More recently, researchers have also begun to examine patterns of cytokines using multiplex assays, which are cost-effective for quantifying numerous analytes in a single sample. Some multiplex assays are ELISA-based, and others use fluorescently tagged antibodies attached to beads, from which analytes are quantified using flow cytometry. Generally, bead arrays are reliable and valid, and analyte ratios correlate well across different multiplex platforms (Breen *et al.*, 2011). However, the measurement of absolute levels of analyte is less reliable using multiplex bead assays than when using single-analyte ELISAs (Eishal & McCoy, 2006), and reliable detection of cytokines present at low concentrations is challenging using multiplex assays (Zhou *et al.*, 2010).

Numerous studies have observed associations of negative mood states and stressful life events with elevated levels of pro-inflammatory cytokines (see Chapter 35), which like elevated CRP levels, are interpreted as biomarkers of low-grade systemic inflammation. However, similar to other immune assays that rely on samples collected from the periphery, it is important to remember that most immune activity is localized in tissues. In addition, many cells of the body produce immune mediators (e.g. Interleukin(IL)-6 is secreted by immune and endothelial cells, myocytes and adipocytes (Papanicolaou *et al.*, 1998)). Thus, circulating levels of immune biomarkers may not provide a comprehensive picture of ongoing immune processes. Finally, there are a number of challenges to establishing baseline levels of circulating cytokines, including natural variability related to diurnal variation and/or subclinical disease states. In future work, the time of sample collection should be consistent within and between subjects, and researchers should consider multiple assessments over time to provide a reliable measure of inter-individual variability in cytokine levels.

In-Vitro Assessments of Immune Function

Other PNI studies employ *in vitro* measures of immune function. These permit the examination of more specific immune pathways, but are of less clear clinical significance.

Proliferative Assays

Lymphocyte proliferation assays are used as a measure of adaptive immune function in PNI research. In this assay, leukocytes are incubated with tritiated thymidine and an experimental antigen (mitogen), which non-specifically stimulates lymphocytes to divide. As cells divide, they absorb the thymidine, and the level of radiation can be measured as an index of cell proliferation. Higher levels of cell division are taken to reflect greater cellular immunocompetence. Findings show that acute and chronic psychological stress associate with decreased proliferative responses (Segerstrom & Miller, 2004). Limitations of this whole-blood assay include (1) inadequate control for numbers of different leukocyte subtypes, which are known to change in response to psychological stress; and (2) questions regarding the temporal stability and clinical significance of observed individual differences.

Cytokine Production

Other assays measure cytokine production by cells that are stimulated *in vitro*. Here, whole-blood or isolated cell subtypes are incubated with mitogens, such as the T-cell stimulant phytohemagglutinin (PHA), or endotoxins, such as the macrophage stimulant lipopolysaccharide (LPS). The stimulated cells produce cytokines that are quantified by ELISA. The most commonly measured cytokines following LPS stimulation are IL-6, IL-1β and tumor necrosis factor (TNF)-α, providing a measure of the competence of the inflammatory response. In contrast, when cells are stimulated with PHA, T-cells are activated and interferon (IFN)-γ, IL-2 and granulocyte macrophage colony-stimulating factor (GM-CSF) are most commonly assessed (Zhou *et al.*, 2010), providing a measure of adaptive immune competence. As with proliferative assays, it is important to consider the impact of cell subtype numbers in the culture. Results of these assays also vary as a function of stimulant concentration or incubation duration (Zhou *et al.*, 2010), which makes comparisons across laboratories using different protocols difficult.

Natural Killer Cytotoxicity (NKCC)

NK cells play an active role in surveillance and destruction of tumor and virally infected cells. Thus, their ability to function is of relevance to susceptibility to infection and the onset and progression of cancer. The ability of NK cells to destroy tumor cells (NK cell cytotoxicity) is most commonly assessed using a chromium release assay. Here, NK cells are cultured with chromium-labelled tumor cells. As tumor cells are destroyed, chromium is released, providing a measure of efficiency of killing. In these assays, care is needed to ensure that observed cell lysis results from NK cell activity, rather than the number of NK cells in the culture or other non-specific factors. Thus, assays should control for NK cell number and include both positive and negative controls that assess total cell lysis (by a detergent) and no effector cells (no lysis), respectively, in order to calibrate the efficiency of killing by the effector cells. Results of studies that employ this assay show an association of decreased NKCC with stressful life events (Segerstrom & Miller, 2004).

Genetic Profiling

While the immune measures discussed so far focus at the level of the immune cell and proteins released by these cells, there is growing interest in understanding molecular and genetic mechanisms that contribute to the regulation of cytokine production. These studies have begun to examine gene expression by (1) quantifying amounts and types of promotors that stimulate transcription of messenger ribonucleic acid (mRNA) (i.e. gene transcription elements); and (2) quantifying amounts of mRNA, the genetic transcript that codes for protein. Cytokine mRNA can be measured using quantitative polymerase chain reaction (qPCR) (see Brookout *et al.*, 2006). With regard to gene transcription elements, PNI researchers are particularly interested in nuclear factor κB (NF-κB) and the glucocorticoid receptor, as both are important in cytokine transcription and the regulation of pro-inflammatory states. These transcription elements are assessed individually or, more recently, as common transcriptional control pathways for global gene expression (e.g. using the Transcription Element Listening System (TELiS); Cole *et al.*, 2005). The use of TELiS in PNI research has enabled the identification of

pathways that may contribute to immune dysregulation. In particular, it can be advantageous for researchers investigating psychosocial predictors without *a-priori* hypotheses about what pathways might be dysregulated. Thus, it is a primarily data-driven approach to understanding genome-wide regulation pathways.

Evaluation of genetic regulation as a proxy for immune functioning imports a number of challenges. Specifically, levels of mRNA may not directly correspond to the amount of protein released by cells or to systemic immune function. Assessment of the association of these measures with cytokine levels, markers of inflammatory function, and physical health is necessary before their clinical significance can be determined.

Measurement Confounds

For all PNI measurements, it is important to consider other factors known to influence the association between psychosocial constructs and immune outcomes (e.g. confounding variables, such as age, sex, race/ethnicity, education level and body mass index (BMI) (O'Connor *et al.*, 2009)). Other factors that may contribute to variation in immune measures include hydration status, current and past exercise history, caffeine intake, current and past immunosuppressive medications, active infection or current disease, shift work and pregnancy, and should be carefully considered in future work.

Conclusions

In this chapter, we have presented a variety of immune measures used in the field of PNI. The measures range from those that have clear clinical relevance to broad screens for system-wide immune dysregulation and more targeted measures that permit the examination of specific immune pathways. We have included in our descriptions the strengths and limitations of each approach with the hope that future researchers will carefully consider the measures that are most germane to their research question.

Finally, it is important to point out that when selecting measures to examine associations between psychosocial constructs, immune function and health, it is crucial to consider the question of measurement timing. Recent evidence suggests that psychological experiences that are more proximal to the immune assessment generate more observable effects on immune function (Graham-Engeland *et al.*, 2016). However, stable or trait factors (e.g. neuroticism, chronic stress, symptoms of psychopathology) are also known to moderate immune system function. It is not yet clear if critical periods of immune vulnerability exist when these associations become established. In this regard, recent attention has focused on the possibility that early life experiences may program the immune system for life and exert health affects across the lifespan (Miller *et al.*, 2011).

In addition, recent trends in PNI research have moved from assessing very specific immune pathways such as NKCC to broad system-wide methods such as peripheral cytokine profiles and gene transcription. While we have presented a rationale for system-wide measurement of immune dysregulation, it is also possible that we have traded specificity for ease of measurement. One advantage of such system-wide measurements is that these measures are more accessible to PNI researchers with little immunological methods experience. However, general popularity and lack of *a-priori* hypotheses may result in large amounts of data that cannot be meaningfully interpreted. In sum, studies investigating the complex temporal relationship between psychological factors and immune function are invaluable in understanding the relationship between psychosocial factors and progression to disease. When selecting an immune measure, it is crucial to consider the question of timing, as well as the immune pathway through which the psychosocial factor may impact a specific disease process.

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50 Social Support Assessment

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Social Support Assessment

Social support is best understood as a meta-construct. In the broadest sense, social support refers to any process through which social relationships promote health and wellbeing (Cohen *et al.*, 2001). Social support has been defined as the functions performed by significant others (Thoits, 2011), a social network's provision of psychological and material resources to support coping with stress (Cohen, 2004) and the commitment, caring and advice provided through relationships or networks (Umberson, 1987). For decades, researchers have persistently focused on and confirmed the beneficial outcomes of social support, culminating into a substantial body of empirical support (Thoits, 2011). For example, social support is linked to biomarkers, brain volume, morbidity and mortality (Cohen *et al.*, 2015; Hamrick *et al.*, 2002; Molesworth *et al.*, 2015), stress, wellbeing, quality of life, substance abuse, mood and affect (Chou & Chronister, 2012; Chronister *et al.*, 2013; Cohen & Lemay, 2007; Kawachi & Berkman, 2001), employment, work stress, housing, poverty, stigma, homicide rates, victimization and health care access (Button *et al.*, 2012)

Social support encompasses numerous theories, constructs and measures, some of which are anchored in the social and behavioral sciences, others affiliated with medical disciplines, and still others studied within the context of public health, computer science and business. Social support is also informed by, and intersects with, personal and sociocultural factors, requiring scholars and practitioners to consider how these factors inform the meaning of social support. Social media have also altered the meaning and process of social support, with claims that online relationships are replacing many aspects of in-person connections (Wellman *et al.*, 2001). The complexity and cross-disciplinary nature of social support contributes to difficulties drawing conclusions, determining efficacy and formulating interventions. In addition, the persistent emphasis on confirming beneficial outcomes has inadvertently led to the neglect of understanding intervening mechanisms (Thoits, 2011); and, while social support implies beneficial intentions or consequences, well-intentioned acts of support also result in negative consequences – coined by Rook and Pietromonaco (1987) as *negative ties* or by Kim (2015: 233) as 'the dark side of social embeddedness'. Considering the complexities of this meta-construct, the purpose of this chapter is to provide an in-depth review of the current state of social support – the various terms and theories, the research base, intervening mechanisms and methods of measurement.

Structure

The most common approach to deconstructing social support is dividing social support into *structure* and *function*. Structural nomenclature typically includes social network, social ties, social integration, social embeddedness and social capital – all of which are operationalized slightly differently, but generally refer to the scaffold from which potential support and resources originate. The construct 'social network' has the longest and most pronounced history, rooted in Durkheim's (1897) seminal study finding that suicide was most prevalent among those who were neither married nor had close ties with their community or church.

Social network measures generally assess the number and diversity of people or entities (e.g. park, church, library) in a person's network, the social roles (family, friend, neighbor, pastor, store owner) in one's network and the connections, patterns, density and boundedness of these connections. Social network researchers use these data points to examine the potential availability and exchange of tangible and intangible resources between the entities (Wasserman & Faust, 1994). The focus of social network analyses is a visual depiction of the exchange and flow of potential resources for an individual or community. Social network theory assumes that a person's network influences individual behavior and attitudes in a positive way, by facilitating information, resources and opportunities that influence healthy behaviors (Berkman *et al.*, 2000). Statistically speaking, social networks have a main or direct effect on outcomes (Cohen *et al.*, 2001). For example, close friends going to the same gym provides direct support for health promotion (Berkman *et al.*, 2000). Beneficial social networks have been linked to lower mortality rates, cardiovascular health, cancer survival and functional improvement (Nyqvist, *et al.*, 2014; Thoits, 1995). Neuroimaging studies show larger brain volumes and neural integrity among those with larger and more diverse social networks (Bickart *et al.*, 2012). In addition, studies show